

Treatment of infectious infertility

S.P. Brinsko

Department of Large Animal Clinical Sciences, Texas A&M University, College Station, TX

Introduction

Infectious infertility has repeatedly been identified as major source of economic loss to the equine breeding industry for over 50 years. Despite the development and use of a variety of antimicrobial agents, apparently little progress has been made in reducing the percentage of mares that remain barren due to infectious etiologies which casts some doubt as to the role of bacteria as primary causative agents.^{1,2} Reasons for this are not completely understood, likely because infectious infertility is a multifactorial phenomenon involving breeding management, diagnostic and treatment modalities and inherent resistance to infection.

Far too often the veterinarian's antimicrobial armamentarium is relied upon to overcome less than optimal breeding hygiene and management. This practice will not improve the overall fertility on a breeding farm. Instead, the veterinarian should play an active role in the breeding program by accurately assessing the condition of the mare's reproductive tract during estrus and scheduling breedings as close as possible to ovulation. Limiting the number of breedings required per cycle and instituting the use of minimum contamination techniques reduces the potential for uterine contamination whether natural cover or artificial insemination is utilized. By being integrally involved with the breeding program, the veterinarian is better able to correctly identify problem mares and initiate therapy when needed.

An important aspect of addressing infertility is correctly identifying and treating mares that are truly infected. Unfortunately, many breeding farms are under the erroneous assumption that unless mare has a negative bacteriologic uterine culture, she is unfit to breed. The primary role of bacteriologic culture of the mare's reproductive tract is not to determine whether or not a mare is infected, but rather to identify causative organisms and obtain antimicrobial sensitivity patterns so that appropriate therapy can be instituted. It cannot be over-emphasized that a positive bacteriologic culture in the absence of concurrent signs of inflammation does not indicate infection. Ignoring this fact results in treatment of noninfected mares and more importantly, other factors which could be contributing to their infertility may be overlooked. Likewise, a negative aerobic culture in the presence of clinical, cytologic, or histopathologic signs of inflammation suggest the culture should be repeated and that other causes of inflammation should be investigated. Although anaerobes, viruses and mycoplasma may be isolated from the endometrium, their clinical significance is largely unknown. Uteri of mares with accumulations of purulent material may yield no bacterial growth when cultured. Apparently, the nature of such fluids may somehow inhibit the recovery of bacteria. Pneumovagina and urovagina can cause endometritis without a concurrent bacterial contribution to the inflammation.

Treatment of infectious infertility begins with correcting predisposing causes. Mares with intact uterine defense mechanisms do not become infected even when challenged with massive bacterial inocula, whether naturally or experimentally introduced.^{3,4} Apparently, the initial uterine response to the inoculum is the same for resistant and susceptible mares. However, susceptible mares are unable to maintain an effective response or to mechanically clear the uterine lumen of contaminants so as to prevent infection. In order for a mare's uterus to become infected there must be a breakdown in her humoral, cellular or mechanical uterine defense mechanisms.⁵⁻⁷ Defects in the mechanical barriers probably occur most commonly and are the most easily corrected. The vulvar labia, vestibulovaginal seal, and the cervix are the three mechanical barriers to ascending infection in the mare. Disruption of any one of these barriers, as is common in older mares due to age-related changes, multiple foalings or trauma, predisposes the uterus to repeated contamination which can overwhelm the uterine defense mechanisms. Surgery to correct pneumovagina and/or urovagina, improving breeding techniques to enhance hygiene and elimination of excessive breedings are the most efficient and beneficial means by

which therapy for infections infertility is initiated. Many mares spontaneously overcome endometritis once the source of repeated uterine contamination is eliminated. A Caslick's operation (vulvoplasty) can be one of the most effective means of managing infectious infertility.

Keywords: Mare, infertility, endometritis

Therapeutic strategies

Over the years intra-uterine infusion with a variety of antibiotic and antiseptic solutions has been utilized in an attempt to eliminate infectious endometritis in mares. These substances have ranged from agents such as kerosene, floor cleaners, chlorine and iodine solutions to potent antibiotics. Unfortunately, many of these treatments were instituted without knowledge of their efficacy or potential detrimental effects. As a result, numerous mares have been rendered permanently infertile due to irreparable damage caused by therapies which were more damaging than the original condition being treated. The use of chlorhexidine solution for intra-uterine infusion is strongly discouraged, since it can have devastating effects on the mare's reproductive tract.⁸ Veterinarians must adhere to the basic tenet of "do no harm" when treating genital infections just as with any other organ system. Therefore, the drug and its vehicle should be relatively nonirritating. Almost any substance instilled in the mare's uterus, including physiological saline, will induce some degree of an inflammatory response. However, it is the intensity and duration of this response which is of primary concern with regard to fertility, especially when treatment is performed close to breeding and/or ovulation. Inflammation persisting beyond five days post-ovulation can adversely affect fertility by causing early embryonic death either directly or by inducing premature luteolysis.

Antibiotic therapy

The traditional approach to antibiotic therapy for the treatment of infectious endometritis has been via intrauterine infusion; however, some practitioners report satisfactory results using systemic administration of various antibiotics.^{2,9} While eliminating the potential for repeated genital tract contamination during treatment by the systemic approach is advantageous, lower antibiotic concentrations are generally achieved in the endometrium and uterine lumen depending on the antibiotic used.¹⁰⁻¹² While the effectiveness of systemic treatment of endometritis has not been determined by controlled studies, the fluoroquinolones appear to show promise for systemic treatment of endometritis in mares. Therapeutic endometrial levels of enrofloxacin (Baytril®, Bayer Animal Health, Shawnee, KS) can be achieved when the drug is given orally or parenterally. Unfortunately, this drug has poor activity against *Streptococcus sp.*, which is the most common bacterial cause of equine endometritis. Although ampicillin can achieve high concentrations in the endometrium when given parenterally, administration at four to eight hour intervals is required to maintain adequate levels.¹⁰ Systemic administration of antibiotics for the treatment of endometritis would therefore necessitate larger doses given more frequently, thereby increasing the cost of treatment. In contrast, when ampicillin (3 grams) is administered via intrauterine infusion, endometrial concentrations of the drug still exceeded minimal inhibitory concentrations for *Streptococcus sp.* 24 hours after treatment.¹³ Since the vast majority of genital infections in the mare are limited to the endometrium, they are likely to respond most favourably to local therapy. However, more severe infections of the uterus and other genital tissues such as postpartum metritis would warrant systemic use of antibiotics.

Topical treatment of the endometrium by infusion of antibiotics through the cervix constitutes the vast majority of treatments for endometritis. When this approach is utilized, scrupulous attention must be paid to aseptic technique. Uterine infusion should be continued for a minimum of three to five days. The volume of the drug and its vehicle should be sufficient to distribute the drug throughout the uterus and provide contact with the entire endometrial surface area. Volumes of 200-250 ml are commonly used but often result in a portion of the drug exiting

through the cervix, especially when the mare is in estrus. Smaller volumes of 60 to 120 ml are adequate to attain the desired result in most mares when combined with gentle uterine massage per rectum. A list of drugs commonly used for the treatment of bacterial endometritis is provided in Table 1.

Antibiotics should be selected based on *in vitro* culture and sensitivity patterns so that they are as specific as possible for the organisms involved. Even though *in vitro* and *in vivo* sensitivities may differ, the temptation to routinely use broad spectrum antimicrobial agents must be discouraged since indiscriminate use can lead to the development of resistant strains and/or overgrowth of more pathogenic bacteria, yeasts or fungi. Another consideration regarding the antibiotic selection is antibiotic-neutrophil interaction. Several antibiotics (e.g. gentamicin, amikacin, tetracyclines, and polymixin B) have been reported to interfere with neutrophil function.⁷

Often times, temporal constraints imposed by the limited breeding season in the equine do not permit the luxury of waiting for culture and sensitivity results before instituting therapy. In these situations, therapeutic agents should be chosen based upon knowledge of the most common causative organisms. The majority (70-80%) of aerobic bacteria confirmed to be associated with endometritis in mares are, in descending order of frequency, *Streptococcus zooepidemicus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*.^{2,6} With this in mind, an antibiotic such as ampicillin which is generally effective against *Strep. zooepidemicus* and many strains of *E. coli* would be an appropriate choice while awaiting laboratory confirmation. Unfortunately, veterinary sources of ampicillin are now limited and the cost of the drug has increased dramatically in recent years. In addition, some practitioners have encountered increased resistance of *E. coli* to ampicillin. Timentin (ticarcillin/clavulanate) and gentamicin are usually effective against most of the causative organisms, but for the reasons discussed above, they should not be used indiscriminately. Enrofloxacin is very effective against *E. coli* as well as a number of other endometrial pathogens. However, intrauterine use of enrofloxacin is not recommended in the mare because its high pH results in an inflammatory response that can take up to two weeks to resolve.¹⁴ Another therapeutic approach that can be utilized while awaiting culture and sensitivity results is uterine lavage. Uterine lavage is especially advantageous if the mare has been unsuccessfully treated with antibiotics previously and where yeast or fungal infections are suspected.

Uterine lavage

Uterine lavage alone or in conjunction with antibiotic therapy appears to be beneficial in the treatment of infectious endometritis.¹⁵ The rationale for using uterine lavage in the treatment of uterine infections is based upon: 1) reduction of bacterial numbers and removal of exudates from the uterine lumen, 2) enhanced physical clearance of uterine contents by stimulation of uterine contractions, and 3) recruitment of "fresh" circulating neutrophils and possibly opsonins by inducing transient irritation of the endometrium.⁵ Uterine lavage should improve the efficacy of intrauterine antibiotic treatment by reducing foreign material within the uterine lumen. This is especially true for antibiotics of the aminoglycoside and polymixin groups which become highly bound to purulent material.^{16,17}

Uterine lavage is typically performed by repeated instillation of one to 1.5 liters of a warmed (42-45 °C) solution by gravity-flow through a large-bore (8 mm inner diameter) balloon-cuffed catheter. Nulliparous mares may only be able to accommodate 750 ml of lavage fluid. Once the desired volume is infused, the catheter can be clamped and the uterus massaged per rectum to distribute the solution throughout the uterine lumen. The effluent is then collected in a clear receptacle to assess volume and clarity. This process is repeated sequentially, several times for several days depending on the character of the effluent. An appropriate antibiotic is infused daily once the effluent is relatively clear. Daily lavages can usually be discontinued when the

effluent from the first lavage of the day returns with a similar appearance to that which was instilled into the uterus.

Preferred media for uterine lavage are generally isotonic saline or other balanced salt solutions such as lactated Ringer's solution (LRS), with or without dilute povidone-iodine added. Care must be taken when using povidone-iodine solutions since concentrations $\geq 2\%$ have been shown to induce severe inflammatory responses in the equine endometrium.^{18,19} Stock povidone-iodine solutions are typically 5% or 10% povidone-iodine, equivalent to 0.5% or 1% available iodine, respectively. Inflammatory changes were not detectable in equine endometrial biopsy samples six days after treatment with a 0.05% povidone-iodine solution (5 mL of 10% stock solution in one liter of saline).²⁰ Bactericidal activity of povidone-iodine in vitro is maintained at concentrations as low as 0.01 to 0.005%.^{21,22} Postbreeding uterine lavage appears to be a viable treatment alternative for mares susceptible to uterine infection, particularly for those mares that suffer from chronic postbreeding endometritis despite the use of minimal contamination techniques. A primary concern is the minimum time interval between breeding and uterine lavage which will not adversely affect fertility. Initial reports of successful postbreeding therapy combining uterine lavage followed by plasma infusion delayed treatment until ovulation had occurred. Performing uterine lavage as soon as possible after breeding however should minimize the time available for microbial contaminants to multiply and become established. Uterine lavage performed within two hours of insemination reduces pregnancy rates in normal mares. However, uterine lavage using either physiologic saline or a 0.05% povidone-iodine solution at four hours post-insemination has no detrimental effect on fertility.²³ The ability to perform uterine lavage soon after breeding facilitates removal of bacteria and debris so that uterine contamination is less likely to progress to uterine infection. This technique should be especially advantageous for treating susceptible mares which, due to breed restrictions, must be bred by natural cover and thus are at risk of a higher level of uterine contamination. For mares that have significant luminal fluid while in estrus, uterine lavage with LRS can also be performed immediately prior to breeding without adversely affecting fertility.²⁴

Plasma infusion

In the early 1980's, intrauterine infusion of autologous plasma became a popular treatment for infectious infertility; particularly in mares with chronic postbreeding endometritis. Both serum and plasma provide neutrophil-enhancing proteins involved in the opsonization of bacteria within the mare's uterus.^{5,7} Although autologous plasma is recommended for this treatment, heterologous plasma has been used. The possibilities of hypersensitization and transmission of infectious agents should be considered if heterologous plasma is used. The techniques for harvesting and handling plasma for intrauterine infusion have been described.⁵ Successful use of intrauterine plasma infusion has been reported in clinical settings; however, controlled studies present conflicting evidence regarding the beneficial effects of this treatment for correcting infectious infertility. In recent years, this treatment modality has largely gone out of vogue.

Bacteria-free filtrate

Intrauterine infusion with bacteria-free filtrate of *Streptococcus zooepidemicus* may improve fertility of some barren mares.²⁵ The rationale for this treatment modality is based upon the filtrate's ability to chemically stimulate an acute inflammatory response within the uterus, thus recruiting "fresh" neutrophils and opsonins.

The uterus is infused once during estrus with 50-80 ml of filtrate which results in an intense inflammatory response that peaks six to ten hours after inoculation. Since non-functional neutrophils and other debris within the uteri of chronically infected mares may interfere with the function of the newly recruited neutrophils, it is likely that removing this material by performing uterine lavage prior to filtrate inoculation would enhance the desired response.

Immunomodulators

Over the years, a number of products have been used empirically to overcome endometritis by stimulating the mare's immune system. These include levamisole, mebendazole and nonviable *Propionibacterium acnes* (EqStim®, Neogen Corporation, Lexington, KY). Controlled studies evaluating the efficacy of these products for the treatment of equine endometritis are lacking.

Recently, the USDA approved an emulsified product derived from the cell wall of *Mycobacterium phlei* (Settle®, Bioniche, Athens, GA) for the treatment of endometritis caused by *Streptococcus zooepidemicus*. This product is reported to modulate the endometrial immune response, reduce bacterial contamination of the uterus and improve pregnancy rates when compared to placebo treated mares. Routes of administration are intravenous or intrauterine and the product can be used as a stand alone therapy or in conjunction with other therapeutic modalities such as antibiotics or uterine lavage.

Hormonal therapy

During estrus, the uterus of the mare is dominated by estrogen and is more capable of eliminating uterine infections than is the progesterone dominated diestrual uterus. Factors which may contribute to the estrous mare's resistance to infection include decreased microbial binding to the endometrium, enhanced neutrophil function and improved physical clearance mechanisms. Mares with acute endometritis often have shortened estrous cycles. This results from the inflamed endometrium releasing endogenous prostaglandin, causing premature luteolysis. Exogenous prostaglandin administration five to six days post-ovulation can be used to mimic this response in chronically infected mares, thereby increasing the percentage of time that these mares are in physiologic estrus. Exogenous administration of estrogens to cyclic mares, on the other hand, had not been demonstrated to be beneficial in the treatment of endometritis. Most commercially-available estrogens are esterified or otherwise altered to increase their potency and duration of action, making the mare's response to such preparations unpredictable.

Ecbolics such as oxytocin and prostaglandin, are commonly used to treat endometritis by aiding in the evacuation of uterine contents with or without concurrent uterine lavage. However, it is the author's opinion that if the endometritis has an infectious etiology, ecbolics alone will be less effective than combining the treatment with uterine lavage or antimicrobial therapy. Oxytocin (20 units IV or 20 to 40 units IM) is the most common ecbolic used and it can be administered during estrus and after ovulation with out detrimental effects, provided that it is not administered within four hours of insemination. Prostaglandins can also be used, but they should be used more judiciously because of their longer duration of action and colic-like side effects. When administered at a dose of 250 µg IM, the prostaglandin analog, cloprostenol (Estrumate®, Schering-Plough Animal Health, Summit, NJ) is a very effective ecbolic with fewer side effects than dinoprost tromethamine (Lutalyse®, Pfizer Animal Health, New York, NY). Unlike oxytocin, prostaglandins only should be used with caution on or after the day of ovulation on the cycle in which a mare is bred because progesterone levels are adversely affected and pregnancy rates can be reduced.^{26,27}

When older, maiden mares are bred, it is common for them to suffer from persistent postbreeding endometritis. This is often due to failure of the cervix to relax, resulting in poor uterine clearance and fluid accumulation. The use of a prostaglandin E₁ analog, misoprostol (Cytotec®, G.D. Searle & Co., Chicago, IL) enhances cervical softening and dilation. A thick paste is made by mixing crushed tablets with a small amount sterile lubricating jelly and applying the paste in and on the cervix. Doses ranging from 200 µg to 2000 µg have been used. Lower doses may require four to six hours for maximal effect, while higher doses reportedly are faster acting. In humans, this drug can induce strong uterine contractions, but this has not been

observed in mares. The naturally occurring prostaglandin E₂, dinoprostone, available from a number of manufacturers in suppository and gel forms for cervical ripening in humans, has also been used in mares. Misoprostol appears to be as efficacious as dinoprostone however, dinoprostone is much more expensive.²⁸

Mycotic endometritis

Fungal and yeast infections of the equine uterus occur most commonly in older mares which have undergone intensive intrauterine antibiotic therapy or repeated uterine manipulations such as embryo transfer. These mares usually have poor perineal conformation and/or other disruptions of their uterine defense mechanisms resulting in chronic uterine contamination and therefore, repeated treatment. It is not uncommon for mares with mycotic endometritis to be concurrently infected with resistant strains of *Pseudomonas* or *Klebsiella*.^{29,30} Fungi and yeasts are common environmental and external genital contaminants^{31,32} which can be introduced at coitus, during gynecologic procedures, or as a result of pneumovagina. The most frequently isolated organisms appear to be species of *Candida* and *Aspergillus* although many other yeasts and molds have been reported.^{30,32}

Therapy of mycotic endometritis, as with bacterial endometritis, should be based upon culture and sensitivity results. Many yeast infections (*Candida* spp.) can be treated with nystatin, whereas amphotericin B is recommended for fungal infections (*Aspergillus* spp.), although it is also effective against *Candida*. Most therapeutic regimens employ human vaginal preparations. Common therapeutic drugs for fungal and yeast infections are presented in Table 2. It is important to treat the vaginal and vestibular vaults as well as the clitoral area to help ensure elimination of the organisms. Saline or sterile water can be used as a vehicle, but sterile water is the recommended diluent for amphotericin B, since a precipitate forms when saline is combined with this drug.

Good clinical results can be achieved when using povidone-iodine solutions to treat intrauterine mycotic infections however, great care must be taken with this approach. Higher concentrations of povidone-iodine are generally required to eliminate mycotic infections than are required to treat bacterial infections. In the author's opinion, concentrations exceeding 2% povidone-iodine should not be used to treat genital tract infections in mares. Some mares are most sensitive than others to the effects of povidone-iodine and must be closely monitored for signs of hypersensitivity. Inflammatory responses severe enough to result in transluminal adhesions are possible.

Recently, the use of lufenuron (Program® suspension for cats, Novartis Animal Health Greensboro, NC) in conjunction with uterine lavage has reported to be successful for treatment of yeast and fungal endometritis in the mare.³³ Lufenuron is an insect development inhibitor that works by interfering with chitin formation. Since fungal and yeast organisms are surrounded by chitin-rich cell walls it is postulated that the development of these organisms should also be disrupted by treatment. Fungal and yeast infections are notoriously difficult to resolve and as with other therapeutic modalities, anecdotal reports of lufenuron therapy have been mixed, however a number of the reports are encouraging.

Uterine lavage prior to infusion of any antimycotic agent would likely be a valuable adjunct to therapy for the same reasons described for bacterial infections. After the therapeutic course of antimycotics has been completed, correction of conformational defects which contribute to uterine contamination must be performed to prevent re-infection.

Summary

Therapy of infectious infertility begins with correcting predisposing factors. Therapeutic agents should be selected based on efficacy, specificity and safety. Uterine lavage used in conjunction with other therapeutic regimens is likely to improve response to therapy. Simply treating uterine infections without eliminating the cause is an exercise in futility. Repeated

intrauterine infusion of antimicrobials is no substitute for sound reproductive management and could prove to be detrimental.

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Table 1. Suggested Intrauterine Antibiotics

Drug	Dose	Comments
Amikacin sulfate	2 grams	Gram-negative spectrum; buffer with equal volume of 7.5% NaCO ₃
Ampicillin	1-3 grams	<i>Streptococci</i> and some <i>E. coli</i>
Ceftiofur sodium (Naxcel®)	1 gram	Broad spectrum
Gentamicin sulfate	1-2 grams	Broad spectrum; buffer with equal volume of 7.5% NaCO ₃
Kanamycin sulfate	1-2 grams	<i>E. coli</i> : toxic to sperm
Penicillin (K ⁺ or Na ⁺ salt)	5 million units	Economical & very effective against <i>Streptococci</i>
Polymixin B	1 million units	<i>Pseudomonas</i> ; inactivated by organic debris
Ticarcillin/clavulanate (Timentin®)	3-6 grams	Broad spectrum

Adapted from 8.

Table 2. Suggested Intrauterine Antimycotic Agents

Drug	Dose	Comments
Amphotericin B	200-250 mg	Fungi & yeast; dilute in 100-250 mL of sterile water, makes a relatively insoluble suspension
Clotrimazole	500-700 mg	Yeast; crush tablets and mix with 40-60 mL of sterile water
Lufenuron (Program® suspension for cats)	540 mg	Fungi & yeast; dilute in 60 ml saline; treat once after uterine lavage
Miconazole	200 mg	Yeast & fungi; dilute in 60 ml saline & infuse daily up to 10 days
Fluconazole	100 mg	Fungi & yeast; adjust pH to 7 & infuse daily for 5-10 days
Povidone-iodine	1-2% (v:v)	Yeast & fungi; note strength of stock solution; lavage daily 5-10 days
Vinegar	2% (v:v)	Yeast; 20 mL/L saline, lavage daily 5-10 days

Adapted from 8.