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Chapter 14

Infection and Infertility in Mares

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Additional information is available at the end of the chapter

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Abstract

In cyclic mares, the uterine environment can easily disturbed due to inflammatory processes that occur secondary to microbial invasion. Different aerobic and anaerobic bacteria can enter the uterus during natural mating, artificial insemination, reproductive examination or parturition. The postpartum period is a critical phase since due to relaxation of the uterus and cervix may favor recurrent infections air intake (pneumovagina) or urine collection in mares with poor perineal conformation. Infections are mainly caused by opportunistic or commensal microorganisms, such as *Streptococcus zooepidemicus, hemolytic Escherichia coli* and *Staphylococcus aureus*. Other microorganisms like *Taylorella equigenitalis, Klebsiella pneumoniae* and *Pseudomona aeruginosa* are transmitted through venereal route. Regarding to the fungal endometritis, the most common fungi include *Candida* and *Aspergillus*. These microorganisms cause infertility as a result of repeated inseminations during the breeding season and proliferate when the natural immune system is weakened in mares with advanced age and multiparous, or after repeated use of antibiotics. Indeed, in susceptible mare to endometritis, uterine defense mechanisms involving phagocytosis and opsonization by neutrophils, local synthesis of antibodies, mucociliary activity, vascular and myoelectric activity permeability are compromised, leading to fluid accumulation in response to inflammation and infertility.

Keywords: cycling mare, infectious diseases, reproduction

1. Introduction

The ability to maintain a uterine environment compatible with embryonic and fetal life is essential for reproductive efficiency in horses. However, the uterine environment is easily disturbed by an inflammatory process following aerobic and anaerobic bacterial invasion, which can occur during natural breeding, artificial insemination (AI), reproductive examination, parturition, postnatal infection (pneumovaginal infections), and mostly during a delayed postnatal cleaning of the uterus as a result of poor conformation [1].

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These bacterial uterine infections cause conception and embryo survival failures despite many repeated breeding during the season. In the horse industry, endometritis due to uterine infectious of bacterial origin brings about 25–60% economic losses, leading to infertility. In pregnant mares, these infectious diseases can appear as failure to conceive, early fetal losses, mid-gestational abortion, placentitis, birth of a septic neonate, postpartum metritis, or delays in rebreeding and can be related with other systemic pathologies of viral, bacterial, and fungal origin [2]. Besides in nonpregnant mares, these infections are most often caused by opportunistic or commensal and venereal microorganisms, with a large variety of species have been isolated.

The healthy mare has three functional genital seals forming a barrier between the external environment and the uterine lumen [3, 4].

- Lips of vulva: examination of vulvar and perineal conformation should be included in all prebreeding examinations or evaluations for infertility. The vulva should be a vertical position aligned with the anal opening. The labia should be tight, with most of length below the tuber ischii. The vulvar lips may become parted as a consequence of malformation caused by previous traumatic injuries. In older multiparous mares, there is a tendency for extreme relaxation of the vulvar lips, particularly during estrus, as well as tilting of the dorsal aspect of the vulva becomes horizontal as it is pulled cranially over the tuber ischii. These anatomic changes predispose the mare to pneumavagina (windsucking) and pneumouterus, ultimately causing urine to pool in the cranial vagina producing ascending infection and contaminate the uterus when the cervix is open. Pneumovagina may lead to an urovagina (urine pooling within the vagina) when the vestibule and urethral opening are displaced cranially. In this situation, contamination with fecal material adds to the increased risk of infection.

- Vulvovaginal constriction: immediately in front of the external urethral opening is the vulvovaginal constriction or vestibular seal. In genitally healthy mares, this forms the second line of defense against aspirated air and fecal material. In a normal mare, the vestibulovaginal area remains sealed even when the vulvar labia are parted. Compromised vestibulovaginal sphincter function is suspected when air is sucked into the vagina of compromised secondary to rectovaginal tears and other foaling injuries.

- Cervix: forms the important third (and last) protective physical barrier to protect the uterus from the external environment. The cervix must also relax during estrus to allow intrauterine ejaculation or insemination of semen and drainage of uterine fluid, late pregnancy, and the immediate postpartum period. An inflammation of the cervix is usually associated with endometritis and/or vaginitis.

If the closure of the vulva is compromised, it results in the development of a pneumovagina with consequent aspiration of bacteria and other contaminated products [5]. The initial development of vaginitis can result in cervicitis and acute endometritis and therefore can lead subfertility. Usually, in mares, contamination of the caudal reproductive tract with bacteria during pregnancy can result in embryonic death. In late pregnancy, it can result in the development of placentitis and abortion [4, 6].

The more severe conformational abnormalities result in failure of the vulval closing, increasing fecal contamination since the vulva forms a platform in which feces can collect. In these cases, the vulval lips are angled at 25° for even 50° to the vertical. According to Bradecamp [6], defective vulval conformation can be:

- Congenital, rare to find.
- Acquired, which is due to vulval enlarging resulting for the repeated foaling, injury to perineal tissue and poor body condition (old, thin mares). Older and pluriparous mares are frequently affected with pneumovagina. However, in cases of young mares that are in work and have little body fat and/or poor vulval conformation, it can develop these pathology.

Pneumovagina might occur during estrus when the perineal tissues are more relaxed. Some mares make a noise while walking; however, the diagnosis of other mares may be difficult by the absence of noises. The pathognomonic sign is the presence of hyperemia and a frothy exudate in the anterior vagina, on examination with a speculum. Poor cervical dilation may reduce uterine clearance, while cervical damage or incompetence may predispose to infection. Finally, susceptible mares may accumulate more fluid within their uterus than normal mares because of a greater production of glandular secretions secondary to inflammation. The consequence of decreased physical clearance is that bacteria, inflammatory by-products and fluid remain in the uterine lumen, inducing more inflammation, mucosal cell damage, and fibrosis. The persistent inflammation may result in premature luteolysis. Ultimately, chronic inflammation results in degenerative changes within the endometrium and reduced fertility [5–7].

Real-time ultrasound examination of the uterus may reveal the presence of air or urine as hyperechoic or hypoechoic foci seen at the opposed luminal surfaces, respectively. Cytological and histological examination of the endometrium may demonstrate significant numbers of neutrophils indicative of an endometritis [6]. The clinical presentation of acute or chronic reproductive tract infections in the mare is salpingitis, cervicitis, and vaginitis [2, 5].

2. Vulvitis, vaginitis, and cervicitis

Vulvitis (inflammation of the vulva), vaginitis (inflammation of the vagina), and cervicitis (inflammation of the cervix) can develop due to different reasons such as difficult labor, chronic contamination of the reproductive tract due to poor conformation, sexually transmitted diseases, or mating. Bruises and hematomas (a pool of blood under the surface of the skin) of the vagina may be found in mares following delivery of a foal. Severe inflammation of the vulva and vagina, including local tissue death, may also occur [8]. Infectious vaginitis and cervicitis may occur as part of the uterine infection process or as a result of local irritation or laceration. Vaginal injuries secondary to breeding or parturition may lead to abscess formation and adhesions [9].

The sinus and fossa clitoral (the folded lining near the clitoris) should always be considered as a location of bacterial growth. The clitoral swabs are taken from the clitoral fossa and the

clitoral sinuses to rule out acquired *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Taylorella equigenitalis*. The signs of severe inflammation can include an arched back, elevated tail, poor appetite, straining, swelling of the vulva, and a foul smelling, watery discharge. Signs begin 1–4 days after birth and last for 2–4 weeks. In most cases, supportive care and treatment with antibiotics are sufficient [10].

Among causes that produce infectious vulvitis and vaginitis include contamination by *P. aeruginosa* and *K. pneumoniae* or venereal transmission produced by equine coital exanthema, contagious equine metritis (CEM), and dourine. Although the primary route of transmission is venereal, outbreaks have been documented in which transmission occurred through contaminated supplies and instruments or by the use of a single glove for rectal examination of many mares [11].

P. aeruginosa and *K. pneumoniae* cervicitis can be spread between horses by venereal transmission. Bacteriological studies should be routinely performed on recently introduced mares and stallions to prevent such infections. Culture is also indicated if there is an increased incidence of endometritis on a stud farm. Pre- and post-ejaculation urethral swabs and semen obtained from stallions should be cultured. Routine washing of the stallion penis with antiseptic solution before and after breeding is contraindicated because it may disturb the normal bacterial flora of the penile surface and promote growth of these pathogenic bacteria [1, 12]. Mares infected with *P. aeruginosa* and *K. pneumoniae* discharge greenish-tinged pus with a sweet "grape-like" odor by endometritis.

Equine coital exanthema is a benign venereal disease caused by equine herpesvirus type-3 (EHV-3). EVH-3 is a member of the subfamily Alphaherpesvirinae [13]. Although the primary route of transmission is venereal, outbreaks have been documented in which transmission occurred through contaminated supplies and instruments or by the use of a single glove for rectal examination of many mares [14]. Clinical signs in mares might develop 4–8 days after sexual contact and are clearly expressed by the presence of numerous circular red nodules up to 2 mm in diameter on three different parts of the genital tract: vulvar and vaginal mucosa, the clitoral sinus, and perineal skin. These lesions primarily develop into vesicles, then into pustules and eventually rupture, leaving shallow, painful, ulcerated areas that may amalgamate into larger lesions. Edema can develop in the perineum and may extend between the thighs. Sometimes, ulcers will be found on the teats, nasal mucosa, and lips. Secondary infection of the ulcers by *Streptococcus* spp. is common, causing ulcers which exude a mucopurulent discharge, and the mare may become febrile. Without these secondary bacterial infection occurs, skin healing is complete within 3 weeks, but clitoral and vaginal ulcers heal slowly. Skin lesions persist for long periods as unpigmented scars; however, pregnancy rates are not reduced. Lesions in stallions are similar to those described in mares and are found on both the penis and prepuce. Therefore, copulation may be difficult because intromission is painful, and the stallion usually refuses to mount and copulate. If copulation does occur during the ulcerative stage, ulcers can cause bloody ejaculates, reducing sperm viability [11]. Although coitus is the major route of exposure for stallions and mares, mares can be infected by AI or thorough indirect contact with contaminated veterinary instruments or equipment, gynecological examination or testing for pregnancy [11, 14, 15].

Dourine also produces vulvitis, vaginitis, and cervicitis in the mare. Dourine is sexually transmitted disease caused by the protozoan parasite, *Trypanosoma equiperdum.* This pathology is spread during natural or artificial breeding, foaling, and in the milk of infected mares. Transmission from stallions to mares is more common, but mares can also transmit the disease to stallions. The incubation period is a few weeks to several years. *T. equiperdum* can be found in the vaginal secretions of infected mares and the seminal fluid, mucous exudate of the penis, and sheath of stallions. Affected animals include swelling of the vagina and vulva and mucopurulent vaginal discharge pus by their vulva (females) or urethra (males). Inflammation of vulva and vagina may extend along the perineum to the ventral abdomen and mammary gland. The genital region, perineum, and udder may become depigmented. Clinical signs of dourine can be nonspecific and include fever (temperature greater than 38.6°C), conjunctivitis, weight loss, skin plaques that may become depigmented, and neurologic signs [1, 16]. Dourine usually not causes endometritis, but abortion can occur with more virulent strains [17–19]. Approximately 50–70% of infected horses die [1, 16, 18, 20].

CEM is a transmissible, venereal disease of horses produced by the bacterium *T. equigenitalis.* Compared with other breeds, Thoroughbred horses appear to be more severely affected by the disease. Due to the animals may be asymptomatic, the disease is difficult to detect and control. CEM is a serious disease because it is highly contagious and can have a devastating effect on equine reproductive efficiency. Transmission may also occur indirectly by AI or contact with contaminated hands, instruments used for practitioners or at breeding facilities following international horse shipments. Undetected carrier mares and stallions are the source of infection of the disease during the breeding season. Normally, a carrier stallion can infect several mares before the disease is diagnosed. The sites of persistence in mares that are clitoral carriers are the clitoral sinuses (medial and lateral) and the clitoral fossa [21], for an extended period of time [18]. Mares with CEM shows edema and hyperemia of the vaginal mucosa, cervix and endometrium [18], resulting in infertility, failures to conceive (revealed by an early return to estrus after breeding), or spontaneous abort [22].

Other microorganisms that have been isolated from fossa and sinus clitoral are *Escherichia coli*, *Streptococcus faecalis*, *Corynebacterium* spp., *Staphylococcus aureus*, β-hemolytic Streptococcus, *Bacillus*, *Enterobacter aerogenes*, Pasteurella spp., α-hemolytic Streptococcus, Citrobacter, and Proteus [23]. When suspected carrier status level of the clitoris, the clitoris is advisable to treat/lobby before examining the uterus to prevent the risk of transmission of infection to the cervix.

3. Endometritis

Despite significant research and study, endometritis continues to be a major clinical problem in broodmare practice and a major source of subfertility. Appropriate diagnosis and treatment are imperative when attempting to get these mares in foal. Many cycling mares fail to conceive due to infections in their reproductive tracts and for this reason they are called "dirty mares." Dirty mares or mares with endometritis refer to the acute or chronic inflammatory process

involving the endometrium. Reduction of fertility associated with endometritis—both acute and chronic—has been recognized for many years. This subfertility is due to an inappropriate environment within the uterus for the development of the embryo. In some cases, the endometritis may cause early regression of the corpus luteum (CL). One of the main obstacles in producing the maximum number of live, healthy foals from mares bred during the previous season is the mare, which is susceptible to persistent, acute endometritis following breeding [24–26]. A combination of a bacteriological and a cytological examination improved the diagnostic performance in subfertile mares [27].

Positive cytology to *E. coli* and β-hemolytic streptococci is highly associated with the presence of neutrophil in the stratum compactum and spongiosum on uterus. The low volume, lavage technique is a rapid and accurate method for diagnosing mares with endometritis, and the risk of false-positive samples is considered to be minimal when compared with other flushing techniques described [28].

The key to successful management of these mares is to identify them before or shortly after breeding and manage them appropriately. Treatment generally consists of a combination of uterine lavage and ecbolic administration to enhance uterine clearance and administration of intrauterine antibiotics [29–32].

Overall, endometritis is classified as follows [33]:

- Venereal infectious endometritis.
- Nonvenereal infectious endometritis.
- Persistent post-mating endometritis.
- Endometriosis (chronic degenerative endometritis).
- Chronic infectious endometritis.

The uterine lumen of the normal fertile mare is bacteriology sterile despite the fact that the reproductive tract is contaminated with bacteria from the act of breeding, foaling, and veterinary procedures. As it has been previously expressed mares with imperfect vulval conformation can input air with bacteria into the genital tract, which can develop into endometritis. The uterus responds to these bacteria with a rapid influx of neutrophils killing the bacteria rapidly (within 24 hours). Then, these inflammatory products are mechanically removed, and the endometritis resolves itself. Usually, the failure to resolve this inflammation results in what is commonly known as "susceptible" mare. This "susceptible" mares have a delay in uterine clearance, and the inflammatory products accumulate as uterine fluid. Such mares have a reduced pregnancy rate due to an inappropriate environment for the early development of the embryo [34]. However, the reproductive tract of mare possesses various mechanisms to protect itself against infection: physical barriers as vulva, vestibulovaginal sphincter, and cervix, local immune mechanisms and the physical ability to eliminate products of inflammation, as described below. The uterine infections become established when one or several of these natural defense mechanisms fail or become overwhelmed. These infections become established when normal defense fails to clear potentially pathogenic organisms that

are introduced into the uterus. The most common sources of uterine contamination include coitus, parturition, AI, septic genital examination, and manipulation. Age, parity, number of barren years, and uterine biopsy grade influence likelihood of persistence of infection [2].

3.1. Mechanisms of defense of uterus in the mare

3.1.1. Physical barriers

The uterine cavity is protected from ascending infection by several anatomic structures. The first line of defense in the prevention of contamination of the vagina and eventually the uterus is provided by the seal of the normal vulvar labia. The second physical barrier is the vestibulovaginal sphincter. And the third important anatomic barrier is the cervix. However, in some mares, compromised cervical function is observed, and its entity may remain open during anestrus and even diestrus. The most common cause of cervical incompetence is a lesion consequent to dystocia [3]. A plan for treatment and prevention of uterine infection should include a plan to reestablish normal barrier function. Surgical procedures such as episioplasty, vestibulovaginoplasty, and rectovaginal tear repair should be considered if indicated and reestablish the uterine contractility in the elimination of bacteria, fluid, and inflammatory products from the uterus after breeding [35].

3.1.2. Immunity and uterine defense

An adaptive immune response in the mare's uterus has been demonstrated. The endometrium of the mare is inhabited by T lymphocytes. Genitally normal mares had greater numbers of CD4+ (TH cells) and CD8+ cells (TC cells) in the stratum compactum than in the stratum spongiosum. The density of these cells was either increased during estrus or found to be independent of cycle stage. Also it was not influenced by age and larger numbers of CD4+ and CD8+ cells that are present in the uterine body than in the uterine horns. Following insemination or mares with endometritis, the number of CD4+ and CD8+ cells is increased. Thus, the number of CD4+ cells doubled in lymphoid aggregates, and the number of CD8+ cells in the luminal and glandular epithelium increases. Therefore, an adaptive response is initiated following antigenic stimulation of the endometrium [24, 36].

As the most common etiological agent in bacterial endometritis, *Streptococcus equi* spp. *zooepidemicus* (*S. zooepidemicus*) is commonly used in most experimental models because of its relative ease of laboratory handling and identification. Antigens of *S. zooepidemicus* are processed through an endocytic pathway and are presented on the membrane surface of cells that express class II major histocompatibility complex (MHC) molecules. Presentation of class II MHC molecules to CD4+ cells is limited to "professional" antigen-presenting cells (APCs), such as dendritic cells, macrophages, and B cells. "Nonprofessional" APCs, for instance, certain epithelial cells, fibroblasts, and vascular endothelial cells, can present antigen in the context of class II MHC molecules. But APCs cells fail to deliver a co-stimulatory signal and present antigen for short-term periods during a continued inflammatory response. Cells in the equine endometrium expressing MHC class II include macrophages, monocytes, dendritic cells, lymphocytes, vascular endothelial cells, and uterine luminal epithelium. Expression of MHC

II molecules was greater in normal mares in estrus than in diestrus. The distribution of these molecules was predominantly under the luminal epithelium, with occasional foci in the stratum compactum and infrequently in the stratum spongiosum. This pattern is reliable with antigen presentation [36–38].

On the other hand, cytokines play an important role in the reproductive processes [39]. The complexity of their regulation is due to pleiotropism of cytokines, where each cytokine has multiple target cells of different organs and where responses may differ according to cell type. The response to endometritis is mediated by inflammatory mediators such as leukotriene B4 (LTB4) and prostaglandins (PG) E2. Mares susceptible to endometritis have a higher expression of pro-inflammatory cytokines (interleukin-1 β-I; L-1β), IL-6, and tumor necrosis factor-α (TNF-α) during estrus and IL-1β and TNF-α during diestrus [24, 34]. An overregulated endometrial gene expression of pro- and anti-inflammatory cytokines (IL-1β, IL-6, IL-8) and a systemic acute phase response (APR) have been described in mares with experimentally induced *E. coli* endometritis [40], as it has gene expression of cytokines in response to AI with dead spermatozoa in resistant and susceptible mares [24, 36].

In response to endometritis, endometrial mRNA transcripts of pro-inflammatory cytokines are excellently regulated in resistant mares. These resistant mares have an initial high-expression levels followed by normalization within a short period of time. By contrast, susceptible mares have an extended expression of pro-inflammatory cytokines, leading to the hypothesis that an unbalanced endometrial gene expression of inflammatory cytokines might play an important role in the pathogenesis of persistent endometritis [36, 38]. In addition, endometritis gives rise to a systemic APR and an up-regulated endometrial gene expression of serum pro- and anti-inflammatory cytokines and serum amyloid type A (SAA) [28, 36].

The contact of endometrium with infectious agents results in altered synthesis and secretion of inflammatory mediators (cytokines and arachidonic acid metabolites) and disturbs endometrial functional balance of PGE2, PGI, PGF2α, and leucotrienes [41]. The events leading to endometritis are initiated by a local reaction to the primary antigen, with production of inflammatory mediators, especially PGE2, and neutrophil influx. Increased vascular permeability resulting from proinflammatory mediators exacerbates the neutrophil influx and leakage of serum proteins into the uterus [2, 42]. PGF2α is considered as the most accurate markers of inflammation during endometritis for use in practice [42]. Furthermore, in sustained endometritis in mares, PG may not only cause early luteolysis or early pregnancy loss but may also be related to endometrial fibrosis pathogenesis by stimulating collagen deposition [43].

3.1.3. Immunoglobulins

The predominant immunoglobulins (Igs) in the uterine secretions are IgG, IgM, and IgA produced within the endometrium. Uterine Ig concentration does not differ between mares susceptible and resistant to endometritis, suggesting that this is not a major factor in susceptibility to infection. Susceptible mares tend to have slightly higher concentrations of intrauterine Ig than do resistant mares, but susceptible mares are less efficient at opsonizing streptococci during acute infection [44, 45]. The inoculation with *T. equigenitalis* results in both local and systemic titer increases in antibody [1]. Following intrauterine inoculation with *S. zooepidemi-*

cus, this activity is not only strain specific but also comprises heat-stable and heat-labile components. In general, mares susceptible to endometritis have similar or higher levels of free Ig in the uterus. The common inference is a dysfunction in the humoral response to intrauterine infection, which does not contribute significantly to enlarge susceptibility to endometritis. Investigation of bacterial Ig-binding proteins, would lead to a better understanding of the humoral response to intrauterine infection and its role in susceptibility to endometritis. Certainly, Ig-binding proteins have been identified in uterine secretions and deplete hemolytic complement activity in vitro [44].

3.1.4. Neutrophils

In addition to the traditional functions, neutrophils are able to release DNA in response to infectious stimuli, forming neutrophil extracellular traps and killing pathogens [46]. Neutrophil chemotaxis is induced by bacteria, endotoxin, spermatozoa, semen extenders, and sterile water and saline solutions. A massive entry of neutrophils into the uterine lumen occurs in both susceptible and resistant mares after local exposure to foreign proteins. In some mares, this stimulation causes a persistent-induced endometritis. Therefore, neutrophils play an important role in this phenomenon, and their effects are exacerbated if bacteria are present.

Susceptible mares have higher nitric oxide (NO), which is a bactericidal agent produced by macrophages and neutrophils following incorporation of microorganisms than can cause myometrial relaxation in their uterine secretions and greater inducible NO expression compared with resistant mares. The NO facilitates smooth muscle relaxation, but its role in persistent endometritis is a possible role of NO, either directly or in a NO-associated pathway, in delayed uterine clearance [47]. The activated neutrophils also are an important source of reactive oxygen species (ROS), which can play a role in the pathogenesis of endometritis in mares [42, 48].

Resistant mares are able to eliminate most fluid in response to the effects of oxytocin and PG on the myometrium. Susceptible mares fail to eliminate fluid often because of intrinsic endometrial or myometrial pathology that reduces uterine contractions less efficient in uterine clearance. The phagocytic activity of neutrophils is higher on entry into the uterine cavity [44]. Phagocytic activity may be highest during estrus since in ovariectomized mares treated with estrogens neutrophil phagocytic activity was greater. Phagocytic activity of circulating neutrophils is no different between susceptible and resistant mares; however, phagocytic activity and life span of uterine neutrophils are significantly reduced in susceptible mares. Susceptible mares also have additional uterine clearance problems and accumulate more fluid, which may contribute to a reduction in the viability of neutrophils [24, 44].

Young mares experimentally inoculated with *S. zooepidemicus* clear infection within a few hours, whereas barren mares inoculated with *S. zooepidemicus* and *P. aeruginosa* have a delayed elimination of bacteria [37].

Opsonizing activity in the uterus has a peak of 8 hours after inoculation with *Streptococcus*. Studies using heat-treated uterine fluid suggest that complement is not a primary opsonizing factor in the uterus. In this way, the uterine environment of endometritis susceptible mares

seems to be hostile to complement. In contrast, the opsonizing capacity to serum and degree of serum complement activity does not differ between susceptible and resistant mares [44, 49].

3.1.5. Physical clearance of infection

The prevention of persistent infection is due to physical clearance of pathogens and inflammatory debris from the uterus and is most effective during estrus [50]. However, mares susceptible to infectious endometritis are unable to eliminate bacteria from the uterus in the immediate post-ovulatory period [51]. Younger mares are able to eliminate both *S. zooepidemicus* and nonantigenic particles more quickly than older mares.

Some anatomic changes, such as pendulous uteri or broad ligaments, defective myometrial activity and degenerative changes to the vascular and lymphatic drainage of the uterus, are also involved in delayed uterine clearance and the pathogenesis of the endometritis. Ulceration, degeneration, or lack of cilia of the endometrium may be involved in failure of mucociliary clearance [52, 53].

In susceptible mares, myometrial contractions are less frequent and of shorter duration and intensity, perhaps because of increased fibrosis or another biochemical factors affecting uterine contractibility. Alghamdi et al. [47] informed that uterine contractions are reduced in the presence of NO, which is found in high concentration in susceptible mares.

3.1.6. Antibacterial activity of uterine secretion

Strzemienski et al. [54] reported that cell-free uterine flushes from mares in mid-diestrus possess antibacterial activity. However, Johnson et al. [55] have failed to demonstrate inherent antibacterial activity of uterine fluid from noncycling mares or from E2- or P4-supplemented ovariectomized mares. The discrepancy in the results from these studies may be based on any qualitative and quantitative differences between the uterine secretions from cycling and noncycling mares. Recently, it has been identified in the equine endometrium an antimicrobial and immunomodulator member of the transferring gene family that is expressed by epithelial cells and neutrophils. Lactoferrin's antibacterial property lies in its ability to sequester-free iron, thereby inhibiting bacterial growth. Although lactoferrin expression was overregulated during early estrus, protein staining was uninfluenced by cycle and was most intense in the glandular epithelium. According with Kolm et al. [56], expression of lactoferrin was increased in mares with delayed physical clearance during early estrus, which might represent a response to inflammation. From the point of view of host–pathogen interactions, unless a diminished response in lactoferrin expression and production were observed, it is unlikely to explain how this could be a factor in susceptibility to endometritis.

3.1.7. Mucociliary clearance in the mare

It has been suggested that mucociliary clearance may play an important role in the clearance of infections and that disruption of mucociliary currents in the susceptible mare leads to persistence of infection [33]. Mucus production and secretion and optical density are increased during estrus in mares with delayed clearance. The biological implication of these alterations

in the mucus is unknown. The effects of fluid accumulation and uterine pathogens on mucociliary clearance are basis for future research [57]. Bacterial pathogens of the uterus affect the elasticity and stickiness of the uterine mucus. It was identified that *K. pneumoniae* and other gram-negative bacteria lead to the viscosity of the mucus causing a decrease in mucociliary activity, while β-hemolytic streptococci decrease the viscosity of the mucus. Additionally, it has been reported that an increase in PGE_2, LTB4, arachidonic acid metabolites and an increase in vascular permeability causes the entrance of *S. zooepidemicus* into the uterus. Therefore, if uterus cleaning delays, subclinical endometritis occurs [33].

3.2. Opportunistic infection endometritis

Infection produced by opportunistic microbes is a major cause of infertility in the mare and inflicts major losses on the equine breeding industry due to early embryonic loss, placentitis, birth of septic foals, and postpartum metritis. Early pregnancy loss is estimated to affect 25–40% of the broodmares and uterine infections reported in 25–60% of barren mares [2].

3.2.1. Bacterial endometritis

The organisms most frequently isolated from mares with acute endometritis are *S. zooepidemicus* (β-hemolytic), *E. coli* (*haemolytica*), *P. aeruginosa,* and *K. pneumoniae* [2, 58–60].

At a rate of up to 50% of the endometritis cases, *S. zooepidemicus* is globally the most considerable bacterial endometritis agent in mares [50, 58]. This most commonly isolated pathogens from the uterus of mares, suffering from infectious endometritis associated with increased age, parity, and poor vulvar conformation [28, 50, 61]. Endometritis produced by *S. zooepidemicus* can origin from a reservoir of dormant bacteria residing within the endometrium, and not only as an ascending infection [37, 62]. However, these bacteria can be introduced into the uterus by breeding because bacteria often are introduced into the uterus during coitus or AI [2].

Other commensal bacteria isolated from reproductive tract of mare include *Actinomyces pyogenes, Proteus* spp., S*taphylococcus* spp., and *Citrobacter* spp. These bacteria are occasionally supported by cytologic of histopathologic evidence of concurrent inflammation. α-Hemolytic Streptococcus, *Enterobacter* spp., and *Staphylococcus epidermidis* are rarely causes of endometritis and should be considered simple contaminants [2, 24]. *Corynebacterium* spp. and anaerobic bacteria such *Bacteroides fragilis* may occasionally cause endometritis in mares [26, 63]. Anaerobic bacteria and mycoplasmas have been suggested as possible causes of endometritis from postpartum and foal heat in the mare samples when the evidence of inflammation is present without aerobic bacteria [2]. The resulting disease is characterized by endometritis, vaginal discharge, and a devastating effect on fertility.

The pathogenicity of bacteria depends on their ability to adhere to the endometrium, preventing their removal by normal uterine clearance mechanisms. Adhesive proprieties of *S. zooepidemicus* are probably mediated by fibronectin-binding proteins and hyaluronic acid capsule [62]. Resistance to phagocytosis is often observed with *S. zooepidemicus* and *K. pneumoniae.* This resistance is probably mediated by antigenic variation, antiphagocytic M-protein–like, hyaluronic acid capsule or polysaccharide, and Fc receptors on phagocytic cells.

M-protein-like surface proteins capable of depriving the bacterium of unspecific and specific immune reactions caused by attaching to the Fc region of IgG and IgA. The M-like proteins also bind fibrinogen [64]. Streptococci-binding fibrinogen to the M-like protein attaches to phagocytes too, yet they are not internalized. *S. zooepidemicus* is able to resist complement-mediated cell lysis, which might be mediated by the M-protein-like. The antigenicity of the M-protein-like is mainly responsible for the mounting of a protective immune response. Bacterial toxins promote deterioration of complement and exacerbate uterine inflammation [64–66].

In contrast to a true sexually transmitted diseases, persistent infectious endometritis is often the result of contamination of the uterus by the mare's fecal flora combined with compromised uterine defenses [24, 67]. Different bacteria such as *P. aeruginosa, K. pneumoniae, S. zooepidemicus,* and *E. coli* can be sexually transmitted in horses, but the magnitudes of exposure to these microorganisms are determined by the particular strain involved and active participation of the mare's uterine defense mechanisms [24]. Once the bacterium attaches and colonizes mucous membranes produces endometritis. This process is promoted by extracellular enzymes and toxins. Many strains of *P. aeruginosa* produce exotoxin A, which causes tissue necrosis due to blocking protein synthesis of host cells. Pseudomonas and other bacteria survive in nature by forming biofilms on surfaces. A biofilm is a structured consortium of bacteria embedded in a self-produced polymer matrix consisting of polysaccharide, protein, and extracellular DNA. A bacterial biofilm is a complex aggregation of microorganisms growing on a solid substrate. Biofilms are characterized by structural heterogeneity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances, which greatly increase in the resistance to antibiotic therapy. It has been proposed that endometrial biofilms are responsible for the cases of chronic endometritis that appears to be nonresponse to conventional treatment [68].

3.2.2. Fungal endometritis

Candida spp. and *Aspergillus* spp. are the most common fungal organisms isolated from the uterus of mares with endometritis. The incidence of fungal infection in mares with endometritis is estimated to vary from 0.1% to 5%. Fungal organisms isolated from the equine uterus include *Aspergillus* spp., several *Candida* spp., *Cryptococcus neoformans, Fusarium* spp., *Hansenula anomala, Hansenula polymorpha,* several *Rhodotorula* spp., *Scedosporidium apiospermum, Saccharomyces cerevisiae, Trichosporon beigelii, Torulopsis candida, Acremonium* spp., *Actinomyces* spp., *Fusarium* spp., *Aspergillus fumigatus, Aspergillus glaucus, Aspergillus niger, Monosporium apiospermum, Monosporium* spp., *Aureobasidium pullulans, Mucor* spp., *Candida albicans, Nocardia* spp., *Candida ciferii, Paecilomyces* spp., *Candida famata, Penicillium* spp., *Candida guillermondii, Pseudallescheria boydii, Candida krusei, Rhodotorula glutinis, Candida lusitaniae, Rhodotorula minuta, Candida parapsilosis, Rhodotorula rubra, Candida pseudotropicalis, Rhodotorula* spp., *Candida rugosa, Candida stellatoides, Candida tropicalis, Torulopsis glabrata, Candida zeylanoides, Circinella* spp., *Trichosporon cutaneum, Coccidiodes immitis, Trichosporon* spp., *Cryptococcus humicolus,* and *Yarrowia lipolytica* [69].

Most mares presented with fungal endometritis have a history of previous bacterial endometritis. These mares usually undergo intense therapy that includes frequent uterine lavages and

intrauterine infusion of antibiotics. The frequent uterine manipulation, associated with anatomical problems leading to pneumovagina, results in chronic contamination of the uterus. In addition, antibiotics drained from the uterus alter the normal bacterial flora in the vagina, predisposing to an excessive growth of opportunistic fungal organisms, making the vagina and external genitalia the primary reservoir for pathogens. Affected mares tend to be old and pluriparous with poor perineal conformation or maiden mares with cervical incompetence. Mares may have been treated repeatedly with intrauterine antibiotics, have normal or abnormal estrous cycles, may be presented with a history of anovulatory follicles, or have endocrine dysfunction such as equine pituitary disorders or insulin resistance. Prolonged progesterone therapy may predispose mares to fungal endometritis because cervical drainage is decreased and uterine muscular activity and neutrophil function are altered [4]. Other factors contributing to fungal infections include the presence of a moist environment, exposure to a large number of fungi and the presence of necrotic focus as occurring with trauma, abortion, and retained placenta [4, 70].

Diagnosis is based on the presence of fungal elements and inflammatory cells in endometrial smears. Yeast appears as small, round, single cell, brown to black spores on cytological smears obtained from infected mares, whereas molds have long filamentous hyphae [4, 71]. It has suggested that the hyphae are more invasive than yeast and, consequently, more difficult to treat and eliminate. *Candida albicans* can be present in both yeast and hyphal forms and therefore can penetrate deeper into the endometrium and/or growth intracellularly. However, in endometrial cytology and histology used to diagnose fungal endometritis, fungal elements only are visualized in the lumen of the uterus and not penetrate deeper in the endometrium [71].

Another important observation about the difficulty in treating fungal infections is the ability of certain species to produce biofilms, both *Candida* spp. and *Aspergillus* spp. Biofilms also give microorganisms the ability to adhere strongly to virtually and surface; therefore, proper sterilization of uterine catheters and other equipment is paramount to prevent dissemination of pathogens [69, 72].

Prolonged antibiotic therapy may be a predisposing factor for yeast overgrowth [69]. The use of antibiotic-containing semen extenders for AI may be partially responsible for the apparent increase in the number of mares with fungal endometritis. Transmission of fungal organisms from stallions has not been demonstrated, although fungi have been cultured from the urethra (*Mucor* spp.), fresh semen (*Absidia* spp.), and extended semen (*Candida* spp.) of stallions [33, 69].

Cladophialophora bantiana conducted to endometritis with infertility and uterine fluid accumulation with numerous black, hairy granules. Microscopically, the fluid presents in numerous partitions, dark fungal hyphae, and conidia in chains [73].

In terms of impairment of fertility, the significance of these organisms in the mare and the stallion is not yet well established [1]. *Mycoplasma* spp. has been isolated most frequently from the external genitalia and semen of clinically normal and infertile stallions, but their exact role in uterine infection is not well established [18]. In vitro, *Mycoplasma equigenitalium* produces a consistent cytopathic effect on the ciliated epithelium of the oviduct. *M. equigenitalium, M.*

subdolum, and *Acholeplasma* spp. are associated with infertility, endometritis, vulvitis, and abortion in mares. *M. equigenitalium* and *M. subdolum* were isolated from the genital tract of mares (5–34%) and aborted equine fetuses (7%). Also, in some situations, these organisms have been associated with endometritis, infertility, and balanopostitis in stallions [1], whereas, in other situations, they have been found in the absence of any evidence of reproductive dysfunction [18].

Chlamydia spp. has been demonstrated in the genital tract of both the stallion and the mare. While their presence is not always associated with evident clinical disease, certain species such as *Chlamidia abortus* and *Chlamidia psittaci* have detected in cases of abortion, salpingitis, and reduced semen quality in the stallion [74].

3.3. Pyometra

Pyometra may be produced by accumulation of a pus accumulation in the uterus in addition to the persistence of the CL beyond its normal lifespan [75].

Pyometra can be caused by different causes. Including interference cleaning liquid is described from the uterus, obstruction of flow caused by the cervix closed by hormonal influence or cervical pathology such as fibrosis and adhesions, or secondary to trauma, such as experienced during dystocia. Progesterone from a persistent CL can close the cervix. Similarly, exogenous progesterone administered continuously cleaning the uterine avoided. Endometrial cups have been observed as a cause of pyometra where no fetuses or fetal membranes were found within the uterine lumen [76].

Intrauterine accumulation of purulent material was observed in mares with open cervix [77]. These mares may have an innate resistance to a reduced endometrial infection, which can progress to a pyometra [4]. The most common organism associated with pyometra in the mare is *S. zooepidemicus, E. coli, Actinomyces* spp., *Pasteurella* spp., *Pseudomonas* spp., *Propionibacterium* spp., and *Candida rugosa* [78, 79].

Mares with pyometra have vulvar discharge when the cervix is relaxed or open. The pus is often creamy, it may be variable, with higher volumes associated with, watery, thin gray appearance. Smaller volumes are associated with pus cheesy exudate thickened. Rarely are clinical signs of systemic disease [79].

3.4. Venereal infectious endometritis

The bacterial diseases with potential capacity of be transmissible through fresh-cooled or cryopreservated semen are *S. zooepidemicus, P. aeruginosa, K. pneumoniae, T. equigenitalis*, and *T. asinigenitalis*. Among viral diseases that can be transmitted venereal are equine arteritis (EAV) and equine herpesvirus 3 or equine coital exanthema virus, and one is a protozoan infection (*T. equiperdum*) [18, 80].

Exist other diseases that may be transmitted very infrequently by this route or that potentially could be disseminated through contamination of semen. These diseases are as follows:

- Internal genital infections of the testes, epididymis, and accessory sex glands, the major of which are bacterial in nature, such as *S. zooepidemicus, Salmonella abortus equi*;
- Acute to chronic systemic diseases characterized by circulation of the respective causal agents in the bloodstream, as equine infectious anemia (EIA), equine piroplasmosis;
- Infections of the urinary system with the potential for contamination of the urogenital tract, such as leptospirosis, equine rhinitis A virus infection;
- A miscellany of infective agents, including viruses, bacteria, mycoplasmas, chlamydiae, fungi, and yeast that may shed in semen [18].

Infections caused by *P. aeruginosa* and *K. pneumoniae* are often considered venereal diseases because the organisms are often introduced during coitus, AI with infected semen, or genital manipulations. *K. pneumoniae* identify as capsule types 1, 2, and 5 are highly pathogenic [1]. *K. pneumoniae* capsule types 7 and 39 have been incriminated in causing endometritis in the mare by AI, presumably with infective fresh-cooled semen [81].

Although *K. pneumoniae, P. aeruginosa,* and *S. zooepidemicus* are commensal organisms of penis and prepuce in the stallion, in cases of disturbance as a result of indiscriminate washing of the penis or too frequent washing with a surgical scrub or detergent soap. Under such circumstances, there is the potential for colonization of the penis and prepuce with the mentioned bacteria. These organisms, which rarely produce clinical disease in the stallion, can give rise to endometritis with reduced fertility in susceptible mares, especially in mares with a pre-existing defect in uterine clearance [15]. Transmission of these bacteria occurs venereally, either natural breeding or AI with infective semen [18, 82].

3.4.1. Contagious equine metritis (CEM)

CEM is a transmissible, exotic, venereal disease caused by *T. equigenitalis.* This bacterium is closely adapted to the specific environmental conditions of the equine genital tract, whereby it is the only venereal transmissible bacterial agent in horses [18].

Thoroughbred horses appear to be more severely affected by the disease than other breeds. Because animals may be asymptomatic, the disease is difficult to detect and control. Due to its high contagiousness, CEM is a serious disease and can have detrimental consequences on equine reproductive efficiency. When CEM becomes established in the United States, the horse industry suffered great economic losses [1].

Initial exposure to the disease usually results in infertility. An infected mare may fail to conceive or abort. The disease frequently is associated with an endometritis [18, 83]. Abortion due to *T. equigenitalis* infection is very rare [84].

The exposure of the mare to *T. equigenitalis* can result in clinical or asymptomatic infection. After an incubation period of 2–12 days, affected mares developed odorless, grayish-white mucopurulent vulvar discharge of variable consistency and volume, which can last for up to 2 weeks or slightly longer [85]. The discharge is associated with endometritis, cervicitis, vaginitis, vulvar discharge, and return to estrus after a shortened diestrous period [86].

The infertility is temporary (only a few weeks), with adverse effect on a mare's fertility. Persistence of *T. equigenitalis* in the reproductive tract of a chronically infected mare not interfere with the maintenance of the birth of a healthy foal [18, 21]. The mare, though asymptomatic, is still infectious and can remain a carrier for several months [18, 21, 22].

In contrast to the mare, exposure of the stallion to *T. equigenitalis* does not result in infection, much less the development of any clinical signs in the vast majority of cases [87]. The stallion becomes an unapparent carrier of the bacterium, which persists as a commensal on its external genitalia without causing any adverse local or systemic effects. On very rare occasions, exposure may result in an ascending infection of the reproductive tract in the stallion [88]. In addition, *T. asinigenitalis* is transmitted through venereal for breeding or AI and causes endometritis, cervicitis, and vaginitis in experimentally infected mare [89].

3.4.2. Equine viral arteritis (EVA)

Equine viral arteritis (EVA) is a contagious viral infection affecting both mares and stallions. Prevalence of EVA ranges from 1–3% in Quarter Horses to 7% in Arabians and Thoroughbreds and to 80% in Standardbreds. Mares clinically affected with EVA may show fever, limb edema, anorexia, depression, inflammation around the eyes, nasal discharge, skin rash, and abortion. The significance of EVA infection in stallions is that certain strains can develop carrier status in 30–60% of infected stallions. Carrier stallions can transmit the virus by natural breeding or AI with fresh, cooled, or frozen semen. Mares bred with EVA-infected semen may lead to outbreaks of abortion and deaths in foals [90]. Due to these reasons, EVA is responsible for major restrictions in the international movement of horses and semen. Serologic or blood testing is used for screening both mares and stallions. Detectable antibody titers develop 2–4 weeks following exposure and are maximal at 2–4 months and remain stable for several years. If a stallion is serologically positive, the presence or absence of virus in his semen should be determined to confirm if he is a chronic carrier or shedder of the virus. The carrier state has only been documented in adult stallions. It should be emphasized that not all seropositive stallions are shedders and carriers of the virus [91].

3.5. Internal genital infections

In the stallion infection of the testes, epididymis and accessory glands may be a localized or part of a systemic disease. Though rare in occurrence, orchitis caused by a range of bacteria including *S. abortusequi, S. zooepidemicus, Burkholderia mallei, Brucella abortus, Actinobacillus equuli, P. aeruginosa, K. pneumoniae, Staphylococcus* spp., *Proteus vulgaris,* and *E. coli* can have detrimental effect for the stallion's fertility and have opportunity for venereal transmission by coitus or AI with contaminated semen to the mare [18].

3.6. Systemic diseases

Due to their potential to be transmitted by the venereal route acute and chronic systemic infectious diseases, they have come under consideration. These diseases included Eastern equine encephalomyelitis and Western equine encephalomyelitis, West Nile encephalitis,

vesicular stomatitis, African horse sickness, EIA, and equine piroplasmosis. They can also pose a risk of venereal transmission if at the time of breeding or semen collection there is trauma of the stallion's genitalia, bleeding, and contamination of the ejaculate with blood containing the respective etiological agent [18].

To date, there is no evidence of occurrence of venereal transmission of any of the aforementioned diseases, with the exception of piroplasmosis, in which mare showed *Babesia* because of venereal transmission when blood from an infected stallion contaminated semen [92].

3.7. Chronic infectious endometritis

Usually, an underlying condition, such as pneumovagina, predisposes the horse to chronic infectious endometritis. The definitive diagnosis is by biopsy should show endometrial infiltration with lymphocytes and plasma cells. Chronic infectious endometritis is more common in older mares and primiparous mares with poor perineal conformation. The predisposing factors for chronic infections in mares include self-repeated contaminations, cervix fibrosis, cervical tears or adhesions, and/or "mare older maiden" syndrome and mares in which holes uterus well below the edge of the pelvis. The organisms most frequently isolated in cases of chronic infectious endometritis include the same of acute (*S. zooepidemicus, E. coli, K. pneumoniae, P. aeruginosa,* and *Candida* or *Aspergillus*). Long-term chronic, refractory infections typically involve yeast and/or gram-negative bacteria [93]. *S. zooepidemicus* is one of the most frequently pathogens isolated from uterus of mares suffering infectious endometritis. As described previously, it has the capacity to cause chronic infection latent deeply reside within the endometrial tissue [28]. Chronic inflammation may lead to fibrosis and periglandular mucus production by inadequate uterine epithelial or endometrial glands. If the elasticity, viscosity, or changes in the amount of mucus or if the cilia are damaged or denuded endometrial epithelial cell, uterine drainage will be diminished, which contributes to the accumulation of fluid and infertility [93].

A close examination of the reproductive system by rectal ultrasound can provide evidence of chronic inflammation or infection. The accumulation of fluid within the uterine lumen, endometrial edema, the presence of hyperechoic spots within the uterine lumen, and an even greater thickness of the uterine wall can all be signs of chronic infection. Culturing of endometrial biopsies or uterine fluids is more sensitive for the identification of *E. coli* when compared with culture-swab methods. Endometrial cytology identifies twice mares with acute inflammation in the culture when compared with cervical swab. A vaginal speculum examination shows evidence of inflammation and also allows to evaluate the competition lobby-vaginal sphincter. The culture of material obtained from the uterus, not always allows the diagnosis for the presence or absence of bacteria in cases of clinical endometritis [94, 95]. Obtaining a sample of endometrial cytology and further culture was used to increase the diagnostic accuracy, providing clear evidence of inflammation in conjunction with a positive culture. Mares with chronic infections often have long-standing inflammatory changes. In these cases, the prognosis is guarded because of the chronic nature of the infection and predisposing anatomical defects. Surgical correction of conformational abnormalities may try to use the Caslick procedure [93].

3.8. Chronic degenerative endometritis

Chronic degenerative endometritis or endometriosis is degenerative change that occurs in older mares or following repeated inflammation of the uterus. Degenerative fibrosis can be the result of normal aging processes or may be the end-product of a life of continuous reinfection: anyway, healing uterine mucosa causes infertility in older mares [34]. Problems related to weaken reproductive structures can cause urinary retention, a condition in which the mares do not empty completely urine, especially during estrus. Thus, the retained liquid can cause inflammation and prevent conception. The use of antibiotics is not always good. One of the disadvantages of using antibiotics is the fact that kills good and bad bacteria, leaving the animal with no natural protection against future bacterial or fungal invasions. The definitive diagnosis can only be achieved by biopsy, which shows degenerative histological changes in the uterus [93].

3.9. Persistent post-mating endometritis

Inflammation of the endometrium is caused by a response to exogenous materials introduced directly into the uterus at breeding, as components of the semen, extender in the case of AI, bacteria, and other debris [24, 96]. Two hormones, PGF2α and oxytocin, regulate myometrial contractions after the influx of neutrophils into the uterine lumen and their phagocytic activity after opsonization of the target [67]. This uterine defense mechanism reaches a pick at around 6–12 hours post-mating or AI [97]. In normal mares, most of the inflammatory products are cleared by physical uterine mechanisms within 48 hours after breeding, and the infection is cleared before the embryo leaves the fallopian tube and enters to the uterus on about days 5–6 post-ovulation [98], the uterine inflammation has to be under control by 96 hours post-ovulation to maximize survival of the embryo [67]. A susceptible mare with persistent post-mating endometritis is unable to clear such fluid by 96 hours, and the resulting prolonged inflammation generates an embryo-toxic environment. In addition, premature lysis of the CL is caused by PGF2α and subsequent progesterone deficiency, all contribute to embryo mortality and infertility [99]. This is more common in older and multiparous mares. They present with a history of short cycling and often and vaginal discharge approximately 2 weeks post-breeding [100].

4. Oophoritis and salpingitis

After abdominal surgery or peritonitis, infectious inflammation of the ovaries (oophoritis) with abscessation and peritoneal adhesions may occur. Oophoritis could be a consequence of repeated transvaginal ultrasound-guided follicular aspiration [101, 102]. Affected mares present abdominal pain, anorexia, fever of unknown origin, and weight loss. Transrectal ultrasonography can help in the diagnosis of these infections. For the extend evaluation of the lesions and confirmation of the diagnosis, laparoscopy may be achieved. Ovariectomy is usually required for treatment of this condition [103]. Although it is rare in the mare, salpingitis may result from ascending infection of *Chlamydia* spp. as *Chlamidiaabortus* and *Chlamidia psittaci* after partum [74]. Salpingitis has been described in mares with CEM. Bilateral salpingitis in mares results in sterility [103].

5. Postpartum metritis

Postpartum uterine infections are of particular importance because of their severity and effect on the general health of the mare. The incidence of postpartum metritis—i.e., infection of the uterus within 7–10 days postpartum, sometimes involving the endometrium, myometrium, and perimetrium—in foaling mares is low but increases when birthing trauma and/or retained placenta occurs [2, 3]. Septic postpartum metritis is often a result of nonhygienic manipulation during foaling, obstetric manipulations, and retained placenta. Mares with postpartum may present severe systemic complications as endotoxemia and laminitis. The etiology of septic/toxic metritis is associated with uterine atony or inertia. Trauma to the uterus, autolysis of placental remnants, and excessive lochia accumulation likely contribute to rapid growth of gram negative as *E. coli* and *K. pneumoniae* bacteria and production of toxins, which may be absorbed into the bloodstream, particularly when expulsion of contents is delayed or when the normally intact uterine mucosal barrier is damaged. Disruption of the endometrial mucosal barrier occurs during dystocia or gradually progresses after retention of fetal membranes leading to bacterial overgrowth and absorption of produced toxins. This process normally develops septic/toxic metritis and/or laminitis. Treatment consists of daily uterine flushers, systemic antimicrobial therapy, and therapy for endotoxemia. Laminitis and dehydration should be immediately initiated in affected mares [3, 104].

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References

[1] Samper JC, Tibary A. Disease transmission in horses. Theriogenology 2006;66:551–559.

[2] Tibary A, Pearson LK, Fite CL. Reproductive tract infections. In: Sellon DC, Long MT, editors. Equine infectious diseases, 2nd ed. St. Louis, Missouri: Saunders Elsevier; 2014; p. 84–105.

[3] Blanchard, TL. Postpartum metritis. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2530–2536.

[4] Leblanc MM, McKinnon AO. Breeding the problem mare. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2620–2642.

[5] Newcombe JR. Why are mares with pneumovagina susceptible to bacterial endometritis? A personal opinion. J Equine Vet Sci 2011;31(4):174–179.

[6] Bradecamp EA. Pneumovagina. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2537–2544.

[7] Parrilla-Hernandez S, Ponthier J, Franck TY, Serteyn DD, Deleuze SC. High concentrations of myeloperoxidase in the equine uterus as an indicator of endometritis. Theriogenology 2014;81(7):936–940.

[8] McKinnon AO, Jalim SL. Surgery of the caudal reproductive tract. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2545–2558.

[9] Sertichm PL. Cervix adhesions. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2721–2723.

[10] Pollock PJ, Russell TM. Cervical surgery. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2559–2563.

[11] Barrandeguy M, Thiry E. Equine coital exanthema and its potential economic implications for the equine industry. Vet J 2012;191(1):35–40.

[12] Arighi M. Developmental abnormalities of the male reproductive tract. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 1109–1112.

[13] Sijmons S, Vissani A, Tordoya MS, Muylkens B, Thiry E, Maes P, Matthijnssens J, Barrandeguy M, Van Ranst M. Complete genome sequence of equidherpesvirus 3. Genome Announc 2014;2(5):e00797-14.

[14] Barrandeguy M, Vissani A, Lezica FP, Salamone J, Heguy A, Becerra L, Olguin Perglione C, Thiry E. Subclinical infection and periodic shedding of equid herpesvirus 3. Theriogenology 2010;74(4):576–580.

[15] Lu K, Morresey PR. Infectious diseases in breeding stallion. Clin Tech Equine Pract 2007;6:285–290.

[16] Scacchia M, Cammà C, Di Francesco G, Di Provvido A, Giunta R, Luciani M, Marino AM, Pascucci I, Caporale V. A clinical case of dourine in an outbreak in Italy. Vet Ital 2011;47(4): 473–475.

[17] Robinson EM. Dourine infection in young equines. Onderstepoort J Vet Sci Anim Ind 1984;23:39–40.

[18] Timoney PJ. Contagious equine metritis. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2399–2409.

[19] Pascucci I, Prowido A, Camma C, Di Francesco G, Calistri P, Tittarelli M, Ferri N, Scacchia M, Caporale V. Diagnosis of dourine outbreaks in Italy. Vet Parasitol 2013;193:30–38.

[20] Claes F, Agbo EC, Radwanska M, Tepas MF, Baltz T, De Waal DT, Goddeeris BM, Claassen E, Buscher P. How does *T. equiperdum* fit into the Trypanozoongenus?. A cluster analysis and multiplex genotyping approach. Parasitology 2003;126:425–431.

[21] Timoney PJ, Powell DG. Isolation of the contagious equine metritis organism from colts and fillies in the United Kingdom and Ireland. Vet Rec 1982;111(21):478–482.

[22] Breuil MF, Duquesne F, Leperchois E, Laugier C, Ferry B, Collin G, Petry S. Contagious equine metritis cases reported in France since 2006. Vet Rec 2015;177(13):340.

[23] Ricketts SW, Young A, Medici EB. Uterine and clitorial cultures. In: McKinnon AO, Voss JL, editors. Equine reproduction. Philadelphia, USA: Lea and Febinger; 1993; p. 234–245.

[24] Troedsson MHT. Endometritis. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2608–2619.

[25] Aitken GJ. Subclinical fungal endometritis in an 8-year-old Hanoverian mare. Can Vet J 2012;53(2):196–198.

[26] Buczkowska J, Kozdrowski R, Nowak M, Raś A, Staroniewicz Z, Siemieniuch MJ. Comparison of the biopsy and cytobrush techniques for diagnosis of subclinical endometritis in mares. Reprod Biol Endocrinol 2014;4:12–27.

[27] Overbeck W, Witte TS, Heuwieser W. Comparison of three diagnostic methods to identify subclinical endometritis in mares. Theriogenology 2011;75(7):1311–1318.

[28] Christoffersen M, Söderlind M, Rudefalk SR, Pedersen HG, Allen J, Krekeler N. Risk factors associated with uterine fluid after breeding caused by *Streptococcus zooepidemicus*. Theriogenology 2015;84(8):1283–1290.

[29] Rohrbach BW, Sheerin PC, Cantrell CK, Matthews PM, Steiner JV, Dodds LE. Effect of adjunctive treatment with intravenously administered *Propioni bacterium acnes* on reproductive performance in mares with persistent endometritis. J Am Vet Med Assoc 2007;231:107–113.

[30] Cocchia N, Paciello O, Auletta L, Uccello V, Silvestro L, Mallardo K, Paraggio G, Pasolini MP. Comparison of the cytobrush, cottonswab, and low-volume uterine flush techniques to evaluate endometrial cytology for diagnosing endometritis in chronically infertile mares. Theriogenology 2012;77(1):89–98.

[31] Walter J, Neuberg KP, Failing K, Wehrend A. Cytological diagnosis of endometritis in the mare: Investigations of sampling techniques and relation to bacteriological results. Anim Reprod Sci 2012;132(3–4):178–186.

[32] Davies Morel MC, Lawlor ND. Equine endometrial cytology and bacteriology: Effectiveness for predicting live foaling rates. Vet J 2013;198(1):206–211.

[33] LeBlanc MM, Causey RC. Clinical and subclinical endometritis in the mare: Both threats to fertility. Reprod Domest Anim 2009;44(3):10–22.

[34] Woodward EM, Troedsson MH. Inflammatory mechanisms of endometritis. Equine Vet J 2015;47(4):384–389.

[35] Liu IK, Troedsson MH. The diagnosis and treatment of endometritis in the mare: Yesterday and today. Theriogenology 2008;70(3):415–420.

[36] Christoffersen M, Woodward EM, Bojesen AM, Petersen MR, Squires EL, Lehn-Jensen H, Troedsson MH. Effect of immunomodulatory therapy on the endometrial inflammatory response to induced infectious endometritis in susceptible mares. Theriogenology 2012;78(5):991–1004.

[37] Petersen MR, Skive B, Christoffersen M, Lu K, Nielsen JM, Troedsson MH, Bojesen AM. Activation of persistent *Streptococcus equi* subspecies *zooepidemicus* in mares with subclinical endometritis. Vet Microbiol 2015;179(1–2):119–125.

[38] Woodward EM, Christoffersen M, Horohov D, Squires EL, Troedsson MH. The effect of treatment with immune modulators on endometrial cytokine expression in mares susceptible to persistent breeding-induced endometritis. Equine Vet J 2015;47(2):235–239.

[39] Szóstek AZ, Lukasik K, Galvão AM, Ferreira-Dias GM, Skarzynski DJ. Impairment of the interleukin system in equine endometrium during the course of endometriosis. Biol Reprod 2013;89(4):79.

[40] Christoffersen M, Baagoe CD, Jacobsen S, Bojesen AM, Petersen MR, Lehn-Jensen H. Evaluation of the systemic acute phase response and endometrial gene expression of serum amyloid A and pro- and anti-inflammatory cytokines in mares with experimentally induced endometritis. Vet Immunol Immunopathol 2010;138(1–2):95–105.

[41] Gajos K, Kozdrowski R, Nowak M, Siemieniuch MJ. Altered secretion of selected arachidonic acid metabolites during subclinical endometritis relative to estrous cycle stage and grade of fibrosis in mares. Theriogenology 2015;84(3):457–466.

[42] Nash DM, Sheldon IM, Herath S, Lane EA. Markers of the uterine innate immune response of the mare. Anim Reprod Sci 2010;119(1–2):31–39.

[43] Rebordão MR, Galvão A, Szóstek A, Amaral A, Mateus L, Skarzynski DJ, Ferreira-Dias G. Physiopathologic mechanisms involved in mare endometriosis. J Reprod Immunol 2014;106:41–49.

[44] Troedsson MH, Liu IK, Thurmond M. Immunoglobulin (IgG and IgA) and complement (C3) concentrations in uterine secretion following an intrauterine challenge of *Streptococcus zooepidemicus* in mares susceptible to versus resistant to chronic uterine infection. Biol Reprod 1993;49(3):502–506.

[45] Troedsson MHT, Liu IKM, Thurmon M. Function of uterine and blood-derived polymorphonuclear neutrophils in mares susceptible and resistant to chronic uterine infection: Phagocytosis and chemotaxis. Biol Reprod 1993;49:507–514.

[46] Rebordão MR, Carneiro C, Alexandre-Pires G, Brito P, Pereira C, Nunes T, Galvão A, Leitão A, Vilela C, Ferreira-Dias G. Neutrophil extracellular traps formation by bacteria causing endometritis in the mare. Reprod Domest Anim 2014;49(4):82–87.

[47] Alghamdi AS, Foster DN, Carlson CS, Troedsson MH. Nitric oxide levels and nitric oxide synthase expression in uterine samples from mares susceptible and resistant to persistent breeding-induced endometritis. Am J Reprod Immunol 2005;53(5):230–237.

[48] Krumrych W, Danek J. Chemiluminescence of peripheral blood neutrophils in mares with endometritis. Bull Vet Inst Pulawy 2012;56:51–56.

[49] Brown AE, Hansen PJ, Asbury AC. Opsonization of bacteria by uterine secretions of cyclic mares. Am J Reprod Immunol Microbiol 1985;9(4):119–123.

[50] Causey RC. Making sense of equine uterine infections: The many faces of physiological clearance. Vet J 2006;172:405–421.

[51] Brinsko SP, Varner DD, Blanchard TL. The effect of uterine lavage performed four hours post-insemination on pregnancy rate in mares. Theriogenology 1991;35:1111–1119.

[52] Hurtgen JP. Pathogenesis and treatment of endometritis in the mare: A review. Theriogenology 2006;66(3):560–566.

[53] Da Costa R, Ferreira-Dias G, Mateus L, Korzekwa A, Andronowska A, Platek R, Skarzynski DJ. Endometrial nitric oxide production and nitric oxide synthases in the equine endometrium: Relationship with microvascular density during the estrous cycle. Domest Anim Endocrinol 2007;32(4):287–302.

[54] Strzemienski PJ, Do D, Kenney RM. Antibacterial activity of mare uterine fluid. Biol Reprod 1984;31:303–311.

[55] Johnson JU, Oxender WD, Berkhoff HA. Influence of estrogen on antibacterial and immunoglobulin secretory activities of uterine fluids from ovariectomized mares. Am J Vet Res 1994;55(5):643–649.

[56] Kolm G, Klein D, Knapp E, Watanabe K, Walter I. Lactoferrin expression in the horse endometrium: Relevance in persisting mating-induced endometritis. Vet Immunol Immunopathol 2006;114(1–2):159–167.

[57] Causey RC. Mucus and the mare: How little we know. Theriogenology 2007;68(3): 386–394.

[58] Albihn A, Baverud V, Magnusson U. Uterine microbiology and antimicrobial susceptibility in isolated bacteria from mares with fertility problems. Acta Vet Scand 2003;44(3):121–129.

[59] Maeda Y, Ohtsuka H, Tomioka M, Tanabe T, Nambo Y, Uematsu H, Oikawa MA. Effect of progesterone on the in vitro response of peripheral blood mononuclear cells stimulated by *Escherichia coli* in mares. J Vet Med Sci 2012;74(5):629–632.

[60] Smit LI. Relationships between uterine microbiology, cytology and pregnancy rates in thoroughbred mares 2006–2013 [thesis]. Theses Master thesis. Faculty of Veterinary Medicine. Utrech University; 2015.

[61] Hamouda MA, Al-Hizab FA, Ghoneim IM, Al-Dughaym AM, Al-Hashim HJ. Assessment of endometritis in Arabian mare. J Anim Prod 2012;14(2):99–103.

[62] Rasmussen CD, Haugaard MM, Petersen MR, Nielsen JM, Pedersen HG, Bojesen AM. *Streptococcus equi* subsp. *zooepidemicus* isolates from equine infectious endometritis belong to a distinct genetic group. Vet Res 2013;44:26.

[63] Ricketts SW, Mackintosh ME. Role of anaerobic bacteria in equine endometritis. J Reprod Fertil Suppl 1987;35:343–351.

[64] Timoney JF, Artiushin CS, Boschwitz JS. Comparison of the sequences and functions of Streptococcus equi M-like proteins SeM and SzPSe. Infect Immun 1997;65(9):3600–3605.

[65] Nicholson ML, Ferdinand LR, Sampson JS, Benin A, Balter S, Pinto SW, Richard SF, Facklam R, Carlone GM, Beall B. Analysis of Immunoreactivity to a *Streptococcus equi* subsp. *zooepidemicus* M-like protein to confirm an outbreak of poststreptococcal glomerulonephritis, and sequences of M-Like proteins from isolates obtained from different host species. J Clin Microbiol 2000;38(11):4126–4130.

[66] Wittenbrink MM. Bacterial infections of the equine genital tract. Pferdeheilkunde 2012;28(1):30–32.

[67] Troedsson MH. Uterine clearance and resistance to persistent endometritis in the mare. Theriogenology 1999;52(3):461–471.

[68] LeBlanc MM. When to refer an infertile mare to a theriogenologist. Theriogenology 2008;70:421–429.

[69] Dascanio JJ, Schweizer C, Ley WB. Equine fungal endometritis. Equine Vet Educ 2001;13:324–329.

[70] Stefanetti V, Marenzoni ML, Lepri E, Coletti M, Proietti PC, Agnetti F, Crotti S, Pitzurra L, Del Sero A, Passamonti F. A case of *Candida guilliermondii* abortion in an Arab mare. Med Mycol Case Rep 2014;4:19–22.

[71] Beltaire KA, Cheong SH, Coutinho da Silva MA. Retrospective study on equine uterine fungal isolates and antifungal susceptibility patterns (1999–2011). Equine Vet J 2012;44:84–87.

[72] Stout TAE. Fungal endometritis in the mare. Pferdeheilkunde 2008;24(1):83–87.

[73] Rantala M, Attia S, Koukila-Kähkölä P, de Hoog S, Anttila M, Katila T. Cladophialophorabantiana as an emerging pathogen in animals: Case report of equine endometritis and review of the literature. J Clin Microbiol 2015;53(9):3047–3053.

[74] Wittenbrink MM. Aetiological significance of chlamydial infections in equine reproductive disorders. Pferdeheilkunde 1999;15(6):538–541.

[75] Threlfall WR, Carleton CL. Treatment of uterine infections in the mare. In: Morrow DA, editor. Current therapy in theriogenology. Philadelphia: W.B. Saunders Co.; 1986; p. 730–737.

[76] Vandeplassche M, Spincemaille J, Bouters R. Advanced pyometra with intact endometrial cups in a mare. Equine Vet J 1979;11:112–113.

[77] Kennedy PC, Miller RB. The uterus. In: Jubb KVF, Kennedy PC, Palmer N, editors. Pathology of domestic animals, 4th ed., vol. 3. San Diego, CA: Academic Press; 1993; p. 372–387.

[78] Abou-Gabal M, Hogle RM, West JK. Pyometra in a mare caused by Candida rugosa. J Am Vet Med Assoc 1977;170:177–178.

[79] Hughes JP, Stabenfeldt GH, Kindahl H, Kennedy PC, Edqvist LE, Neely DP, Schalm OW. Pyometra in the mare. J Reprod Fertil Suppl 1979;27:321–329.

[80] Timoney PJ. Aspects of the occurrence, diagnosis and control of selected venereal diseases in the stallion. In: Proceeding of the Stallion Reproduction Symposium Society Theriogenol, Baltimore MD, 1998; p. 76–83.

[81] Klug E, Sieme H. Infectious agents in equine semen. Acta Vet Scand 1992;88:73–81.

[82] Clement F, Vidament M, Guerin B. Microbial contamination of stallion semen. In: Proceeding of International Symposium on Equine Reproduction, Brazil, 1994; p. 199–200.

[83] Timoney PJ, Ward J, Kelly PA. A contagious genital infection of mares. Vet Rec 1977;101:103.

[84] Nakashiro H, Naruse M, Sugimoto C, Isayama Y, Kuniyasu C. Isolation of *Haemophilus equigenitalis* from an aborted equine fetus. Natl Inst Anim Health Q (Tokyo) 1981;21(4):184–185.

[85] Platt H, Atherton JG, Simpson DJ. The experimental infection of ponies with contagious equine metritis. Equine Vet J 1978;10:153–159.

[86] Timoney PJ. Contagious equine metritis. Comp Immunol Microb 1996;19:199–204.

[87] Powell DG. Contagious equine metritis. Adv Vet Sci Comp Med 1981;25:161–184.

[88] Schluter H, Kuller HJ, Friedrich U, Selbitz HJ, Marwitz T, Beyer C, Ullrich E. Epizootiology and treatment of contagious equine metritis (CEM), with particular reference to the treatment of infected stallions. Prakt Tierarzt 1991;72:503–511.

[89] Duquesne F, Pronost S, Laugier C, Petry S. Identification of *Taylorella equigenitalis* responsible for contagious equine metritis in equine genital swabs by direct polymerase chain reaction. Res Vet Sci 2007;82:47–49.

[90] Timoney PJ, McCollum WH. Equine viral arteritis. Vet Clin North Am Equine Pract 1993;9:295–309.

[91] Holyoak GR, Balasuriya UB, Broaddus CC, Timoney PJ. Equine viral arteritis: Current status and prevention. Theriogenology 2008;70(3):403–414.

[92] Metcalf ES. The role of international transport of equine semen on disease transmission. Anim ReprodSci 2001;68(3–4):229–237.

[93] LeBlanc MM. Uterine cytology. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 1922–1928.

[94] Nielsen JM. Endometritis in the mare: A diagnostic study comparing cultures from swab and biopsy. Theriogenology 2005;64(3):510–518.

[95] LeBlanc MM, Magsig J, Stromberg AJ. Use of a low-volume uterine flush for diagnosing endometritis in chronically infertile mares. Theriogenology 2007;68:403–412.

[96] Troedsson MH, Loset K, Alghamdi AM, Dahms B, Crabo BG. Interaction between equine semen and the endometrium: The inflammatory response to semen. Anim Reprod Sci 2001;68:273–278.

[97] Katila T. Uterine defence mechanisms in the mare. Anim Reprod Sci 1996;42:197–204.

[98] Betteridge KJ, Eaglesome MD, Mitchell D, Flood PF, Beriault R. Development of horse embryos up to twenty two days after ovulation: Observations on fresh specimens. J Anatomy 1982;135:191–209.

[99] Rambags BPB. Early pregnancy loss in aged mares: Probable causes and cures. Pferdeheilkunde 2003;19:653–656.

[100] Gores-Lindholm AR, LeBlanc MM, Causey R, Hitchborn A, Fayrer-Hosken RA, Kruger M, Vandenplas ML, Flores P, Ahlschwede S. Relationships between intrauterine infusion of N-acetylcysteine, equine endometrial pathology, neutrophil function, post-breeding therapy, and reproductive performance. Theriogenology 2013;80(3): 218–227.

[101] Bogh IB, Brink P, Jensen HE, Lehn-Jensen H, Greve T. Ovarian function and morphology in the mare after multiple follicular punctures. Equine Vet J 2003;35(6):575–579.

[102] Schlafer DH. Non-neoplastic abnormalities. In: McKinnon AO, Squires EL, Vaala WE, editors. Equine reproduction. Chichester, UK: Wiley-Blackwell; 2011; p. 2697–2706.

[103] Hawkins KL. Bilateral salpingitis, hydrosalpinx and oophoritis in a mare. Cornell Vet 1986;76(1):38–48.

[104] Blanchard TL, Varner DD, Scrutchfield WL, Bretzlaff KN, Taylor TS, Martin MT, Elmore RG. Management of distocia in mares: Retained placenta, metritis, and laminitis. Comp Cont Educ Pract Vet 1990;12:563–571.

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