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## CLINICAL UPDATE ON ENDOMETRITIS THERAPY

### Introduction

Endometritis is a major cause of mare infertility which arises from failure to remove pathogens, spermatozoa and inflammatory exudate post breeding. A complex of mare and microbial components contribute to the pathogenesis of endometritis. Mare factors are advanced age, bad perineal conformation, reduced uterine clearance due to hypo-motility of the myometrium, a pendulous uterus, endometrial and vascular uterine degeneration and fibrosis of the cervix. Similarly, microbial factors are induction of inflammatory reaction in the host, adherence to the epithelium, deep localization in the endometrium, resistance to phagocytosis and viscosity; these factors vary greatly between pathogens. As a result clinical signs of endometritis vary greatly between cases. This represents a challenge for the diagnosis of endometritis which is based mainly on clinical signs and/or the recovery of a uterine diagnostic sample enabling identification of inflammatory cells and/or the presence of pathogens. In particular subclinical endometrial infections are particularly difficult to diagnose since they are characterized by minimal or absent endometrial inflammatory reaction, therefore clinical signs are subtle or present only during certain phases of the estrous cycle and uterine cytology and bacteriology can result negative. One typical example is the subclinical infection caused by some strains of *Streptococcus Equi subsp. Zooepidemicus*, which is able to localize deep into the endometrium and enter a "dormant" state which is characterized by no inflammatory reaction in the host.

### Diagnostics

Rectal palpation and ultrasonography, uterine culture and cytology remain the most common techniques for diagnosis of endometritis, through their respective detection of intra-uterine fluid, uterine pathogens and inflammatory cells. However in mares affected by subclinical infections these diagnostic techniques might show negative results. In these cases a culture from an endometrial biopsy and histochemical examination are more effective in the diagnosis of endometritis (Nielsen 2005). Since the challenge of detecting subclinical infection is related to the quiescent state of the infection, effective ways to re-activate these subclinical infections would facilitate their diagnosis. Often subclinical infection can be re-activated by simple cervical stimulation

or following artificial insemination. A recently study by Petersen et al. (2015) showed that the intra-uterine administration of 10 ml of bActivate (Bojesen en Petersen Biotech, Denmark) was effective in re-activate subclinical *Streptococcus* infection in the 64% of mares presenting reduced fertility.

### Treatment strategies

The goal of the treatment is to promote an improvement on uterine environment for semen and embryo survival by correcting uterine defence, neutralizing virulent pathogens and controlling the post-breeding inflammatory reaction.

**Uterine irrigation.** Uterine irrigation 4 to 8 hour after breeding followed by administration of either oxytocin (10-25 IU i.v. or i.m.) or cloprostenol (250µg i.m.) remains the treatment of choice for improving the physical clearance of the uterus. Mares with fluid before breeding may be irrigated with lactated Ringer's solution 1h before insemination without causing a subsequent decrease in pregnancy rate. **Ecbolic drugs.** Oxytocin induces high amplitude myometrial contractions for approximately 30 min during estrous and in the first 2 days after ovulation. Recommended doses vary between 10 to 25 IU administered IV or IM. Prostaglandin F2alpha analogs such as cloprostenol at a dose of 250µg administered i.m. induces slightly weaker uterine contraction than oxytocin but for a significantly longer period (4 hours versus 30 min).

**Cervical dilatation.** In case of mares presenting cervical fibrosis, as consequence of cervical injuries or aging, the cervix might fail to relax and dilate during estrous. In this case ecbolics alone are ineffective in voiding intra-uterine fluid. Cervical manual dilation associated with the use of ecbolics assists fluid drainage.

**Mucolytics and Chelating compounds.** In case of subclinical infections, due to the localization of the pathogens deep in the endometrium or due to the presence of excessive mucous or biofilm, uterine irrigation and antibiotic treatment alone often fail to eradicate the infection. For this reason the use of mucolytics such as N-acetylcysteine, DMSO, Hydrogen Peroxide, kerosene and acetic acid can be beneficial.

## FROM GESTATION TO A HEALTHY FOAL

Antibiotics and/or antifungal medicines. Endometritis is commonly treated by intra-uterine infusion of appropriate antibiotics or antifungal drugs for 3 to 5 days. The antibiotic/anti-fungal treatment should be preceded by an uterine irrigation in order to eliminate any intra-uterine exudate. Mucolytic and/or chelating agents can be used together with antibiotic/anti-fungal drugs in order to enhance their action. Systemic antibiotics and antifungal drugs have also been used to treat endometritis. If systemic therapy is chosen a concurrent uterine irrigation should be performed to evacuate intra-uterine fluid.

Immunomodulators. Immunomodulators can be used in mares which develop an excessive inflammatory reaction post breeding. Immunomodulation may help to reduce the production of pro-inflammatory cytokines, thus restoring effective inflammatory mechanisms in the uterus. It has been suggested that aging may be an important contributor to this inflammatory system dysregulation. There is evidence that judicious use of corticosteroids may increase pregnancy rates in mares suffering intra-uterine fluid accumulation post breeding. Administration of prednisolone (acetate-9-alpha-prednisolone 0.1mg/kg P.O.) every 12 hours for 4 days beginning 48 hours before breeding was shown to increase the pregnancy rate in mares with a history of intra-uterine fluid accumulation. Regardless of which steroid therapy is chosen, it is important to remember that steroids should only be used in mares in which a bacterial uterine infection is excluded, since in this case their use would only further exacerbate the infection. Platelet rich plasma (PRP) administered in the uterine lumen (20ml) 4 hours after insemination showed to be effective in reducing the neutrophil's afflux to the uterine lumen, downregulating pro-inflammatory cytokines (IL-1beta, IL-6 and IL-8), reducing the formation of intra-uterine fluid and in increasing pregnancy rate in barren mares. Other immunomodulatory treatments such as mesenchymal stem cells, autologous conditioned serum, mycobacterium cell wall extract have also been shown to reduce fluid accumulation, intrauterine neutrophils number after insemination in mare susceptible to post breeding induced endometritis.