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UTERINE DISORDERS IN THE MARE: DIAGNOSTIC APPROACH, TREATMENT AND PREVENTION

Trastornos uterinos en la yegua: Diagnóstico, tratamiento y prevención

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ABSTRACT

The majority of infertility or subfertility cases in mares is caused by uterine pathology. This paper presents the state of the art in diagnostic techniques used to investigate uterine health. Clinical evaluation including physical examination transrectal palpation and ultrasonography as well as endometrial cytology, culture and biopsy remain the cornerstone for working up any case of infertility. Endometritis remains the major infertility causing uterine disorder. New therapeutic strategies have been developed in recent years to deal with infections caused by organisms that produce biofilm. Also, increased understanding of the innate uterine defense mechanisms has generated interest in new therapies. Aging affects uterine health in several ways, but most importantly the development of chronic degenerative disease. New therapeutic approaches are being developed in the hope of slowing down or reversing these degenerative changes. Referral to a specialty hospital may be warranted in some cases for advanced reproductive evaluation.

Keywords: Uterus, endometritis, tumors, biopsy, hysteroscopy, neoplasia

RESUMEN

La mayoría de los casos de infertilidad o subfertilidad en yeguas son causados por patología uterina. Este artículo presenta el estado del arte en técnicas de diagnóstico utilizadas para investigar la salud uterina. La evaluación clínica que incluye el examen físico, la palpación transrectal y la ecografía, así como la citología endometrial, el cultivo y la biopsia siguen siendo la piedra angular para resolver cualquier caso de infertilidad. La endometritis sigue siendo la principal causa de infertilidad y trastornos uterinos. En los últimos años se han desarrollado nuevas estrategias terapéuticas para tratar las infecciones causadas por organismos que producen biofilm. Además, una mayor comprensión de los mecanismos de defensa uterina innata ha generado interés en nuevas terapias. El envejecimiento afecta la salud uterina de varias maneras, pero lo más importante es el desarrollo de enfermedades crónicas degenerativas. Se están desarrollando nuevos enfoques terapéuticos con la esperanza de desacelerar o revertir estos cambios degenerativos. La remisión a un hospital especializado puede estar justificada en algunos casos para la evaluación reproductiva avanzada.

Palabras clave: Útero, endometritis, tumores, biopsia, histeroscopia, neoplasia

INTRODUCCION

Uterine health is the primary driver of reproductive efficiency in the broodmare. The consequences of uterine pathologies affect every step of the reproductive process. Altered uterine environment reduces sperm survival and early embryo development. Degenerative changes in the endometrium are responsible for poor maternal recognition of pregnancy, and poor embryo fixation and placentation leading to early pregnancy loss or abortion (Tibary and Pearson, 2015). The importance of uterine health is well illustrated by efforts to develop methods for early detection of disorders such as endometritis and endometrosis. Data on large numbers of broodmares shows that uterine compromise is the single most common problem in equine reproduction. It is estimated that 25% of broodmares have subclinical endometritis prior to breeding and between 25 and 60% of mares will experience an episode of endometritis in their reproductive career (Rasmussen et al., 2015; Tibary et al., 2014). This is even more important as high performance mares start their reproductive career later in life and are generally kept past their peak reproductive ability as their breeding value increases with performance of progeny. Accurate and timely diagnosis, treatment, and prevention of uterine disease are an essential part of veterinary services aiming to maximize reproductive success while maintain a high standard of welfare for subfertile mares. The objective of the present paper is to present a review of the literature and our clinical experience in diagnosis and management of uterine disorders in the infertile/subfertile mare. Although this paper focuses on the uterus, it is important to stress that general health of the mare and ovarian function can also affect uterine health. Therefore, a thorough history and clinical physical examination should be part of any reproductive evaluation. Other important diseases of the uterus such as contagious equine metritis (Jeoung et al., 2016; Rocha, 2016; Samper and Tibary, 2006) and postpartum septic metritis (Tibary and Pearson, 2012; Tibary et al., 2014) are not considered in the scope of this paper (Tibary and Pearson, 2012).

Methods of investigation of uterine health

In our clinical experience, uterine pathology represents more than 80% of the reasons for subfertility in the mare. Most of the uterine disorders have other underlying causes or predisposing factors. Therefore, a complete breeding soundness examination including general health, examination of perineal conformation, cervical competence and ovarian activity is a must. These aspects are not detailed in the present paper but are important when considering treatment and prevention.

Methods used for the investigation of uterine health vary from "routine" to more specialized techniques depending on the complaint and primary evaluation results. Perineal conformation, transrectal palpation and ultrasonography, endometrial culture, cytology and biopsy should be performed systematically on all mares with a complaint of infertility or subfertility (Rua et al., 2016; Tibary, 2016; Wolfsdorf, 2016). Hysteroscopy should be performed on mares with abnormalities that are identified by transrectal ultrasonography. As a general rule, mares should be examined during the breeding season except when referred for a specific complaint with sudden onset such as vaginal bleeding or mucopurulent discharge, dysuria, suspicion of abortion or early pregnancy loss.

Perineal conformation

The vulva and vestibulo-vaginal sphincter represent the primary anatomical barrier to uterine infection. Perineal conformation is an essential part of the evaluation of predisposition to uterine disorders. This anatomical barrier to infection is compromised by loss of vulvar lips coaptation, severe tilting of the vulva or loss of the integrity of the vestibulo-vaginal sphincter (Figure 1). These defects should be address surgically whenever dealing with the infertile mare.

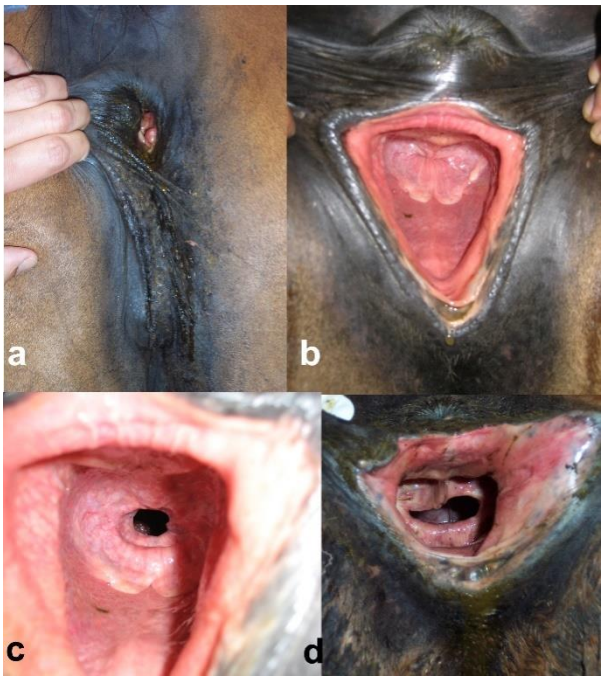

Figure 1. Perineal vulvar conformation: a) Severe cranio-dorsal displacement with compromise of the anal sphincter. b) Dorsal displacement of the vulva with intact vestibular sphincter, c) Partial compromise of the vestibular sphincter, d) Complete incompetence of the vestibulo-vaginal sphincter.

Transrectal palpation and ultrasonography

Transrectal palpation and ultrasonography are a fundamental part of reproductive evaluation in the broodmare. Transrectal palpation of the cervix, uterus and ovaries allows identification of problems that may have implications on uterine function. The size and location of the uterus should be described in relationship to the pelvic brim. A pendulant uterus, characteristic of multiparous mares, predisposes to uterine clearance problems and endometritis. Inconsistencies in uterine behavior vis a vis the dominant hormone (stage of the estrus cycle) at the time of examination should be noted. The uterus should increase in tone under progesterone dominance. Under estrogenic influence (i.e estrus), the uterus should present varying degrees of edema depending on the stage of follicular development and approach to ovulation.

Transrectal ultrasonography is routinely employed to provide a more objective evaluation of the uterus with respect to size, content and tone or edema. The normal uterus should be free of any intraluminal content. The uterine folds are edematous and clearly visible during estrus. Endometrial edema is usually graded from 0 to 3 (0= no edema, 3=maximum edema). It increases during estrus, peak when the follicle is at its maximum diameter then slowly decreased some 12 to 36 hours prior to

ovulation (Figure 2). After ovulation and with the development of the corpus luteum, the uterus should loose all edema and increase in tone. Abnormalities of content and edema are illustrated later in the discussion of specific pathologies. The effect of presence of fluid prior to insemination on pregnancy rate is controversial and probably depends on its amount and nature. In one study, endometrial edema score early in diestrus was highly correlated with *S. equi zooepidemicus* infection (Rasmussen et al., 2015). The presence of intrauterine fluid greater than 1 cm after ovulation decreases pregnancy rate per cycle and increased the risk for early pregnancy loss (Squires et al., 2014).

Doppler ultrasound examination may be helpful in refining the examination. A decrease in uterine blood perfusion was reported in mares with high degrees of endometrial degeneration (Esteller-Vico et al., 2012; 2015; Stolla and Bollwein, 1997). These changes are due to angiosclerosis or vascular elastosis (Ferreira et al., 2008).

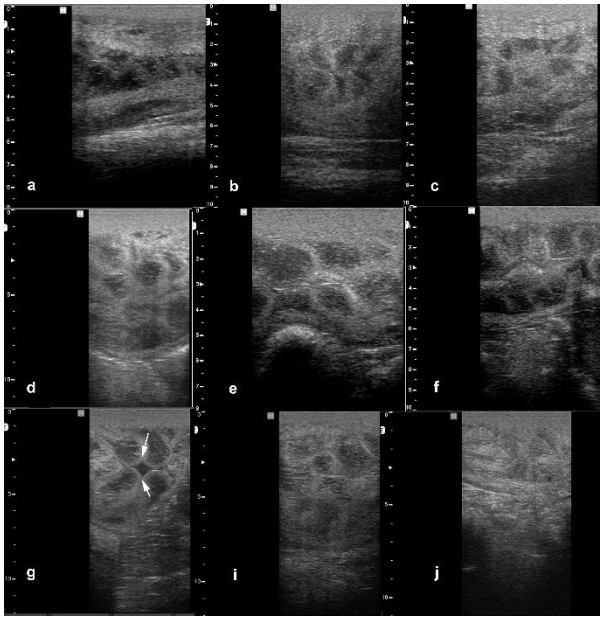

Figure 2. Uterine edema during the estrus. A) day 1 of estrus (edema 1), b) day 2, c) day 3 (edema 2), d-f) day 4 and 5 (edema 3); g) day 6 edema 3 following insemination, note small pocket of fluid (arrows) 6 hours after insemination), j) day 7 (edema 2), day 7) just before ovulation (edema 1)

Endometrial cytology

Cytological examination of endometrial samples is a simple, quick and cheap method to evaluate uterine health. Various sampling techniques have been described (Tibary, 2016). They include swabs, use of the cap of single-guarded swab, contact smears from biopsy, double-guarded cytobrush, and low volume lavage (Kozdrowski et al., 2013). The preferred methods are low volume lavage and the use of a double-guarded cytobrush because they provide better cellularity (Ball et al., 1988; Cocchia et al., 2012; LeBlanc, 2011; Tibary and Pearson, 2012; Walter et al., 2012). Smears directly prepared from the cytobrush or after centrifugation of the flush are stained (Wright-Giemsa or one of its modifications such as Diff-Quick®, Romanawsky or eosin-thiazin) (Buczkowska et al., 2014; Buczkowska et al., 2016). The stained smear is evaluated for presence of polymorphonuclear neutrophil leukocytes (PMNs), eosinophils, organisms, and debris (Figures 3,4). Interpretation may be quantitative (% of PMNs in 200 to 300 counted cells) or semi-quantitative (number of PMNs per high power field, hpf, 400x). There is a discrepancy in the literature regarding the PMNs threshold for diagnosis of endometritis. In general, it is expected to have less than 1 neutrophil per high power field (Bohn et al., 2014). A sample is considered positive if there are on average 2 or more PMNs hpf in at least 10 fields. In a study on 2123 mares, pregnancy rates for mares with <2PMNs, 2 to 5 PMNs and >5 PMNs per hpf were 60%, 49% and 23%, respectively (Riddle et al., 2007). Diagnosis based on the proportion of PMNs in relationship to endometrial cells (300 cells counted) is better than the number of PMNs per hpf but can be time-consuming for the busy practitioner (Kozdrowski et al., 2015). The degree of inflammation is scored based on the amount of neutrophils present (<5% no inflammation, 5-15% slight inflammation, 15-30% moderate inflammation, >30% severe inflammation). Others use the number of PMN/hpf as an indicator of the severity of inflammation (Table 1) (Wolfsdorf, 2016). In recent studies an incidence of 1 to 2% PMNs has been used as an indication of endometritis (Kozdrowski et al., 2013; Ferris et al., 2015).

Table 1. Grading of Cytology results according to Wolfsdorf, (2016)

Grade	Observation
Rare	0-1 in 5 hpf
1+	0-1 /hpf
2+	1-5 /hpf
3+	6-10 /hpf
4+	Too many to count

Presence of microorganisms and debris should also be taken into account and scored after evaluation at high magnification (1000x) (1: no organism in 30 fields, 2: one organism per 30 field, 3: one organism in 10 fields, 4: 2 to 10 organisms per field and 5: 11-50 organisms per field). Presence of debris is scored based as a proportion of particles per high power field (1: <25%`, 2: 25-50%`, 3:50-75%`, 4:>75%) (Card et al., 2004). Debris is generally the result of chronic inflammation and degenerative exfoliated cells and suggest chronic inflammation. Urine crystals may be identified in cases of urometra (Wolfsdorf, 2016).

The technique of sampling affects the quality and sensitivity of cytology results. In our practice, we prefer the use of the cytobrush. However, others found that low volume lavage has slightly better sensitivity. Most studies agree that cytology from a swab is not sensitive (Bohn et al., 2014; Ferris et al., 2015; Kozdrowski et al., 2013). Sensitivity of cytology from cytobrush and from endometrial biopsy were similar (71% vs. 73%) in one study (Kozdrowski et al., 2013). When a threshold of 2% PMNs was used as a cutoff for endometritis, the sensitivity and specificity (sensitivity/specificity) of cytology from cytobrush, uterine lavage and uterine fluid were 70/86, 62/78, and 55/92, respectively (Rua et al., 2018). Sensitivity and specificity of endometrial cytology using low volume lavage is 80% and 67%, respectively. An organism was isolated from the uterus of cytology positive mares in 67% (culture from endometrial biopsies) (Nielsen, 2005) and 64% (culture from swab) (Riddle et al., 2007) of the cases.

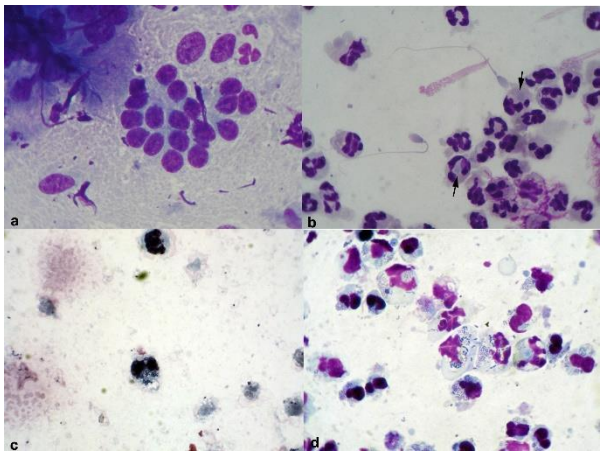

Figure 3. Endometrial cytology: a) normal endometrial cells, b) breeding induced endometritis, note spermatozoa (arrows), c) *Streptococcus equi zooepidemicus* endometritis, d) mixed bacteria endometritis.

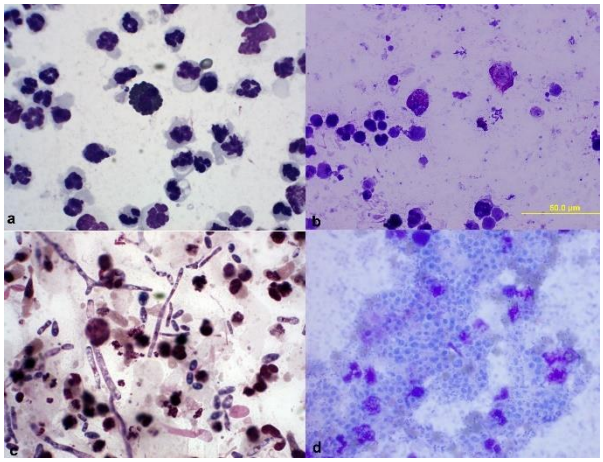

Figure 4. Endometrial cytology: a) PMN's and eosinophil in a mare with urometra, b) *E. coli* endometritis, c) Endometritis due to *Trichosporon spp*, d) endometritis due to *Candida*

Accuracy of cytological diagnosis of endometritis depends on several other factors such as the stage of the cycle at the time of sampling. The agreement between the number of PMNs infiltrated into the endometrial luminal epithelium and stratum compactum and the cytology was poor for samples taken in diestrus, fair in anestrus and moderate in estrous samples (Kozdrowski et al., 2015). Some infections, particularly recent low-grade fungal endometritis, and Gram-negative infections (*E. coli*) are not always accompanied by an increase in inflammatory cells which increases the risk of false negative diagnoses (LeBlanc et al., 2007; Nielsen et al., 2010; 2012; Riddle et al., 2007). It was postulated that some bacteria (i.e. *E. coli*) do not attract PMNs into the uterine lumen compared to others. In one study up to 50% of mares with PMNs on histology had a negative cytology (Nielsen et al., 2012). Several samples may be needed in some cases in order to increased sensitivity of endometritis diagnosis with cytology (Overbeck et al., 2013).

Endometrial culture

The majority of uterine infections are caused by aerobic bacteria and only 0.1% to 5% of cases are due to yeast or mold (Table 2). The most common bacterial isolates are *Streptococcus equi* subspecies zooepidemicus, *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. *P. aeruginosa* and *K. pneumonia* infections are considered venereal (Allen et al., 2011; Samper and Tibary, 2006; Tibary et al., 2014). Other less common aerobic isolates are considered contaminants in some cases. Isolation of 2 or 3 organisms from the same case is not uncommon (Rua et al., 2018; Tibary et al., 2014). *Streptococcus equi* subspecies *zooepidemicus* associated with endometritis in the mare consists of a genetically distinct group (Rasmussen et al., 2013). Fungal infections may be present at the same time as a bacterial infection (Tibary et al., 2014). Isolation and identification of fungal organisms is time consuming. Advanced techniques such as PCR may prove advantageous in rapid diagnosis of these infections (Ferris et al., 2013).

For microbiological examination samples are preferably obtained during estrus with a double-guarded swab or from uterine lavage. Samples should preferably be transported to the laboratory in non-nutritive media or plated directly. The sensitivity of culture from endometrial swabs is only 34% (i.e. risk of a false negative diagnosis of 66%). Many mares with negative culture will produce a positive culture or cytology after initiation of breeding, suggesting the presence of a deep seated persistent infection (Christoffersen et al., 2012a). This is particularly true for *Streptococcus equi zooepidemicus* which can reside deep in the endometrium in chronically infected mares and may give rise to a subclinical persistent infection in mares (Petersen et al., 2009). Detection of the responsible organism is improved if the culture is performed from an endometrial biopsy specimen (sensitivity = 82%) (Buczkowska et al., 2016; Nielsen, 2005; Nielsen et al., 2010).

Low volume uterine flushes may also be used for bacteriological examination. This technique has the advantage of sampling from the entire uterus and has been shown not to affect endometrial biopsy results (Linton and Sertich, 2016). Culture from uterine lavage was reported to be helpful for the detection of *E. coli* and *K. pneumoniae* infections (Wolfsdorf, 2016). The sensitivity and specificity of culture from low-volume uterine lavage was found to be 80% and 67%, respectively (LeBlanc et al., 2007). Contamination of samples can be prevented by using a closed tubing system with a single-use lavage tube, sterile sleeve through a sterile steel speculum as described by Christofferson et al. (Christoffersen et al., 2015). The sensitivity of this technique (75%) was superior to that of uterine biopsy (50%) and swab (30%) (Christoffersen et al., 2015). The sensitivity of culture from endometrial biopsy varies from one study to another probably due to difference in the type of organism involved. It was suggested that sensitivity of bacteriogical culture from the endometrial biopsy are better when *Streptococcus equi zooepidemicus* is the causative organism (Christoffersen et al., 2015). However, in one study, there was no difference in sensitivity of culture from cytobrush samples (50%) compared to culture from endometrial biopsy (63%) (Kozdrowski et al., 2013).

Table 2. Reported from the mare uterus of mares with infectious endometritis/metritis

Isolate	Characteristics
Common pathogenic bacteria	
Streptococcus equi subspecies *zooepidemicus*	Gram positive cocci, facultative anaerobe, beta hemolytic, susceptible to penicillin, ampicillin, and ceftiofur
Escherichia coli	Gram negative rod, susceptible to gentamicin, enrofloaxicin, ciprofloxacin. Strain can show multiple antimicrobial resistance
Pseudomonas aeruginosa	Gram negative rod, biofilm formation, susceptible to ticarcillin + Clavulanic acid, amikacin, ciprofloxacin, gentamicin, imipenem
Klebsiella pneumoniae	Gram negative, encapsulated. Susceptible to amikacin, enrofloxacine and ceftiofur
Common commensal/opportunistic bacteria	
alpha-hemolytic streptococci	Gram positive
Enterobacter spp.	Gram negative, facultative anaerobic, opportunistic (E. faecalis, associated with urometra)
Staphylococcus epidermidis	Gram positive
Acinetobacter spp.	Gram negative, can be multidrug-resistant
Citrobacter spp.	Gram negative
Trueperella pyogenes	Gram positive, facultative anaerobic
Proteus spp.	Gram negative
Staphylococcus spp.	Gram positive
Micrococcus spp.	Gram positive
Corynebacterium spp	Gram positive bacilli
Morganella morgana	Gram negative enterobacteriacae, commensal
Cedecea spp.	Gram negative bacillus enterobabacteriaceae, very rare
Yeast and Mold	
Candida spp.	Yeast
Aspergillus fimigatis	Mold
Cryptococcus neoformans	Yeast (encapsulated)
Fusarium spp.	Yeast-like
Hansenula anomala (Pichia anomala)	Yeast (renamed *Pichia*)
Ogataea polymorpha (Hansenula polymorpha, Pichia angusta)	Yeast
Rhodotorula spp	Yeast
Scedosporium apiospermum	Mold
Saccharomyces cerevisiae	Yeast
Trichosporon beigelii	Yeast

Use of chromogenic agar allows for a rapid identification of bacteria in practice (Beehan and Ferris et al., 2017; McKinnon, 2009). Microbiological results should always be interpreted in association with results of endometrial cytology. The severity of the infection is reported based on the growth of colonies in culture plates (Table 3) (Wolfsdorf, 2016).

Table 3. Grading of culture results according to Wolfsdorf (Wolfsdorf, 2016)

Grade	Observation
Scant	10 colonies or less
Light	Growth on primary streaks only
Moderate	Growth on secondary streaks
Heavy	Growth on last streaks

Endometrial biopsy

Endometrial biopsy is considered by theriogenologists the gold standard for the diagnosis of endometrial pathology and prognostication of the mare's ability to carry a pregnancy to term (Schlafer, 2007; Snider et al., 2011). It has a very high sensitivity and specificity for the diagnosis of endometritis (Amorim et al., 2016b). In addition to acute inflammatory changes, this technique allows detection of chronic degenerative changes and maldifferentiation. In practice, the diagnosis and prognosis of the ability of the mare to carry a foal to term are based on biopsy grade as proposed by Kenney and Doig (Kenney and Doig, 1986) (Table 4). Classification of biopsy is based on a detailed observation of the presence and distribution of inflammation, degree of fibrosis and pathological vascular changes (vasculitis, perivasculitis, estosis, and angiosis) (Figures 5-11) (Schlafer, 2007; Schoon et al., 2000; Snider et al., 2011) There is a significant correlation between biopsy score and pregnancy rate at day 70 (Nielsen et al., 2012). Mares with biopsy grades IIb and III are more likely to have a positive cytology (Buczkowska et al., 2016). Classification does not seem to be affected by prior low volume lavage (Linton and Sertich, 2016).

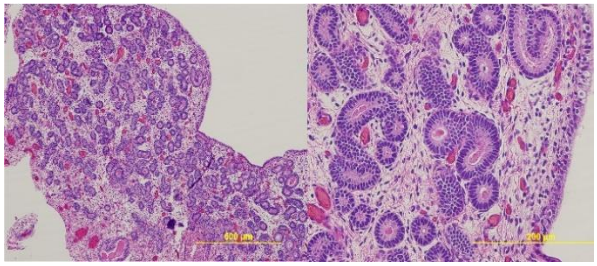

Figure 5. Endometrial biopsy: Normal endometrium (Kenney-Doig's category I).

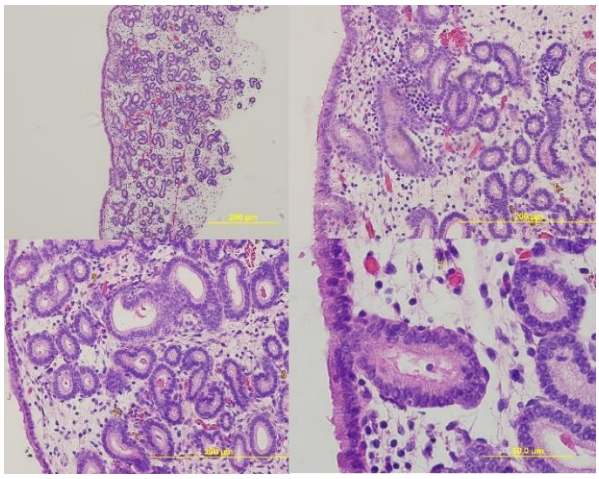

Figure 6. Endometrial biopsy: Slight diffuse inflammation. (Kenney-Doig's category IIa).

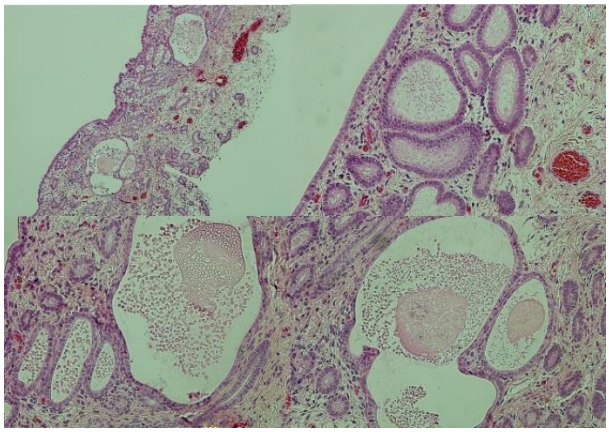

Figure 7. Endometritis, lymphoplasmacytic, diffuse, chronic, moderate, with minimal fibrosis (Kenney-Doig's category IIb-III) cystic dilation of the glands and lymphatic lacunae.

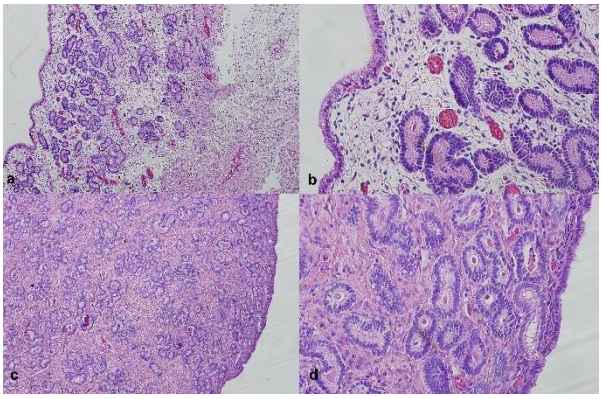

Figure 8. Endometrial biopsy: a-b) Endometritis, diffuse, lymphoplasmatic, chronic with minimal to mild fibrosis (Kenney-Doig's category IIa), c-d) mild to moderate multifocal fibrosis, c-d) Mild to moderate endometrial fibrosis (Kenney-Doig's category IIa).

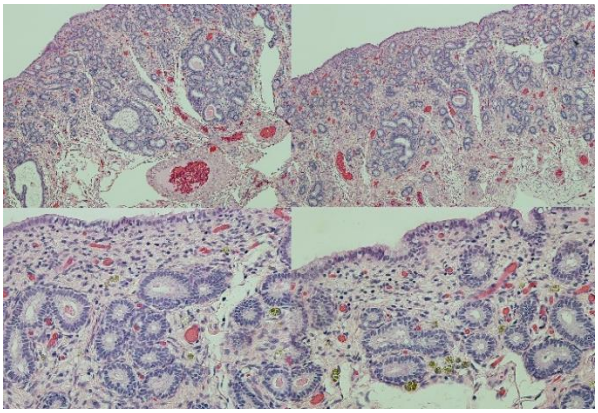

Figure 9. Endometritis, lymphoplasmacytic, multifocal, mild with moderate glandular hyperplasia, moderate fibrosis and edema (Kenney-Doig's category IIb).

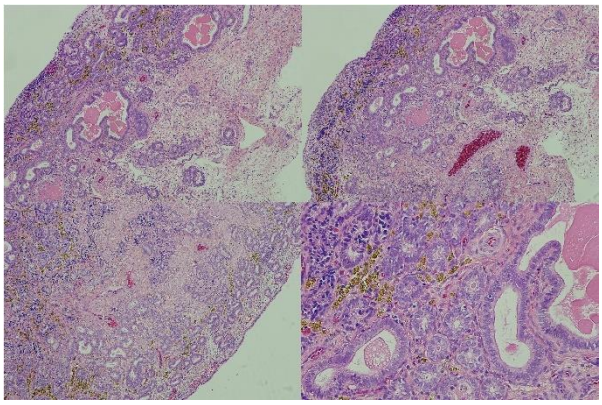

Figure 10. Endometritis, lymphohistiocytic and neutrophilic, diffuse, chronic, severe with multifocal fibrosis, with glandular nesting, chronic hemorrhage, epithelial degeneration (Grade III).

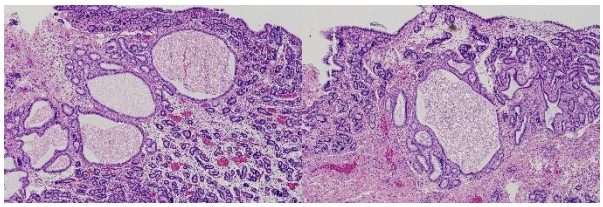

Figure 11. Endometrial biopsy. Cystic dilation and lymphatic lacunae in a mare following abortion.

Table 4. Classification of endometrial biopsy in the mare

Category	Lesions	Foaling rate
I	Normal endometrium, slight scattered inflammation or fibrosis	80-90%
IIa	Slight to moderate diffuse inflammation, slight scattered fibrosis (I<2 fibrotic nest per low power field), some glandular cysts, lymphatic lacunae and possible glandular atrophy at the end of the season	50-80%
IIb	Widespread moderate inflammation, significant fibrosis (2 to 4 nests per field). Widespread glandular degenerative changes and cystic dilation. Glandular atrophy or barren for 2 years or moe	10-50%
III	Severe irreversible inflammatory and degenerative changes. Widespread periglandular fibrosis (>5 nests per field), significant lymphocytic and plasmocytic infiltration), large lymphatic lacunae and history of 2 or more years of infertility	<10%

Hysteroscopy

Hysteroscopy was first described in the 1970's (Mather et al., 1979). Endoscopic equipment is becoming more available in general practice. Flexible videoendoscopes or fibroptic endoscopes (fibroscopes) between 10 and 14 mm in diameter and 160 cm or more in length are adequate for the examination of the entire uterine cavity. Equipment should have an instrument channel. In addition to examination of the uterine cavity, hysteroscopy is also used for the catheterization of the utero-tubal junction, low dose insemination, treatment of uterine cysts, removal of endometrial cups, targeted biopsy, removal of foreign material, and removal of luminal adhesions (Allen, 1994; Mather et al., 1979; Ricketts and Barrelet, 2001; Schnobrich, 2016).

The procedure is generally performed after sedation. Following transrectal evaluation of the reproductive tract, the perineal area and vulva are scrubbed. The flexible endoscope is introduced sterilely into the vagina and through the cervix. The uterine cavity is distended with air and the endoscope is advanced slowly to visualize the body of the uterus and the uterine horns bifurcation. Each horn is examined in its entirety all the way to the utero-tubal junctions. We prefer to perform the examination during the luteal phase because the cervix is tight and allow a better seal during uterine distension.

Narrow-band imaging (NBI) which improves visualization of mucosal and vascular structures, can be used for identification of endometrial vessels and evaluation of vascular densities. This technique may be helpful in the evaluation of blood vessels degeneration and identification of mares affected by endometrosis (Otzen et al., 2016).

Etiopathogenesis, treatment and prevention of specific uterine disease

Endometritis

The importance of this pathological entity is well illustrated by retrospective studies on large numbers of endometrial biopsies. Endometritis was diagnosed in 17% of 2500 endometrial biopsies in one study (Schoon et al., 1997; 2000). More recently, examination of 2405 mare endometrial biopsy showed a prevalence of endometritis of 40.5% and 42.5% in 10 to 15 year-old and 16 to 20 year-old mares, respectively (Ebert et al., 2014). Retired maiden and parous sports mares have a high incidence of endometritis (31% and 41%, respectively) (Kilgenstein et al., 2015).

Studies on the pathophysiology of endometritis in the mare show that the disease is fundamentally due to failure of in situ uterine defense mechanisms and/or uterine clearance (Tibary et al., 2014)). In addition to compromised physical barriers to contamination of the uterus (vulva, vestibular sphincter and cervix), failure of uterine clearance from the fluid generated by the initial inflammation induced by the deposition of semen leads to establishment of endometritis. Early research on equine endometritis showed that some mares are more susceptible to endometritis and others are resistant. Mares that are susceptible to infectious endometritis are unable to eliminate debris and bacteria from the uterus in the immediate post-ovulatory period following mating or insemination. However, it is very difficult to identify susceptible mares without historical data. In the past 3 decades much research has been conducted on the initial reaction of the endometrium to mating or insemination referred to as mating-induced or breeding-induced endometritis. Infectious endometritis may be a complication of persistent breeding-induced endometritis (PBIE, also known as persistent mating-induced endometritis or PMIE) or the result of an overwhelming bacterial or fungal load. Reproductive history, age, parity and previous biopsy scores should be considered when evaluating a mare for susceptibility to PBIE (Amorim et al., 2016b; Morales Muñoz and Castro Sánchez, 2018; Woodward et al., 2012; Woodward et al., 2013).

The equine endometrium has an innate and adaptive immune system including Toll-like receptors, antimicrobial peptides such as beta-defensin (Schöniger et al., 2017; 2018) and different lymphocyte and macrophage subsets (Rudolph et al., 2017) This innate immune system can be deranged by aging and compromised uterine clearance (Schöniger et al., 2018) An increase in spontaneous secretion of PGE2, 6-keto-PGF1a and LTC4 was detected in mares with endometritis particularly those between 16 and 23 years of age (Siemieniuch et al., 2017). Inflammation indicators such as serum amyloid A and

haptoglobin are not useful for diagnosis of subclinical endometritis (Sikora et al., 2016). Equine α-defensin (EBD1), lysozyme (LYZ) and secretory leukoprotease inhibitors (SLPI) have been identified as potential gene markers for susceptibility to endometritis (Marth et al., 2018).

Deposition of semen in the uterine cavity elicits an inflammatory reaction characterized by an influx of PMNs and production of mediators of inflammation (PGE2, PGF2α and leukotriene B4) (Ferrer et al., 2012; Tibary et al., 2014; Troedsson et al., 2001). Mares that are susceptible to PBIE have a higher expression of pro-inflammatory cytokines during estrus (IL-1ß, IL-6 and TNF-α) and diestrus (IL-1ß and TNF-α) (Christoffersen et al., 2012a; Fumoso et al., 2003; Fumuso et al., 2007; Woodward et al., 2013). Uterine inflammation results in an increase in vascular permeability and accumulation of intrauterine exudates and increased concentration of PMNs. The influx of PMNs is promoted by chemotaxis due to activation of the complement cascade by sperm and cleavage of C5 into C5a and C5b. The activated PMNs binds and phagocytize sperm (Troedsson, 2011). During this reaction the production of PGF2α elicits myometrial contractions which help to evacuate inflammatory products and debris from the uterus. Studies comparing endometrial reaction to saline solution, extended semen, frozen-thawed semen, and fresh non-extended semen have shown that all of these types of inseminate induce endometritis. Previous studies have shown that inflammation is of shorter duration when seminal plasma is present (Fiala et al., 2007). Seminal plasma is believed to modulate inflammatory mediators and stimulate myometrial activity. Seminal plasma may also selectively protect live spermatozoa from being bound and phagocytized by PMNs (Troedsson, 2011). However, a recent study showed that addition of seminal plasma to frozen-thawed semen does not affect PBIE and pregnancy rate (Sabatini et al., 2018). More studies are needed on the effect of seminal plasma as there are many confounding factors involved in PBIE (mare age, biopsy score, stallion, semen treatment, previous breeding etc…). New insights on immunologic and inflammatory response of the uterus suggest that these processes are also involved in the development of endometrosis (Klose and Schoon, 2016; Siemieniuch et al., 2016).

The severity of inflammation seems to be dependent on several factors, including bacterial strain, innate immunity and general condition of the female. The intracellular localization of TLRs and TNF-α in the endometrium indicates a key role of endometrial epithelial and stromal cells in the immune response and inflammation (Siemieniuch et al., 2016).

Clinically, Breeding-induced endometritis is evidenced by the presence of intrauterine PMNs, increased endometrial edema, and accumulation of fluid within a few hours of insemination (Figure 12). These signs should resolved within 24 to 36 hours in normal mares. In susceptible mares, the fluid continues to accumulate and eventually a secondary reaction takes place exacerbating the inflammation. It is estimated between 10 to 43% of all broodmares develop PBIE (Newcombe, 1997a; Zent et al., 1998). Mares with subclinical endometritis tend to develop abnormal edema before breeding (Rasmussen et al., 2015). In one study, 55% of mares with intrauterine fluid accumulation had a positive on culture with 81% resulting in growth of *S. equi zooepididemicus* (Christoffersen et al., 2015). This confirms that in many mares with subclinical endometritis, S. zooepidemicus resides deep in the endometrial glands and is only activated after mating (Petersen et al., 2009).

Failure of uterine clearance may be due to a combination of factors including increased nitric oxide (NO) concentration causing smooth muscle relaxation (Alghamdi et al., 2005). An in vitro study reported a dose-dependent myorelaxant effect of NO which was independent of mare age and biopsy grade (Khan et al., 2017). Mechanical factors such as a pendulant uterus in aged mares or a tight cervix are contributing factors. Cervical stenosis is a characteristic of old maiden mares (Tibary, 2011). Failure of uterine clearance may also be caused by weakened myometrial activity and/or poor lymphatic drainage due to degenerative changes (vascular elastosis, fibrosis, lymphatic cysts) (Woodward et al., 2012). Mares with metabolic disorders (equine metabolic syndrome, equine Cushing disease) seem to be more prone to PBIE (Tibary et al., 2014).

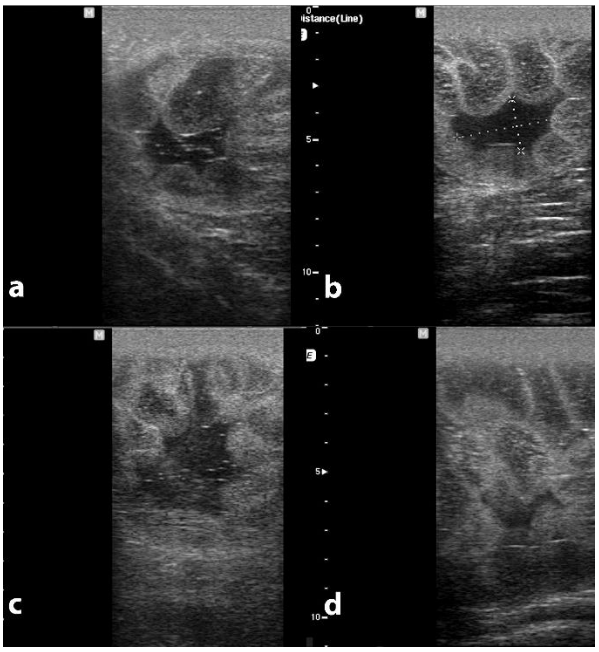

Figure 12. Persistent breeding induced endometritis. a) 6 hours after insemination. b) 12 hours after insemination, c) 24 hours after insemination, d) 6 hours after uterine lavage and treatment with oxytocin.

Infectious endometritis has been identified as a major problem in equine breeding for several decades (Tibary et al., 2014). Vaginal mucopurulent discharge is relatively discrete particularly in chronic infections and is more evident following breeding. Examination of a mare suspected to have endometritis should include a thorough evaluation of perineal conformation, vestibulo-vaginal sphincter, cervix, ultrasonography of the uterus. For subclinical endometritis, a combination of microbiological, cytological, and histopathological examination of endometrial samples is required for precise diagnosis. Microbiological examination of samples from the clitoral fossa is indicated in cases of recurrent endometritis (Tibary et al., 2014).

Prevention and treatment of PBIE are based on strategies to increase uterine clearance. This is accomplished mostly by administration of ecbolics after insemination. Uterine lavage combined to use ecbolic should be considered if fluid accumulation is significant (>20 mm). The uterus can be lavaged with Lactate-Ringer solution or a specially formulated flushing medium containing surfactant. In cases of infection antimicrobial therapy in utero, systemically or a combination of both should be considered.

The use of ecbolic drugs has become commonplace in the management of mares following breeding, particularly if they are prone to developing PMIE. Oxytocin (10 to 20 IU, IM) every 4 hours starting 4 to 8 hours after insemination enhances uterine clearance and improves conception rates (LeBlanc and Causey, 2009). A long-acting synthetic oxytocin analogue (carbotocin) is available in some countries and allows a sustained effect for several hours following a single treatment (Schramme et al., 2008). Cloprostenol (250 µg IM, q 12 hours) has also been used because of its uterotonic effect. However, treatment should be discontinued after ovulation in order to avoid poor corpus luteum (CL) development and risk of pregnancy failure (Nie et al., 2003).

Anti-inflammatory therapy has been advocated to reduce reactions in PMIE-susceptible mares. Dexamethasone used as a single injection (0.1 mg/kg IV or 50 mg total dose) at the time of or one hour prior to insemination improves pregnancy rates in susceptible mares (Bucca et al., 2008; Vandaele et al., 2008; Bucca and Carli, 2011). However, an inhibitory effect on the LH surge and an increased incidence of anovulatory follicles has been reported following administration of 2 injections of dexamethasone prior to ovulation in one study (Ferris and McCue, 2010). Other authors have used 9-alpha prednisolone (0.1 mg/kg, PO, bid) starting 2 days before ovulation and continued until ovulation or up to 2 days after ovulation (Papa et al., 2008). Isoflupredone acetate (20 mg, IM bid for 3 days) was also shown to enhance local defense mechanisms and suppress inflammation (Wolf et al., 2012). The use of corticosteroids has been associated with a reduced killing capacity of PMNs. In one study, a single injection of dexamethasone did not have any negative effect on PMN migration or phagocytic activity. There is limited information on the use of non-steroidal anti-inflammatory drugs (NSAIDs) to manage mares with PMIE. In a small study, vaprofen, an inhibitor of cyclooxygenase-2, was shown to improve pregnancy rates in treated mares (Rojer and Aurich, 2010). In another study on jennies, ketoprofen was able to reduce inflammation but not PMN influx (Vilés et al., 2013). Treatment with isoflupredone (20 mg q 12 hours) for 3 days did not alter nitric oxide concentration in uterine flushing (Wolf et al., 2016). To the best of the authors' knowledge firocoxib has not yet been evaluate for the prevention or treatment of endometritis.

Another approach to treatment and prevention of the PBIE is the use of immunodulators. Immunomodedlars may act to change the inflammatory cascade early in the inflammatory process especially at the level of IL1ß (Woodward et al., 2015). Immunostimulants prepared from cell wall extract of Mycobacterium phlei (Settle®) or as a suspension of Priopionibacterium acnes (EqStim®) have been used in susceptible mares to induce a non-specific cellular response by activation of macrophages and cytokine release (Christoffersen et al., 2012b). These products are administered in utero or intravenously at the beginning of estrus. Administration of P. acnes 8 days before to 2 days after breeding resulted in an improvement in pregnancy and foaling rates (Rohrbach et al., 2007).

Lactoferrin, modulate inflammation and inhibits biofilm formation by gram negative bacteria because of its ability to chelate iron. Preliminary studies showed that in utero infusion of recombinant human lactoferrin modulates inflammatory response to breeding and is safe but therapeutic trials are needed (Fedorka et al., 2018; Fedorka et al., 2017ab; Silva et al., 2017).

Treatment with platelet rich plasma (PRP) was shown to increase growth factors such as transforming factor ß, insulin-like growth factor-I, fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor in the injured area, and local increase in lipid molecules (lipoxin A4). Intrauterine infusion of PRP reduced the inflammatory response to semen deposition in mares with chronic degenerative endometritis. Although this treatment did not affect the level of NO it may increase conception rate in some mares (Reghini et al., 2016; Segabinazzi et al., 2017).

Uterine infusion of antimicrobials have been used for several years in the treatment of endometritis (Table 5). However, some antibiotics may not persist at a sufficient concentration for the entire interval between treatments. The choice of antibiotics for intrauterine administration should consider not only susceptibility of the isolate but also the behavior of the drug within the uterus. Aminoglycosides should be buffered prior to use. Enrofloxacin in its commercial preparation (Baytril®) is extremely caustic to the endometrium and results in severe hemorrhagic endometritis, intraluminal adhesions and deterioration of the biopsy grade (Rodriguez et al., 2012). A newly formulated, water-based suspension of enrofloxacin is not associated with these severe side effects (Schnobrich et al., 2015). Intrauterine infusion of ceftiofur was shown to not maintain MIC for *E. coli* for more than 6 hours while it persisted above MIC for *S. zooepidemicus* for 24 hours (Scott et al., 2016).

Antibiotics can also be used systemically in the treatment of endometritis (Table 6). Systemic administration of sulfadiazine-trimethoprim for 5 consecutive days achieved concentration above the MIC for common pathogens involved in endometritis such as *S. equi zoopidemicus* and *E. coli* (Davolli et al., 2017). Ciprofloxacin concentrations remained above MIC90 for *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in the uterine lumen and endometrial tissue (Trundell et al., 2017).

One of the major challenges in the treatment of endometritis is the presence of biofilm. Biofilm is a community of bacteria that are attached to an interface or to each other that are encased within an extrapolymeric matrix consisting of nucleic acids, lipids, proteins, and exopolysaccharides. Bacteria in biofilm are resistant to antibiotic and innate defense mechanism leading to persistent infection (Ferris, 2016; 2017ab).

Use of solvents or mucolytic agents helps remove exudates, mucus, and biofilm, which potentiate in utero antimicrobial therapy. Intrauterine infusion of dimethyl-sulfoxide (DMSO, 30% solution) was shown to improve uterine biopsy grade and pregnancy rates in barren mares. Hydrogen peroxide solution (20 mL of 3% solution in 60 mL of LRS, 6 to 48 hours after breeding) was used to treat recurrent bacterial endometritis. Intrauterine infusion of N-acetylcysteine (30 mL in 150 mL of saline) in barren mares one day prior to breeding resulted in an improvement of pregnancy rates (LeBlanc, 2009). Oral administration of N-acetylcysteine was found to have an anti-inflammatory effect on the endometrium but does not reduce uterine mucus viscosity in mares (Witte et al., 2012). Infusion of EDTA-tris (250 ml of a 3.5 mM EDTA and 0.05 M tris or 1.2 g Na-EDTA + 6.05 g Tris/ L of H2O, titrated with glacial acetic acid, pH of 8) in utero has been shown to help remove biofilm and improve antibiotic efficacy particularly in endometritis due to gram-negative bacteria. In vitro studies have shown that DMSO (dimethyl sulfoxide, 30% v/v) and antimicrobial peptide mimic (APM, Cyragen®) some efficacy for treatment of *E. coli* (Loncar et al., 2017). Cyragen® is often infused 6 to 8 hours before or 6 to 48 hours after breeding.

Table 5. Antibiotics used for in utero treatment of endometritis in mares.

DRUG	DOSE*	COMMENTS
Gram-Positive Bacterial Infections		
Penicillin sodium or potassium salt	5 million units (U)	Very effective for streptococci; economical.
Ampicillin	1-3 g	Can be very irritating; use at high dilutions; sodium salt precipitates on endometrium that remains in uterus for prolonged period.
Carbenicillin	2-5 g	Reserved for persistent *Pseudomonas* (synergistic efficacy with aminoglycosides); usually given on alternate days with aminoglycosides; slightly irritating.
Gram-Negative Bacterial Infections		
Gentamicin sulfate	500-2000 mg	Highly effective; generally nonirritating when mixed with an equal volume of $NaHCO_3$ and diluted in saline.
Amikacin sulfate	2 g	Use for *Pseudomonas*, *Klebsiella*, and persistent gram-negative infections.
Kanamycin sulfate	1 g	Toxic to spermatozoa; do not use close to breeding.
Polymyxin B	1 million U	Particularly effective against *Pseudomonas*.
Neomycin sulfate	2-4 g	Use for sensitive *E. coli*; can be irritating; do not use near time of breeding.
Gram-Positive and Gram-Negative Bacterial Infections (broad spectrum)		
Cephazolin sodium	1 g	
Ticarcillin	1-6 g	Use for *Pseudomonas*; do not use for *Klebsiella*. Minimum volume 200 mL
Ticarcillin-clavulanic acid	3-6 g	Enterobacter, S.a ureus, B. fragilis. Minumum volume 200 ml 200 mL
Ceftiofur sodium	1 – 2 g	
Chloramphenicol	2-3 g	Can be irritating

Table 6. Antibiotics for systemic treatment of uterine infection in the mares.

Drug	Dose	Remark
Amikacin sulphate	10-15mg/kg, IV or IM, SID	Gram-
Ampicillin Na	29 mg/kg, IV or IM, BID	Gram+ and *E. Coli*
Ceftiofur sodium	2.5 mg/kg IM, BID or SID	Broad spectrum
Ceftiofure sodium crystalline free acid	6.6 mg/kg, IM, 2 doses 4 days apart	Broad spectrum
Gentamicin	6.6 mg/kg, IV, SID	Slow infusion, *Enterobacter* spp., *E. coli*, *Klebsiella* spp., *Proteus* spp., *Serratia* spp., *P. aeruginosa*, *S. Aureus*
Enrofloxacin	5.5-7.5 mg/kg, IV, SID	Slow i.v. infusion; Gram-negative infections caused by susceptible bacteria resistant to alternative
Penicillin G (Potassium)	25,000 IU/kg, IV QID	*S. zoopeidemicus*
Penicillin procaine	25,000 IU/kg, IM, BID	
Ticarcillin + clavulonic acid	50 mg/kg IV or IM q 6-8 hours	
Trimethoprim-sulphonamide	30 mg/kg, PO, BID	*S. aureus*, *E. coli*, *Klebsiella* spp., *Proteus*
Meteronidazole	15-25 mg/kg, PO, BID	*Bacteroides fragilis* metritis

Treatment of fungal endometritis is notoriously difficult and requires both local and systemic use of antifungal drugs (Table 7) in addition to uterine lavage with antiseptics. Disinfectant solutions used include hydrogen peroxide (1-3%), acetic acid (2% or 20 ml white vinegar in 1 liter of saline), povidone iodine (0.1-0.2%) or DMSO 20% (LeBlanc and Causey, 2009). Recent studies on antifungal susceptibility patterns demonstrated that 95 to 100% of fungal isolates of uterine origin are susceptible to polyenes whereas only 47 to 81% are susceptible to azoles. The same study showed that 100% of yeasts are susceptible to polyenes and only 48% are susceptible to azoles. Molds with septated hyphae were susceptible to natamycin and not to fluconazole (Beltaire et al., 2012). Increased yeast resistance to miconazole and mold resistance to ketoconazole was demonstrated (Beltaire et al., 2012). For systemic treatment of fungal endometritis, the most common drugs used are Amphotericin B (0.3-0.9 mg/kg SID, very slowly) Fluconazole (14 mg/kg loading doses, then 5 g/kg IV or PO SID), and Itraconazole (5 mg/kg IV or PO, SID or BID). Oral treatment with fluconazole was shown to reach the endometrial tissue at sufficient concentration (Scofield et al., 2013).

Antiseptics are often used in cases of fungal endometritis. These products should be used carefully as highly concentrated solution of povidone iodine or chlorhexidine can result in exacerbation of endometritis, cervicitis and vaginitis leading to adhesions (Tibary et al., 2014). Chlorhexidine hydrochloride 1 g in 28 ml was shown not to cause significant endometrial changes (Fraser et al., 2017).

Treatment should also consider correction of anatomical defects. Topical N-butylscopolammonium bromide (Buscopan®) and PGE1 (1 to 2 mg of misoprostol) creams may help with cervical dilation and expulsion of intrauterine fluid in cases of stenosis/fibrosis (Tibary, 2011). Vestibulo-vaginal sphincter and perineal conformation defects should be corrected surgically (vestibulo-vaginoplasty, urethral extension) (Tibary et al., 2014). Electroacupuncture in association with administration of ecbolic drugs is increasingly used in practice but controlled studies are still lacking (LeBlanc, 2010). Laparoscopic uteropexy, reduction of the size of the board ligament can be considered in mares with very pendulant uterus (Brink and Schumacher, 2010).

Table 7. Antimycotics used for in utero treatment of endometritis in mares.

DRUG	DOSE*	COMMENTS
Nystatin	0.5-2.5 million U	Primarily for yeast (e.g., *Candida albicans*) in the growing phase; insoluble, suspend in 100-250 mL sterile water and vigorously mix immediately before infusion.
Amphotericin B	100-200 mg	For infections with *Aspergillus*, *Candida*, *Mucor*, or *Histoplasma;* dilute in 100-250 mL sterile water, a relatively insoluble suspension.
Clotrimazole	500-700 mg	For yeast infections (*Candida* spp.); crushed tablets mixed with 40 mL sterile water.
Fluconazole	100 mg	For *Candida* spp. infections. Need to adjust the pH to aboid acidic nature
Miconazole	200-700 mg	Most efficacious for yeast infections (*Candida* spp.) and some resistant fungal infections; infuse once daily for up to 10 days; dilute in 40-60 mL sterile saline before infusion

Prevention of endometritis can be accomplished by reducing the number of inseminations, use of minimum contamination breeding and use of techniques to enhance uterine clearance in all mare that present high risk of susceptibility. Many practitioners suggest infusion of an antibiotics after mating to prevent endometritis. However, a recent study showed that a single post-mating infusion of penicillin does not improve pregnancy rate (Scoggin et al., 2017). New molecular and immunological tests for early recognition of mares at risk for endometritis are being developed and may help if developing strategies in the prevention of PMIE and its complications (Marth et al., 2018; Rudolph et al., 2017).

Endometrosis

Endometrosis, a term introduced first by Kenny in 1992, describes a chronic endometritis characterized by degenerative changes of the endometrial glands and stroma surrounding them (Fiala et al., 2010; Snider et al., 2011). This degenerative process causes an abnormal differentiation of the endometrial glands, periglandular as well as stromal fibrosis and endometrial cystic dilation (Ricketts and Barrelet, 1997). It is mainly characterized by extensive periglandular collagen fiber deposition in the stroma. In vitro studies suggest that neutrophil extracellular traps (elastase, cathepsin G, myeloperoxidases) released during response to an infection may be involved in tissue damage acting as endometrial fibrogenic mediators (Rebordão et al., 2018). Endometrial degenerative changes are brought about by periglandular inflammation and hypoxia due to angiosclerosis. Synthesis of collagen fibers and profibrotic growth factors further exacerbate these modifications. Vimentine and α-actin expression increases in the fibrotic nests and causes changes in the extracellular matrix. Two types of fibrosis have been described based on periglandular cells morphology (destructive vs. non-destructive). Furthermore, fibrosis is classified as active or inactive depending on the amount of fibrotic nests of the destructive type (Hoffmann et al., 2009b; Lehmann et al., 2011). Maldifferentiation of the endometrium resulting from degenerative changes alters expression of protein such as uterocalin, uteroglobulin, calbindin D9k and uteroferrin which play an important role in embryo metabolism and viability (Hoffmann et al., 2009b; Lehmann et al., 2011).

Around 60 to 70% of all equine endometrial biopsies show some degree of endometrosis (Lehmann et al., 2011). Age of the mare but not number of pregnancies is strongly associated with development of these degenerative changes (Ricketts and Barrelet, 1997; 2001; Lehmann et al., 2011). In general, mares aged 11 years or more show increased endometrosis and reduced fertility (Schoon et al., 2000). It is estimated that 30% of broodmares >18 years are affected (Alvarenga and Carmo, 2009). There is a significant association between inflammatory cells infiltration and degree of endometrosis. (Kenney and Doig, 1986; Lehmann et al., 2011) Fibrosis is likely due to activation of stromal fibroblasts by growth factors and cytokines released by the inflammatory cells following an infectious endometritis (Hoffmann et al., 2009b; Kiesow et al., 2011; Walter et al., 2001). Endometrosis can also be exacerbated by impairment of cervical drainage (Reilas et al., 2016) and intrauterine infusion of peanut oil to prolong luteal activity and suppress estrus in performance mares (Campbell et al., 2017).

Doppler ultrasonography may be helpful in detecting some vascular changes in mares with recurrent embryonic loss and severe degenerative changes and elastosis. Mare with endometrial biopsy scores of IIb or III tend to have a higher uterine artery vascular resistance index (Bollwein et al., 1998; Oikawa et al., 1993; Ousey et al., 2012). Sclerosis of small arteries adjacent to the endometrium may be seen on hysterosopic evaluation of the uterine cavity (Inoue et al., 2000).

Degree of severity increases with number of barren years a mare and is positively correlated to incidence of early pregnancy loss (Kenney and Doig, 1986; Lehmann et al., 2011; Ricketts and Barrelet, 1997). Increased incidence of early pregnancy loss in mares with endometrosis is likely due to alterations in estrogen and progesterone receptors expression and prostaglandin synthetase mRNA transcription and prostaglandin secretion which render the stroma independent from hormonal control which normally regulated uterine function (Hoffmann et al., 2009ab; Szóstek et al., 2012). It is important to note that endometrosis has been associated with changes in the oviduct (fibrosis) and may be an indicator of collagen increase in the oviduct and plugged uterine tube in some infertile mares (Pinto-Bravo et al., 2018).

Several strategies have implemented to "treat" or attempt to "reverse" the pathological changes due to endometrosis. These include chemical curettage using kerosene and stem cell therapy. According to Ricketts and Barrelet, 75 to 87% of affected mares respond to uterine curettage (Ricketts and Barrelet, 2001). Chemical curettage (uterine infusion with 50 to 100 mL of kerosene) was shown to restore fertility and improve biopsy grade (Bracher et al., 1997). The mechanism of action of this treatment is not clear and improvement may be due to sloughing of the endometrium and reactivation of the endometrial glands or reduction of mucus and clearing of cystic glandular dilation (LeBlanc and Causey, 2009). However, this treatment remains controversial.

Treatment of mares with CED with platelet rich plasma (PRP, 10 mL) was shown to reduce inflammatory response after breeding and PMNs influx but it did not reduce the levels of NO (Reghini et al., 2016). Treatment with PRP, 24 hours before mating, reduced PMI and increase conceptions rate (Segabinazzi et al., 2017).

A promising approach to treatment of mare with endometriosis has been proposed and consists of intrauterine instillation of mesenchymal stem cells to promote remodeling of the endometrium (Mambelli, 2011). Mesenchymal stem cells therapy was shown to modulate the inflammatory response following insemination (Ferris et al., 2012). Hysteroscopic injection of mesenchymal stem cell has been attempted but its efficacy has not yet been fully evaluated (Alvarenga et al., 2016).

The use of aspirin or pentoxyfillline in mares with poor vascular perfusion and blocked lymphatics has been advocated by practitioners but its efficacy has not been fully investigated (Wolfsdorf, 2016).

Uterine cysts

Although referred to as endometrial cysts, the authors prefer the use of the term "uterine cysts' in describing large (>10 mm) cysts seen on ultrasonography. In contrast, endometrial cysts are microscopic lesions which rarely reach 10 mm in size and are characterized by endometrial glandular dilation. Around half of subfertile mares have uterine cysts (Bracher et al., 1992). Age, parity and history of endometritis are major predisposing factors. Uterine cysts are often the consequence of CDE and vascular changes and impaired lymphatic drainage (Ferreira et al., 2008). They are usually located at the base of the uterine horns but can also be located anywhere in the uterus. Large uterine cysts in the uterine body can protrude through an open cervix. The size of the cysts increases significantly during estrus and in the immediate postpartum period. Uterine cysts can be luminal or transmural. Their ultrasonographic appearance varies from a single well circumscribed cyst to a multilobulated appearance (Figures 13,14). Their effect on fertility depends on number and size (Tannus and Thun, 1995). They can compromise uterine clearance, transuterine embryo mobility and may interfere with implantation after fixation.

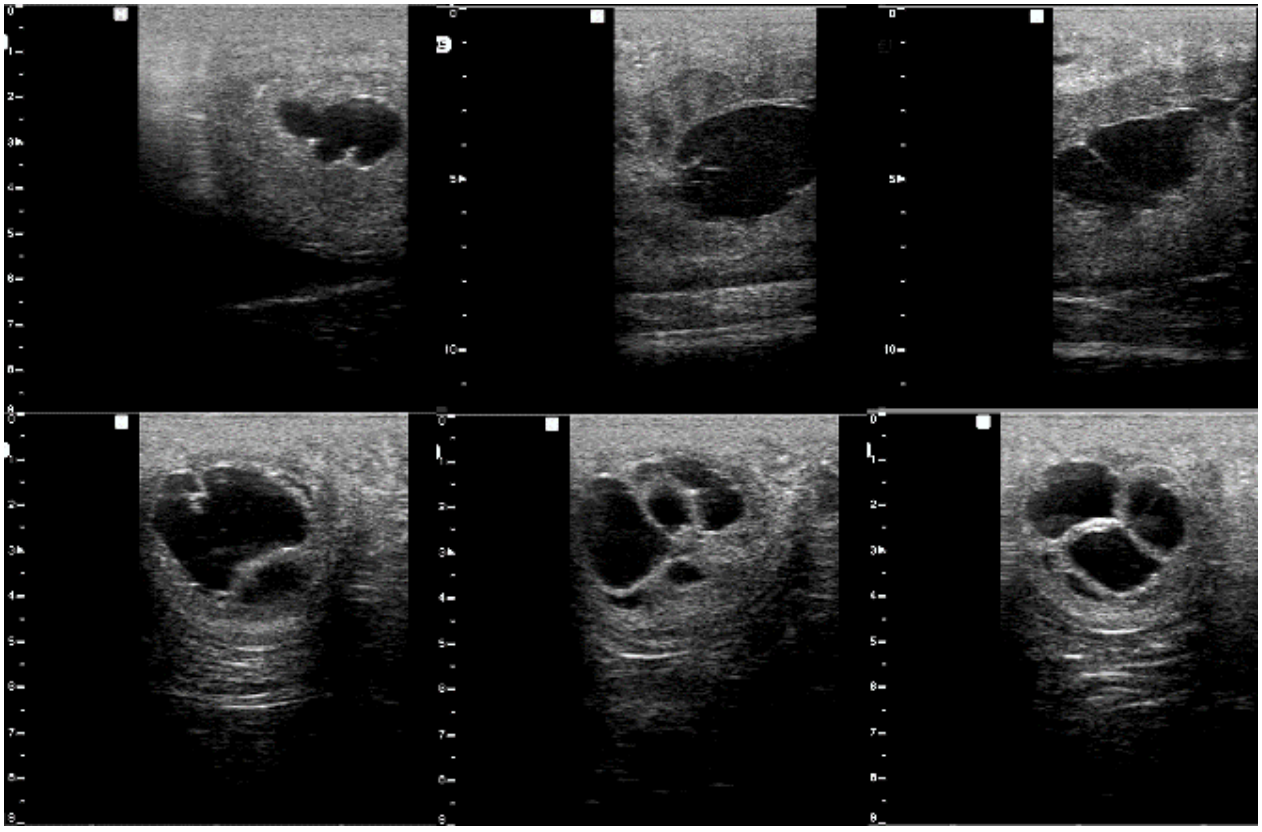

Figure 13. Ultrasonographic appearance of uterine lymphatic cysts.

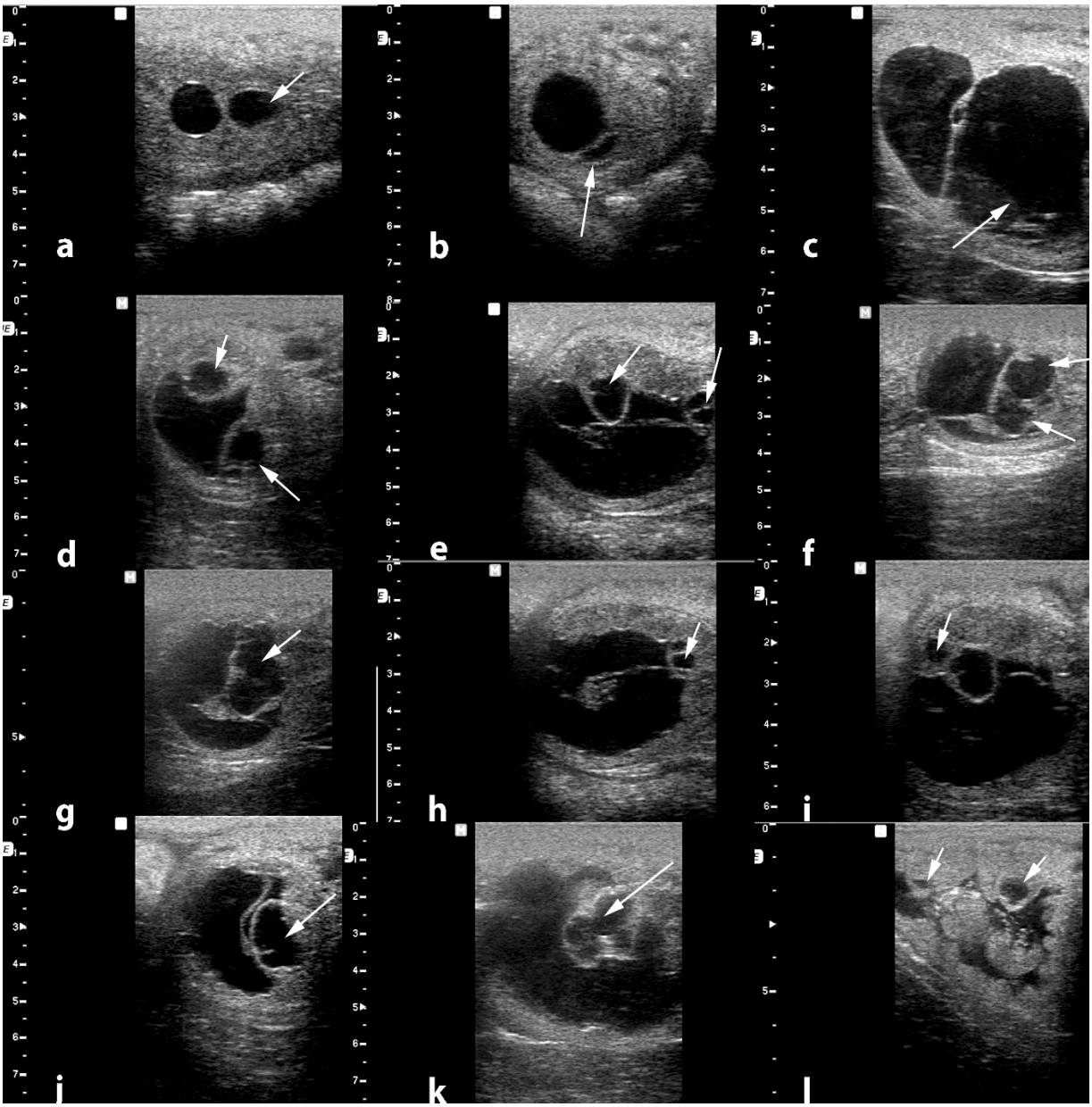

Figure 14. Ultrasonographic appearance of embryonic vesicle adjacent to uterine cysts (note evidence of embryo loss in i)

Several treatments options can be considered for removal of uterine cysts including chemical curettage, endoscopic rupture with a biopsy instrument, manual ablation, loop electrocautery, electrocoagulation, and laser ablation (Figure 15) (Carluccio et al., 2018; Miller and Ferrer, 2014; Rambags and Stout, 2005; Scherrer, 2015). Neodymium/yttrium (Nd:YAG) ablation via hysteroscopy is considered the treatment of choice for large uterine cysts (Blikslager et al., 1993). There is a risk associated with overuse of the laser. In cases where several cysts are present, multiple sessions may be required. Our standard protocol is to laser the cysts during diestrus in order to provide a good visualization of the uterine cavity. The uterus is flushed with LRS after each session and the mare is treated with NSAID. Recently, in a small trial on 8 mares, ethanol sclerotherapy has been shown to eliminate uterine cysts and restore fertility. The technique consists of draining the cysts endoscopically then injecting 70% ethanol in saline solution to fill 40% of the original cavity (Carluccio et al., 2018).

Foreign bodies

Abnormal echotexture of the uterine cavity may be due to the presence of foreign bodies. The most common being swabs, cytobrushes (Figures 16, 17), glass marbles (Figures 18, 19) or stallion smegma concretions (bean). Stallion beans are often associated with a severe chronic endometritis or pyometra and require large volume lavage of the uterus. Swabs and brushes are relatively easy to remove via hysteroscopy. Glass marbles, used to prolong diestrus and suppress heat in performance mares, have been associated with several complications (endometritis, adhesions, rupture of the uterus) and their use should be abandoned (Figure 19). Their removal can be very difficult and requires combined transrectal and vaginal manipulation after dilation of the cervix (Amorim et al., 2016a; Runcan et al., 2017).

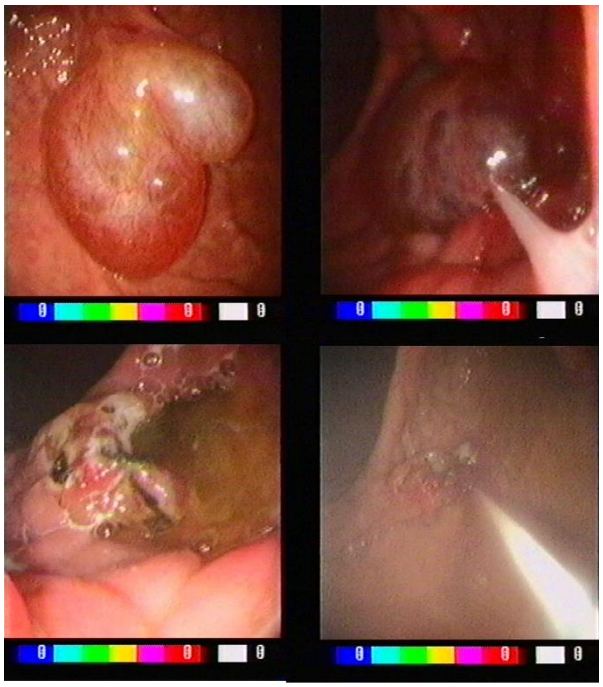

Figure 15. Hysteroscopic laser ablation of a large pediculated uterine cyst.

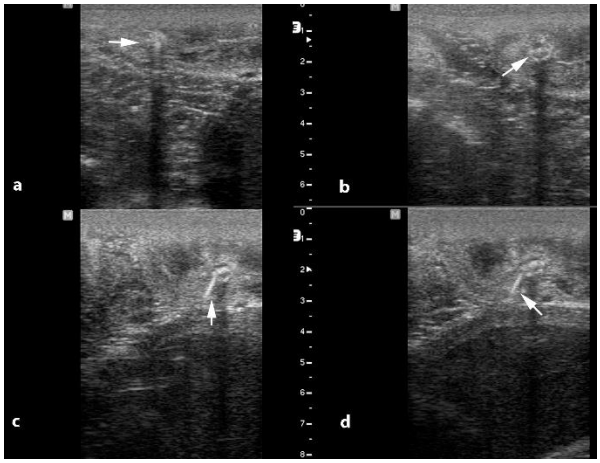

Figure 16. Ultrasonographic appearance of cytobrushes (arrows) embedded into the uterine wall.

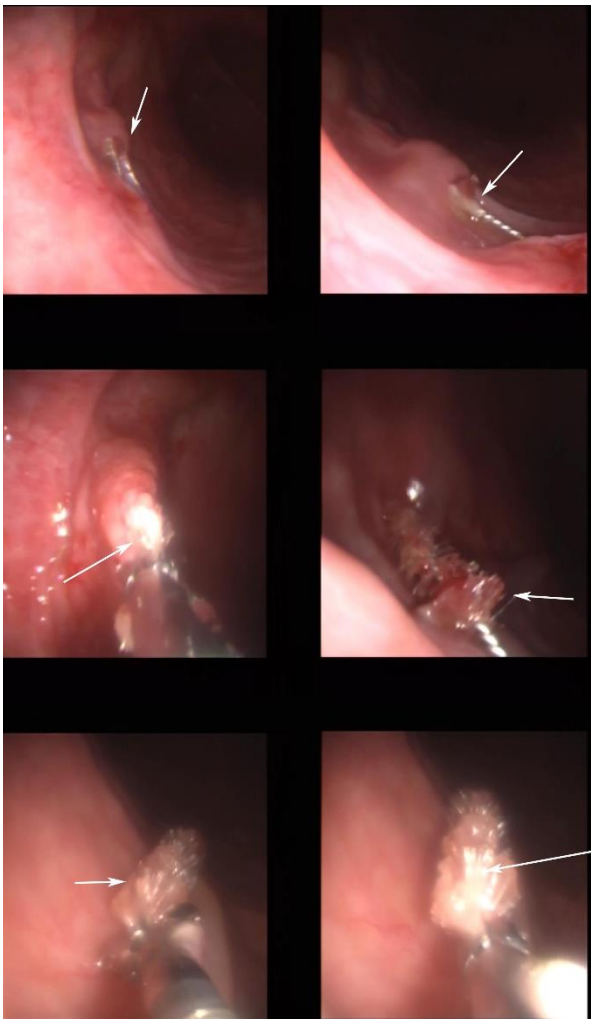

Figure 17. Hysteroscopic retrieval of a cytobrush (arrows) from the endometrium.

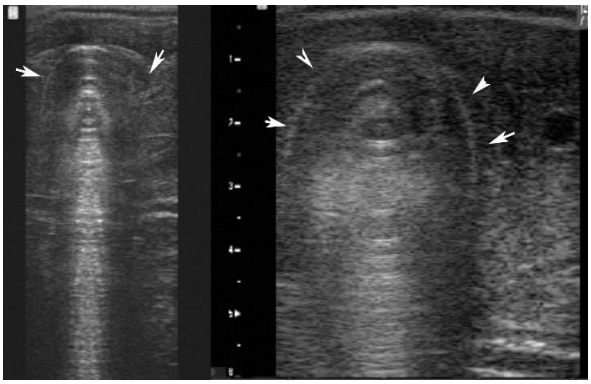

Figure 18. Ultrasonographic appearance of a marble (arrows) within the uterine cavity.

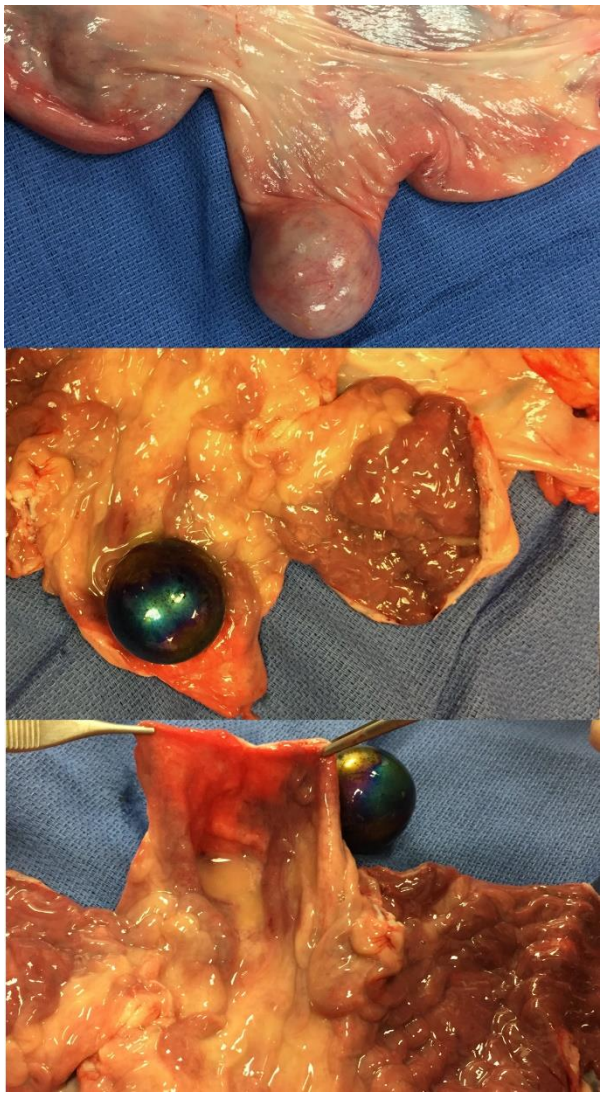

Figure 19. Postmortem examination of a uterus with imbedded glass marble from a mare presented for colic and endometritis. Note the thinning of the uterine wall and the loss of endometrial folds around the marble.

Luminal adhesions

Intraluminal adhesions may be suspected on ultrasonography by the presence of localized fluid or area of increased echogenicity (Figures 20, 21). They can be better visualized by performing ultrasonography while infusing the uterus with a saline solution. Intrauterine adhesions are often due to infusion of the uterus with irritants such as iodine or chlorhexidine solution, Baytril® (Figures 21, 22). They have also been described as a complication of glass marbles (Amorim et al., 2016a; Runcan et al., 2017).

Urometra

Urometra is a consequence of vesico-vaginal reflux and a common cause of infertility in the mare. It is relatively common in the immediate postpartum period following dystocia. Methods used for clinical diagnosis of urometra include interpretation of the appearance of intrauterine fluid via transrectal ultrasonographic examination, the presence of eosinophils on the endometrial cytological exam and detection of calcium carbonate crystals upon microscopic evaluation of the uterine fluid. Vaginal examination should also reveal a pool of urine (Figure 23). Confirmation can be obtained by creatinine concentration of uterine fluid may also aid in assessing the efficacy of treatment of urine pooling in mares. In one study the normal range of creatinine is uterine flush was <0.9 mg/dl while it ranged from 4.1 to 109.2 mg/ml in mares with urometra (Schnobrich et al., 2017). In the postpartum mare, this problem may be associated with urinary bladder atony. In the subfertile mare, treatment required surgical correction (urethral extension) (McKinnon and Belden, 1988; Prado et al., 2012; Schnobrich et al., 2017).

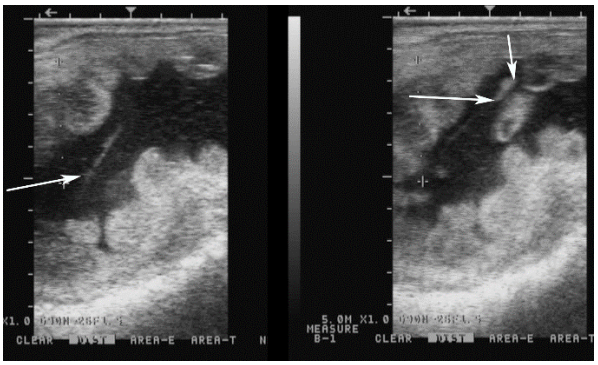

Figure 20. Ultrasonographic appearance of intraluminal adhesions after distention with fluid in a mare that was infused with commercial preparation of enrofloxacine (Baytril ®).

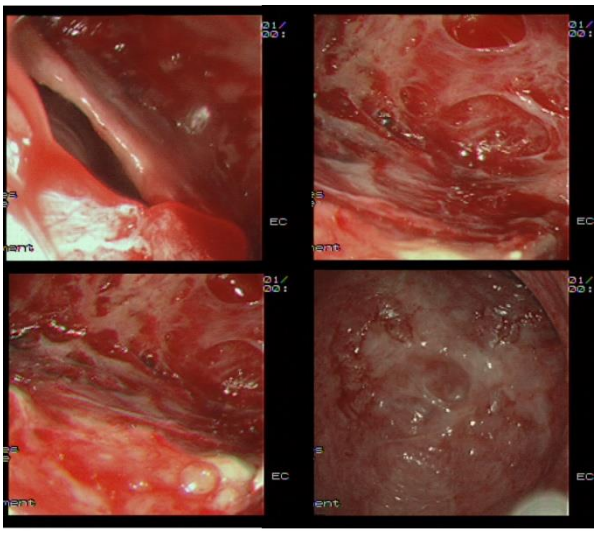

Figure 21. Hysteroscopic examination of the mare in Figure 20 showing severe intraluminal adhesions.

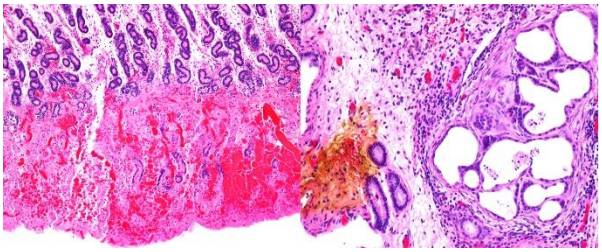

Figure 22. Endometrial biopsy from a mare that received a uterine infusion of Baytril®. Note the severe hemorrhagic peracute endometritis (left) followed by development of periglandular fibrosis and glandular nesting (right).

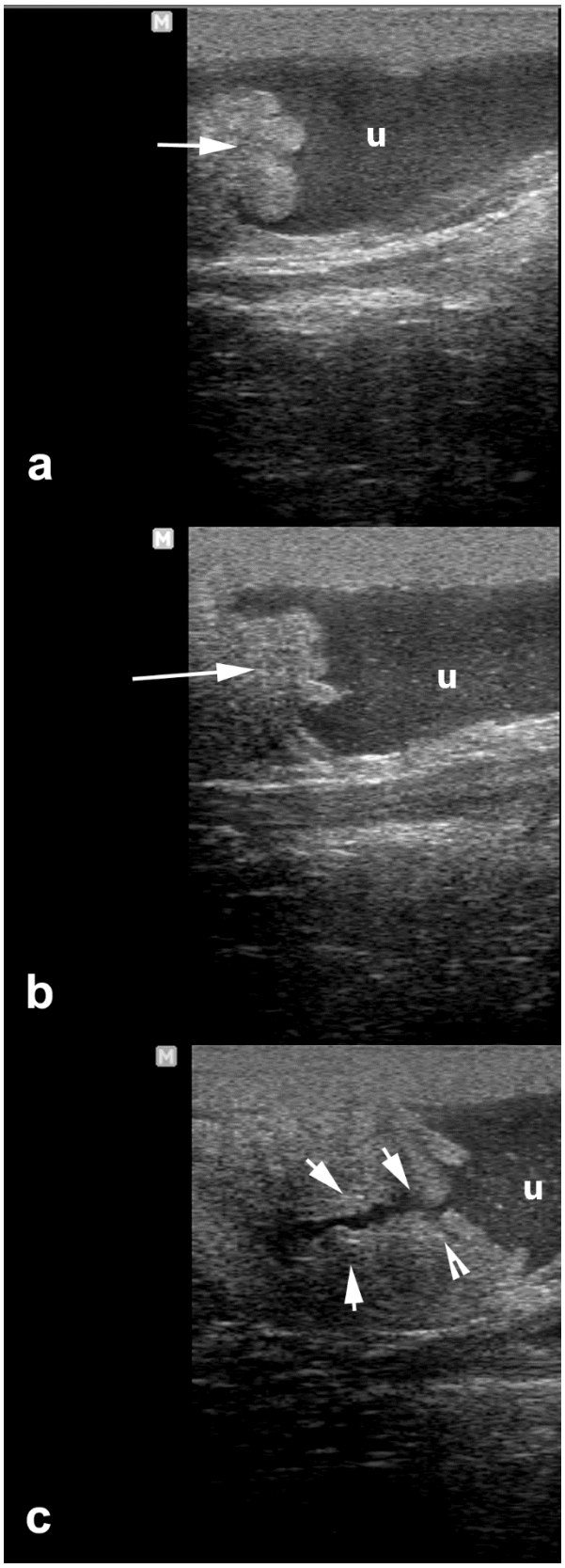

Figure 23. Ultrasonographic image of urine pooling and urometra in a mare. a-b) U= urine in the vagina, arrows indicate the cervix, c) open cervix with urine seeping into the uterus.

Pneumometra, Mucometra and Pyometra

Pneumometra (pneumouterus), presence of air in the uterus is often observed in postpartum mares with poor perineal conformation or following excessive vaginal and cervical manipulation (Figure 24). Mucometra is often observed in mares with segmental aplasia or persistent hymen (Payan-Carreira et al., 2007). Pyometra has been described in mares with severe cervical adhesions, as a complication of glass ball (Amorim et al., 2016a) and in older mares (El-Bahr and El-Deeb, 2016) (Figure 25). Mares with mucometra or pyometra may continue to reproduce via oocyte collection. Treatment of these conditions is considered when the welfare of the mare is a concern and can be approached by cervical wedge resection (Pasch et al., 2017) or hysterectomy (Prestes et al., 2018).

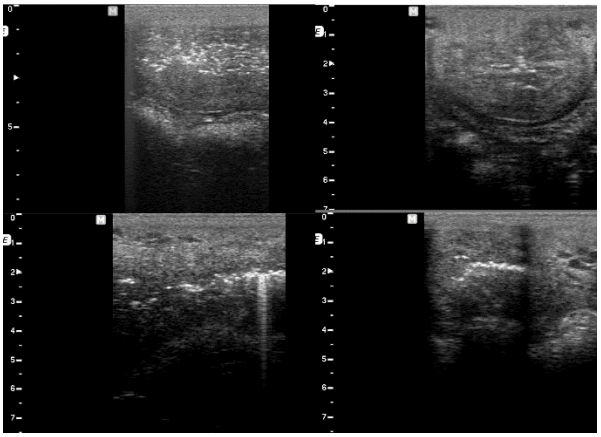

Figure 24. Ultrasonographic appearance of pneumometra in a mare

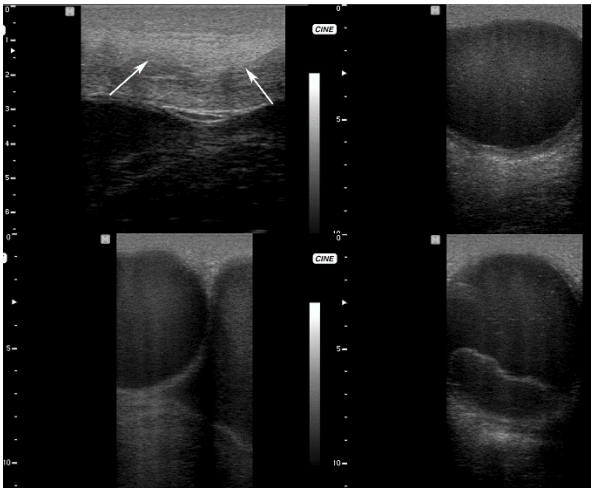

Figure 25. Ultrasonograms of a mucometra due to severe cervical adhesions/stenosis (arrows) in a mare

Congenital disorders

Except for persistent unperforated hymen, congenital reproductive abnormalities are relatively rare. Reported abnormalities include uterus unicornis (Gallacher and Gilbert, 2018; Newcombe, 1997b; Thursby-Pelham, 1997), double cervix and double uterine body (uterus bicorpora bicollis) (Kelly and Newcombe, 2009; Volkmann and Gilbert, 1989), blind vagina (Payan-Carreira et al., 2007).

Total agenesis of the endometrial glands was seen in 2 mares (Witkowski et al., 2017). Most of these abnormalities are discovered during the breeding soundness examination of the maiden mare. However, some mares with uterus unicornis are capable of carrying a pregnancy to term (Gallacher and Gilbert, 2018; Thursby-Pelham, 1997).

Uterine neoplasia

Uterine neoplasia is rare in the mare. Most cases are diagnosed as part of an infertility work up or following a complaint of persistent bloody vaginal discharge or dysuria. Uterine tumors are generally suspected on transrectal palpation and ultrasonography. Confirmation require hysteroscopy and biopsy. The most common uterine neoplasia in mares is leiomyoma which is benign and slow growing (Figures 26, 27, 28). There are several reports of successful treatment of these tumors by manual extirpation (Bradecamp et al., 2017) by partial hysterectomy (Heijltjes et al., 2009; Janicek et al., 2004; Muurlink et al., 2008), or total ovariohysterectomy (Gimplinger et al., 2009). Return to fertility is possible after tumor removal and partial hysterectomy (Quinn and Woodford, 2005). Leiomyomas that originate from the cervix are more difficult to deal with and often reoccur (Romagnoli et al., 1987). In one case, the mare had a septic metritis associated with torsion of a pedunculated uterine fibroleiomyoma (Brandstetter et al., 2005).

The uterus can be a site of metastasis of other tumors such as B cell lymphoma (Claes et al., 2015) and lymphosarcoma (Neufeld, 1973), or primary malignant neoplasia such as fibrosarcoma (Govaere et al., 2011) and adenocarcinoma (Lopez et al., 2017) (Figure 29), angioleiomyoma (Jang and Kim, 2016). Other tumors identified in the mare include fibroma (Figure 30) and rhabdomyosarcoma (Quinn and Woodford, 2005). Euthanasia is the only course of action in cases of malignant uterine neoplasia warrant

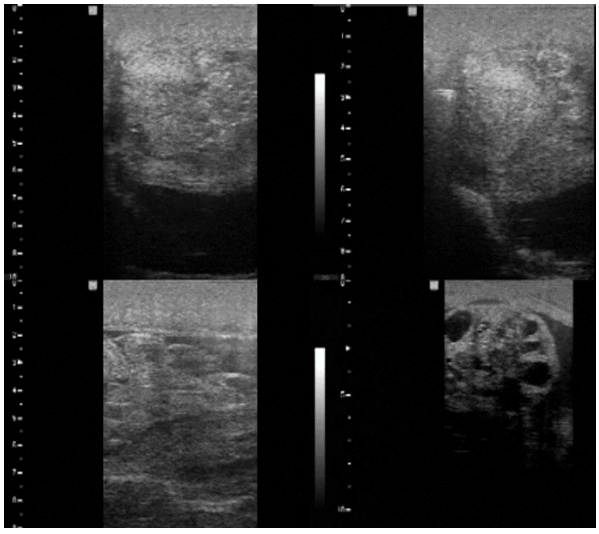

Figure 26. Ultrasonographic appearance of a leiomyoma in a mare.

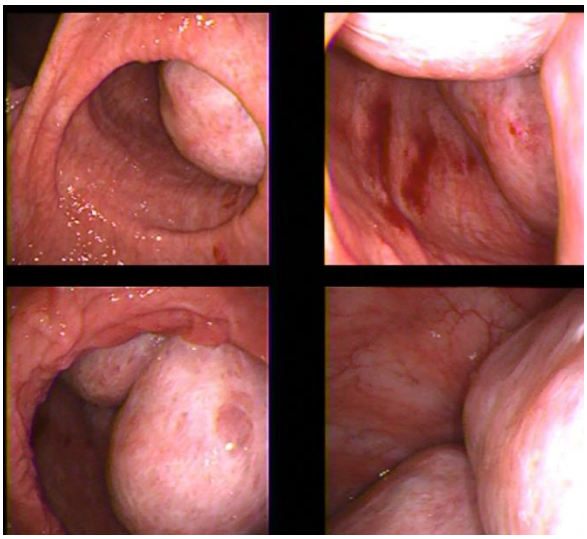

Figure 27. Hysteroscopic examination of the mare in Figure 26.

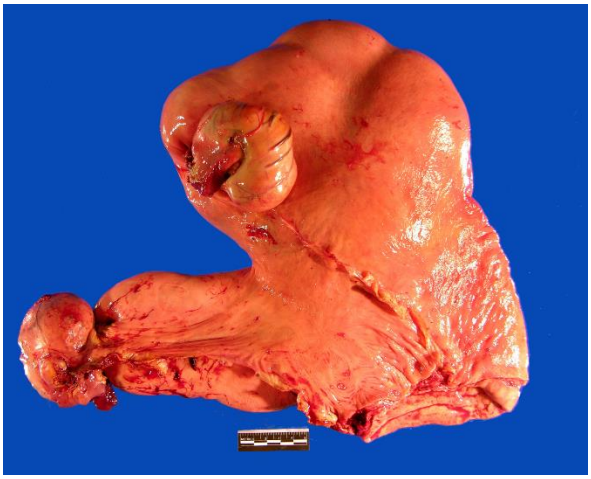

Figure 28. Postmortem examination of the uterus in Figures 26 and 27.

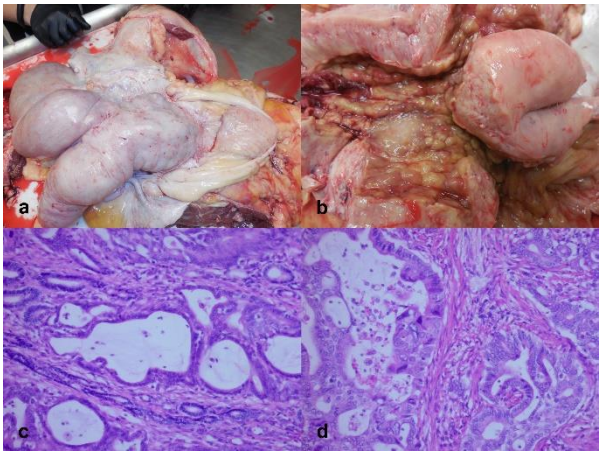

Figure 29. Gross postmortem (a-b) and histopathological (c-d) of a uterine adenocarcinoma in mare presented for dysuria and persistent straining.

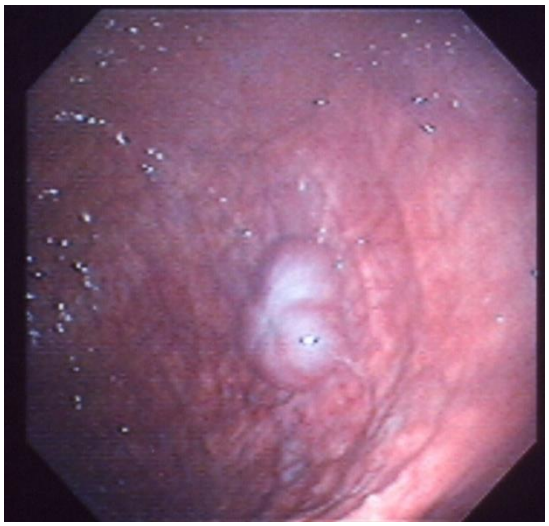

Figure 30. Uterine fibroma in a mare visualized by hysteroscopy

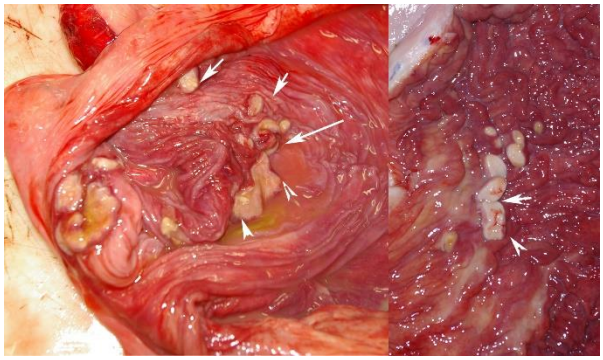

Figure 31. Gross appearance of endometrial cups in the mare (arrows)

Persistent endometrial cups

Endometrial cups originate from binucleate trophoblastic cells from the annulate chorionic girdle region. These cells invade the endometrium between day 36 and 38 of pregnancy and enlarge to form plaques (ulcer-like protuberances) that produce equine chorionic gonadotropin (eCG) responsible for luteinization of follicles and formation of accessory corpora lutea (Figure 32). The lifespan of the endometrial cups is between 60 and 90 days and is highly variable between individuals (Allen and Wilsher 2012, Crabtree et al., 2012) Endometrial cups are destroyed by hypovascular apoptosis and immunological rejection by the maternal lymphocytes, macrophages and eosinophils (Allen and Wilsher 2012). Although rare, endometrial cups may persist and remain functional for weeks or months after pregnancy loss or even normal foaling (Allen and Wilsher 2012, Crabtree et al., 2012, Steiner et al., 2006). Mare with persistent endometrial cups will be anestrous or present abnormal follicular development (anovulatory hemorrhagic or luteinized follicles). Diagnosis may be reached by visualization of hyperechoic areas at the base of one uterine horn, hysteroscopy (Figure 33), biopsy (Figure 34) or determination of serum levels of eCG (Crabtree et al., 2012). Treatment consists of removal by laser ablation or chemical curettage (kerosene infusion). Time to return to cyclicity is variable. Treatment has been associated with bacterial infection (Crabtree et al., 2012).

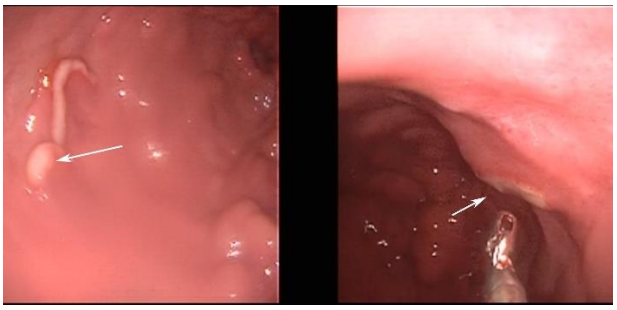

Figure 32. Persistent endometrial cups visualized by hysteroscopy (arrows)

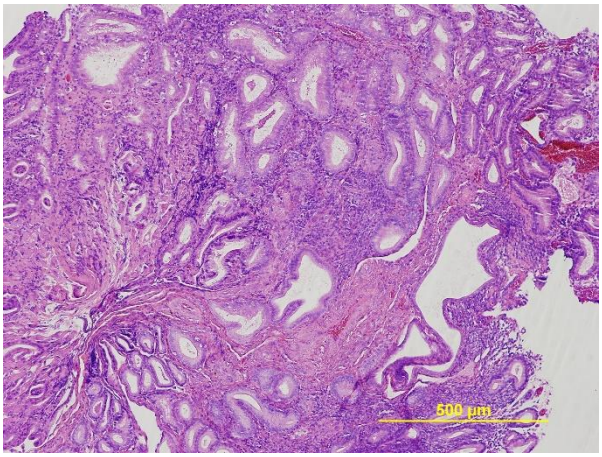

Figure 33. Endometrial biopsy at an endometrial cup site.

CONCLUSION

Diagnosis of uterine disorders requires a methodological approach based on clinical evaluation, imaging of the reproductive tract and laboratory support. Endometritis and endometrosis are the two most common uterine pathologies causing mare subfertility or infertility. Our understanding on the pathogenesis of these pathologies have led to development on diagnostic techniques and therapeutic approaches. Identification of mares that are susceptible to endometritis and their proper management through breeding allows timely conception and maintenance of pregnancy. Combination of traditional approaches and new immulogical techniques have resulted in improved fertility outcome for mares predisposed to uterine infections. Endometrosis continues to be one of the leading pathologies in the termination of the reproductive career of mares. Stem cell therapies shows some promise in the treatment of this degenerative disease but more field trials are needed to verify its efficacy.

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