Chapter

Endometriosis in Mare; What the Mare Can Teach Us When Dealing with Endometriosis in the Woman

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Abstract

Endometriosis is a serious, often irreversible disease of the mare. Often associated with endometritis, this chapter will review our current understanding of pathophysiology, etiology, diagnosis and possible treatments. Endometriosis is a disease complex typically seen in our older mare population. It is important that we understand that although the same term is used to describe a condition in our human patients, it is, however, not the same medical condition as seen in our equine patients. As this disease profile is irreversible with limited treatment options, it causes significant economic strain in our broodmare population.

Keywords: mare, uterus, endometriosis, endometritis, infertility

1. Introduction

This chapter will examine endometriosis in our equine patients, focusing on etiology, diagnosis/prognosis and treatments for this debilitating condition. Endometriosis in the mare is a multifactorial disease, with severity of endometriosis being positively correlated with age. This condition, although with the same name given to a condition seen in women, is not the same in nature, pathophysiology and/or treatment. A detailed comparison between the condition seen in our equine patients and that of women is given below. Further it is utmost important for the scholars amongst us to be aware of the differences between endometritis and endometriosis; although similar and indeed as will be shown, often linked, they again are different conditions. For clarity, endometritis relates to the inflammation of the endometrium, either of an infectious nature (typically bacteriologic) or noninfectious, such as the presence of spermatozoa in the uterine lumen. Whereas endometriosis in the mare is characterized by chronic endometrial degeneration. This condition has serious consequences from an economic standpoint and often leads to mare being infertile.

2. Etiology and pathophysiology of equine endometriosis

Endometriosis is a debilitating condition leading to significant subfertility and often infertility in the mare, causing significant economic loss in our horse breeding population [1, 2]. The term endometriosis is somewhat misleading in our equine clinics. Endometriosis in the mare is a degenerative, chronic condition demonstrated by fibrosis [3] within the endometrium often as a sequelae to chronic deep

rooted infection, typically associated with a number of bacterial species. Although this etiology is not universally recognized [4]. This fibrotic condition in the mare is considered irreversible [5–7], and sadly clinicians are limited in their treatment options for this condition. In our human patients, endometriosis is the presence of endometrial glands and stroma-like lesions occurring outside the uterus [8]. These lesions can be peritoneal lesions, superficial implants, cysts on the ovary or deep infiltrating disease in nature [9]. Thus for the academics amongst us, we must understand the difference between our human and non-human patients with regards to the terminology of endometriosis.

Kenney [10] termed endometriosis in our equine patients based on different alterations to the endometrium based on histopathology [11]. A grading system came into effect in the late 1980s [12]; this was later modified by Schoon [12, 13]. Currently endometriosis is defined as active or inactive periglandular and/or stromal endometrial fibrosis including glandular alterations within fibrotic foci [14]. Single glands and/or glandular nests may be affected in equine edometriosis [15, 16]. In our equine patients, endometriosis is further classified as either destructive or non-destructive forms of fibrosis [17]. Endometriosis is a condition that involves the stroma, progressing to involve around the endometrial glands and is characterized by periglandular fibrosis associated with dysfunction of affected glandular epithelial cells [18–20]. Distinguishing between active and inactive, destructive or non-destructive, is based on the morphology of stromal cells involved in fibrotic foci via pathological examination. For the attending veterinarian, regardless of type of endometriosis, the clinical picture would be one of an aged mare, with a history of multiple pregnancies, and pregnancy failure, often with a number of years (recently) of bareness. In tandem these mares are often observed clinically to have endometritis, the hallmark often being hyperechogenic particular fluid within the uterine lumen on transrectal ultrasonography. Destructive endometriosis is characterized by a strong epithelial vimentin expression, excessive extracellular matrix accumulation, cystic gland dilations and mechanical destruction of those glands [21]. Non-destructive endometriosis is characterized by glandular epithelial cells that are intact whereas their degeneration and necrosis are features of destructive endometriosis [22]. Active stromal cells are characterized by an oval shape, pale cytoplasm, and ovoid hypochromatic nuclei whereas inactive stromal cells are spindle shaped with elongated hyperchromatic nuclei [23]. The cyclicity of our mare patients (mares being long day breeders) and associated seasonal endocrine changes appear to have no effect on the disease process.

Mare's age, repeated insult on the endometrium, multiple pregnancies and parturition have been implicated as etiological factors for the development of the degenerative changes within the endometrium seen in endometriosis [24–27]. Nonetheless, not all of these are universally accepted as etiologic factors, as Hoffman [28] found no correlation between endometriosis and number of foaling (i.e. number of pregnancies carried to term), and indeed that of season and estrous cycle associated changes. Older mares with endometriosis have been shown to have a deficient uterine blood flow during pregnancy with poor placenta microvillus development contributing to increased pregnancy loss, or the birth of weak foals [29]; which also reduced fertility in our managed broodmare populations. Further etiologic factors have been described include periglandular localized endometriosis, focal oxygen deficiency (caused by angiosclerosis) and wound healing after mechanical damage leading to physiological turnover of the basal lamina [30]. In a retrospective study by Ebert et al. [31], found that 90 to 92.5% of uterine biopsies showed signs for endometriosis in age categories of 16–20 years and > 20 years of age, respectively.

Following deposition of semen in the uterus, whether by natural service or artificial insemination, a transient inflammatory process is initiated within the uterus. This

is a normal physiologic event in the mare. This process removes excessive spermatozoa and bacteria that may be induced in the uterus are removed. This process peaks some 12 hours after deposition of semen within the uterus, and is usually completed within 48 hours after insult [32]. It has been suggested that this mechanism of uterine clearance is a critical factor in the uterine defense against infection [33].

Mares susceptible to endometritis have difficulty in clearing inflammatory debris either due to anatomical and/or degenerative defects that interfere with uterine drainage. These defects include a pendulous uterus, impaired myometrium contractility, lymphatic or cervical drainage, atrophy of endometrial folds and disturbed mucociliary clearance. It has been postulated that this decreased physical clearance may increase endometrial periglandular fibrosis [34] and result in decreased pregnancy rates in the mare. There is consensus amongst authorities that there is an initial insult to the endometrium, whether bacteriologic in nature or not, that triggers the start of a complex pathophysiologic process, ending in endometriosis [35–39]. Nonetheless, there are some underlying risk factors to the development of endometriosis. In the initial stages of endometriosis, stromal cells synthesize collagen fibers and differentiate into myofibroblasts, which in turn are responsible for extracellular matrix deposition, eventually ending in endometrial periglandular fibrosis [40]. Periglandular-accentuated mononuclear cell infiltrates (PAMC) have also been suggested as a possible triggering event to endometriosis development [41].

Once established, the endometrium is characterized by abundant fibrosis, ulcer-like holes present on the surface of the epithelium; the cells lack cilia, have few organelles and increased degenerative cell structures [42]. In spite of extensive tissue damage seen in endometriosis, cyclic vascular and non-vascular tissue growth occurs in a coordinated manner as in non-affected mares [43]. Different types of endometriosis are a reflection of different stages of fibrotic process [44]. These areas (endometriosis-affected) of the endometrium exhibit specific differentiation dynamics and become independent from normal uterine control mechanism [45]. Nonetheless, the cardinal feature of endometriosis according to Walter [46] is the deposition of extracellular matrix by myofibroblasts located around the endometrial glands. The epithelial differentiation of the fibrotic uterine glands can be divided into a cycle synchronous, asynchronous and intermediate forms [47]. Initially an epithelial hypertrophy with subsequent epithelial degeneration and glandular dilatation with congestion of secretions is observed, as well as epithelial cell atrophy; there are marked differences in several epithelial enzymatic secretion pathways in the fibrotic foci compared to unaffected glands [48]. Hoffman [49] found that there is a temporary activation of fibrotic stromal cells which were observed after experimentally induced bacterial endometritis likely mediated via profibrotic growth factors and cytokines released by inflammatory cells.

The precise mechanism of endometriosis in the mare is not yet fully understood despite many decades of research. It appears that there is an initial insult, whether non-infectious such as deposition of semen within the uterus or bacterial in origin, results in neutrophil (PMN) migration into the uterine lumen [50]. PMN are the first line of defense (part of the innate immune defense system) against invading microorganisms [51].

It should be noted that endometriosis does not appear to impair PMN functionality [52]. In susceptible mares (in relation to endometritis), those that have a IIB and III endometrial score of biopsy (**Table 1**) have a significant influx of PMN two to twenty-four hours post insult to the endometrium. This PMN hyperactivation and its role in causing severe inflammation and their role in the progression of endometriosis is not fully unknown [54]. PMN appear to cast off the DNA in response to infectious stimuli, forming neutrophil extracellular traps (NETs) [55]. These consist of DNA associated molecule complexes which transport nucleic and cytoplasmic

Category	Histological findings	Estimated foaling rates (to produce a live foal)
I	No significant alterations	>80–90%
IIa	Mild endometritis OR Mild endometriosis OR Mild lymphatic lacunae OR Partial endometrial atrophy during late breeding season	50–80%
IIb	Moderate endometritis OR Moderate endometriosis OR Moderate lymphatic lacunae OR Bareness >2 years OR A combination of two categories from IIa findings	10–50%
III	Marked endometritis OR Marked endometriosis OR Marked lymphatic lacunae OR Deep endometrial atrophy during the breeding season OR Combined presence of three or more IIa findings or 2 or more IIb/III findings	<10%

Table 1.
Categorization of endometrial score proposed by Kenny and Doig [53] and modified by Schoon et al. [12].

proteins, which appear to have immunomodulating properties [56]. PMN play a positive role in infection control, however, they can also have a deleterious effect by their content releasing molecules, which can alter the endometrium potentially contributing to the formation of fibrosis on the endometrium architecture [57].

In inflamed tissues, an intricate network of pro-fibrotic cytokines interacts with extracellular matrix, fibroblasts and other cells to regulate collagen deposition and tissue fibrosis [58]. It is known that in the mare with endometriosis, those that are susceptible to endometritis, there is a release of pro-inflammatory cytokines, including interleukins (IL-1B) and TNFα - both of which have high mRNA expression [59]. However, early in the post insemination period a lower mRNA expression of IL-6 and IL-10 were detected in susceptible PMIE (post mating induced endometritis) mares [60]. Included in that study were mares diagnosed with endometriosis. In a further study, it was shown that *E. coli* induced endometritis showed a sustained expression of pro-inflammatory cytokines (IL-1**β** and IL-8) within the endometrium [61]. Thus it can be suggested that these disturbed expressions of endometrial inflammatory cytokines may play a role in the pathogenesis of endometriosis [62]. Researchers have found that expression levels of IL1RA (an interleukin receptor antagonist) were lower in endometriosis affected endometria compared with non-affected endometria, suggesting a protective role with the endometrium [63].

The first signs of endometriosis on histopathomorphology are atypical morphology and functional differentiation of periglandular stromal cells [64]. The first stage of fibrosis is characterized by large polygonal periglandular stromal cells (type 1) that synthesize collagen fibers [65]. In advanced fibrosis, metabolic active or inactive stromal cells (type II) without signs of collagen synthesis, as well as myofibroblasts, predominate [66]. In the latter, the contractability appears to be affected and may lead to a constriction of uterine glands resulting in glandular dilation [67]. Additionally myofibroblasts may be able to affect the composition and amount of extracellular matrix by secreting different mediators [68]. Typically the endometrium undergoes cyclic changes with typical histomorphological, ezymethistochemical and immunohistocehmical glandular patterns in response to steroid levels [69]. The changes observed in endometriosis on histopathology are independent of the stage of the estrous cycle.

A number of researchers have examined the alteration in secretion pattern of a number of uterine enzymes, namely uteroglobin, uterocalin, calbindin, uteroferrin, and their potential role in the pathogenesis of endometriosis [70–76]. Uteroclain

is the most prominent progesterone dependent uterine derived protein, which is abundantly expressed during pregnancy [77]. Uteroglobin, also progesterone dependent and of uterine origin, is thought to mask the trophoblasts from the mare's immune system, allowing pregnancy to establish [78]. $Calbindin_{D9K}$ is a small cytosolic protein expressed by the endometrium, and has a role in the transport of calcium from glandular epithelia and from the blood supply to the uterine lumen [79]. Uteroferrin again is a endometrial derived progesterone dependent protein that is involved with iron transport during pregnancy [80]. Hoffman [81] showed a synchronous expression pattern: uterocallin and uteroglobin expression were decreased, whereas uteroferrin expression was increased in affected glandular epithelia. Lehman [82] found that affected endometria showed decreased fibrotic stromal cell expression of both estrogen and progesterone receptors compared to unaffected endometria. Normal cyclic dependent expression of these proteins were not observed in affected endometrial tissue, however what is observed is within fibrotic foci, there is a cycle asynchronous patchy protein secretion [83]. Hoffman [84] observed a decrease in uterocallin expression in mares suffering from both destructive and non-destructive fibrosis of their endometrium. Hoffman [85] found that there was decreased expression of $Calbindin_{D9K}$ in fibrotic glands of the endometrium; however, this was not observed by Lehman [86] and therefore is an unreliable marker for endometriosis in the mare. Lehman [87] concluded that uterogoblin and uterocallin should be utilized when trying to refine biopsy classification of endometrium biopsy for our mare population.

Two enzymes that are secreted in abundance in the process of fibrosis in the endometrium, that are capable of degrading collagen IV and laminin, are Tissue Transglutaminase (TG2) and Matrix Metalloproteinase (MMP2) [88]. These enzymes have also been implicated in causing dilation of uterine glands [89]. However, although these enzymes have been implicated in fibrosis, there is contradictory evidence to suggest that there is no correlation between the secretion of these enzymes and the development of endometriosis in the mare [90]. MMP-9 has been shown to degrade collagen IV, the main component of basement membranes [91]. In humans MMP-9 has been reported to be expressed in inflammatory cells as well as glandular and periglandular stromal cells in the endometrium [92].

In a two year experiment where mares were subjected to induced and repeated endometritis researchers found that these endometritis events had no significant exacerbation of the endometriosis observed [93]. Hoffman [94] found in the equine endometrium distinctly reduced ER (estrogen receptors) and PR (progesterone receptors) expression; in fibrotic stromal cells as compared to the unaltered stroma and these markers according to Hoffman [95] are the hallmarks of equine endometriosis. Studies in human patients with endometriosis have found similar results. On the microscopic level it has been reported that the hallmark of endometriosis in the mare is the appearance of concentric arrangement of stromal cells and/or collagen fibers around affected glands [96]. The degree of periglandular fibrosis is determined by the number of periglandular layers of stromal cells and the number of fibrotic nests of glands [97].

Hoffman [98] observed that there is accumulation of fibronectin and proteoglycans particularly in active destructive fibrotic foci and is probably due to an increased number of secretively active myofibroblasts. Hoffman [99] suggests a pathogenesis of endometriosis which the authors describe as conceivable; there is an initial epithelial alteration and activation with a partial thickening of the affected parts of the basal lamina. Only an intact basal lamina is able to suppress the epithelial cell activation and the synthesis of profibrotic growth factors [100]. The early stages of fibrosis are characterized by slight basal lamina alterations with a focal accumulation of stromal cells which synthesize collagen fibers [101].

It has been described in equine endometriosis that there is stromal cell proliferation and their differentiation into myofibroblasts as well as their increased synthesis of extracellular matrix (ECM) occurs in response to a milieu of synergistically and autoinductively acting mediators which might result in a periglandular fibrosis [102].

With different grades of endometriosis, increasing amounts of collagen IV are deposited around the endometrial glands and fibrotic nests [103]. Aresu [104] hypothesized that MMP-9 production would increase with endometriosis; however their results showed no significant increase in this protein level with endometriosis affected mares and controls. They concluded that immunohistochemistry is not useful in clinical practice to evaluate fertility. Hoffman [105] has concluded that it does seem as though endometritis is the initiator to activate the process of endometriosis.

There is clear evidence between age and the degree of endometriosis observed in our equine patients; however the degree of inflammation and grade of endometriosis is poorly correlated [106]. Fibrosis continues to progress even after the inflammatory process has stopped [107]. Therefore this process becomes independent of the initial inflammatory event of which it arose from.

3. Role of prostaglandins in the pathogenesis of equine endometriosis

It has been demonstrated that fibrosis of the lungs is often the result of low grade, chronic inflammation, and this may be true in the development of endometriosis [108]. In addition to the cytokines described above, the role of eicosanoids including prostaglandin E_2 and $F_{2\alpha}$ could provide an alternative pathway to fibrogenesis [109].

The short half-life of prostaglandins would suggest that they act locally via specific receptors [110]. When PGE_2 binds to its E prostanoid receptor it triggers numerous antifibrotic events within fibroblasts, epithelial cells and leukocytes. However when it binds to $PGF_{2\alpha}$ receptors (to which it has lower affinity) it induces fibrosis with lung tissue. In the woman, there is emerging evidence of the role of PG and the development of fibrosis, with PG receptors providing a signaling pathway for their enzymes to cause vasoconstriction, increase myometrial contractions and pain [111]. It has been shown in the mare's endometrium, those suffering with endometriosis, there is altered synthesis of PG and mRNA transcription of prostaglandin synthases [112]. In i*n vitro* studies, it has been shown that decreased PGE_2 production coupled with an increase in mRNA type 1 collagen level due to sustained, low grade chronic infectious stimulus may establish a pathway to endometrial fibrosis [113].

NETs have been shown to decrease prostaglandin E_2 that exerts an antifibrotic response after binding to the E prostanoid receptor [114]. It has been suggested that mares with underlying endometriosis predisposes the uterus to endometritis, rather than the other way around. This is based on observations that *in vitro* induced bacterial endometritis with subsequent treatments was not associated with the progression of endometriosis over a 2 year observation period in 90% of the mares. Whether endometritis is the initiator to endometriosis or vice versa, a mutual influence of endometritis and endometriosis has been postulated by a number of authors [115].

Hoffman [116] found that advanced dedifferentiation of the stromal cells within the fibrotic foci led to inadequate hormone receptor expression that are not able to react to cyclic endocrine changes, becoming independent of hormonal control mechanisms in the uterus.

The establishment of equine endometriosis is a dynamic and complicated process, involving PMN, their role in NETs production and the release of their contents, pro-fibrotic cytokines, interleukins and PG production.

4. Diagnosis

Uterine biopsy is a standard test to evaluate the endometrium, to grade it and most importantly to give the clinician a prognosis of likelihood of the mare to carry a pregnancy to term. This is an indispensable test for evaluating fertility in our mares. Endometrial Biopsy are used to evaluate endometrial health, presence and degree of uterine disease and as a prognostic indicator to future fertility of our equine patients. Evaluation of the degree of endometrial fibrosis is essential as, in contrast to the inflammatory changes, fibrosis is of a permanent nature, and, if it is intense, it becomes the main factor that reduces the reproductive performance of the mare [117].

A detailed description and step by step guide to obtaining a biopsy from a mare's uterus is provided in the book Equine Reproductive Procedures [118], however a brief overview is provided here. It is recommended that a transrectal ultrasound is performed prior to obtaining a biopsy, especially in unknown mares, to rule out concurrent pregnancy. It is also recommended to obtain the sample in either diestrus or early estrus (confirmed by transrectal ultrasonography) and this information should be supplied to the pathologists, to allow for normal alterations of the endometrium due to stage of the estrous cycle to be considered.

The perineum should be thoroughly washed with a non-residual soap and rinsed clean with clean water, and dried with disposable tissue. A sterile obstetrical sleeve with sterile lubricant is worn by the veterinarian, and with the biopsy instrument in a closed position is advanced through the vagina, and carefully through the cervix, with the examiners hand acting as both a guide and protector to the delicate tissues of the reproductive tract. The veterinarian removes his arm from the vagina and inserts it rectally; this is to guide the instrument to the correct location for sampling typically at the base of either of the uterine horns. The biopsy instrument is carefully opened, and with a ventral pressure from the rectum, the endometrial tissue is forced into the cutting basket of the instrument. The examiner then closes the instrument and retracts it from the vagina. The small sample of uterine tissue is then placed into a fixative solution such as 10% formalin or Bouin's solution. The container should be labeled appropriately and sent to the pathologists for interpretation. A single biopsy from this area has been shown to be representative of the entire endometrium [118]. A slight hemorrhagic discharge from the vulva may be seen up to 24 hours post biopsy, and owners should be informed of such.

5. Treatment

There is no satisfactory treatment for equine endometriosis and this is frustrating for all clinicians working within equine theriogenology. The changes to the endometrium are considered by most authorities to be irreversible. However, there is some anecdotal evidence for treatments that revolve around mechanical curettage or use of chemical agents such as kerosene, DMSO and isotonic salts which may be beneficial [119]. Analysis of physical curettage applied to mares will typically cause hyperemia within the endometrium and lead to establishment of endometritis, which can be treated utilizing appropriate antibiotic therapy based on culture and sensitivity. After treatment mares treated with kerosene intrauterine showed an

improved biopsy score; 44% increase, 51% no change, and 5% showed a deterioration of grade [120]. Kerosene is widely used in broodmare practice to potentially revert uterine fibrosis, via endometrial necrosis.

A detailed description and step by step guide to lavaging a mare's uterus is provided in the book Equine Reproductive Procedures [121], however a brief overview is provided here. The mare is retained in adequate stocks, and can be sedated if required. Her tail should be wrapped and held to the side to allow visualization and access to the vulva, without the possibility of contamination from her tail. The vulva and surrounding perineum is washed with a non-residue soap and rinsed. It is then dried with disposal paper. The clinician should put on a sterile, disposal glove and a small amount of sterile lubricant applied to the back of the gloved hand. The assistant should open the sterile y-tubing, avoiding contamination and allow the veterinarian to put the tubing end into his/her hand. The other end of the tubing should be connected to a fluid bag containing approximately 500 mL kerosene. The clinician should open the clasp to allow some kerosene to run through the tubing before it is entered into the uterus to prevent instilling air into the uterus. The clinician should alert the horse of their presence by gently patting the mare of her side with his/her ungloved hand. The sterile glove containing the lubricant should be slowly introduced through the vulva, avoiding any contamination. Clasp the hand around the end of the tubing as you advance through the cervix; this will protect the delicate mucosa from any potential damage. Once the cervix has been located, slowly advance the tubing into the uterus. Utilizing the hand that is inside the mare gently clasp the cervix closed around the tubing and begin instilling the kerosene. Approximately 500 mL should be infused into the uterus. Once delivered, slowly remove your arm from the mare's reproductive tract. Leave the kerosene in the mare for approximately 24 hours.

The following day the mare is returned to the stocks, and her perineum is cleaned as above. The mare is then subjected to a uterine lavage, utilizing Lactated Ringer's solution (LRS). Initially the fluid that is returned from the uterus is cloudy often with particular matter - these are sloughed off parts of the endometrium. Continue to lavage the uterus until the returned fluid runs clear. This may be several liters. Often it is recommended to repeat the uterine lavage the next day. The clinician may utilize the aid of ecbolic agents such as oxytocin given I.V. or I.M. (one unit) to aid in the evacuation of uterine contents.

6. Concluding remarks

Endometriosis is often linked to endometritis in our mare patients. This frustrating disease complex is irreversible and debilitating for the mare and owner alike. This condition once diagnosed leaves the clinician with little options when it comes to treatment choices. Although strides have been made in utilizing enzymatic and protein detection in biopsy sampling for grading of the uterus, this, unfortunately offers the clinician little in terms of possible treatments. Any mare suspected to be suffering from endometriosis should have a uterine biopsy performed. This allows for classification, grading and prognosis, which will help the practitioner to have educated discussions with the mare's owner. If the clinician at hand is working on sport horses, such as show jumpers or quarter horses, options include embryo transfer or intracytoplasmic sperm injection (ICSI). However, should the clinician be working on thoroughbreds for racing, all worldwide jurisdictions ban such measures, and the mare must carry and deliver her own offspring. In these situations, faced with a mare with endometriosis, leaves the veterinarian with little option but to try chemical lavages as

described above, such as kerosene uterine lavage. However, prior to this a biopsy should be obtained to confirm endometriosis, and to allow the clinician to clearly and precisely explain to the owner of the mare, the mare's likelihood of carrying a foal to term.

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