Treatment of placentitis: where are we now?
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Placentitis continues to represent a significant cause of pregnancy loss for the mare. Placentitis is most commonly caused by bacteria ascending through the vagina.\textsuperscript{1,2} \textit{Streptococcus equi} subsp. \textit{zooepidemicus} (\textit{S. zooepidemicus}) is the bacteria most frequently isolated from clinical cases of placentitis.\textsuperscript{1,3} Placental pathology is generally localized to the area of the cervical star with thickening and separation of the chorioallantois from the endometrium.\textsuperscript{1,3,4} Affected mares usually have a vulvar discharge, develop an udder, and deliver a premature, compromised or dead foal. In chronic placentitis, a foal may be born precociously mature for gestational age if premature labor is delayed.\textsuperscript{5} Therefore, the treatment goal in mares with placentitis is to prolong gestation long enough to allow fetal maturation and delivery of viable neonate.

Information from a well-established model of placentitis has directed treatment approaches.\textsuperscript{6-10} While bacterial infection is thought to initiate disease, secondary inflammation and prostaglandin production are likely culprits in premature delivery of foals. Mares with induced placentitis showed higher concentrations of IL-6 and IL-8 in their placentas, elevated concentrations of prostaglandins E\textsubscript{2} and F\textsubscript{2α} (PGE\textsubscript{2} and PGF\textsubscript{2α}) in allantoic fluid and increased duration and intensity of uterine contractions when compared to uninfected, control mares.\textsuperscript{6,7,11} Histopathologic findings from the placentitis model revealed bacteria on the chorionic surface, allantoic and umbilical inflammation, and bacterial colonization in fetal lungs.\textsuperscript{4} It is postulated that fetal infection is established by passage of bacteria through fetal membranes and into amniotic fluid that the fetus inhales or swallows. Therefore, it is likely that both infection and inflammation are important in placentitis-induced preterm delivery. As such, treatment approaches are directed at bacterial eradication, control of inflammation and amelioration of uterine contractions.

Several therapeutic agents that are commonly administered in clinical practice (antimicrobials, anti-inflammatories and progestins) have been tested in mares with experimentally-induced placentitis. Placental drug transfer in mares with placentitis was investigated using a novel \textit{in vivo} microdialysis system to measure drug concentrations in allantoic fluid after administration.\textsuperscript{12,13} Penicillin and trimethoprim sulfamethoxazole (TMS) achieved minimum inhibitory concentration (MIC) against \textit{S. zooepidemicus} in allantoic fluid of mares with induced placentitis, while gentamicin was detectable at concentrations effective to treat \textit{Escherichia coli} and \textit{Klebsiella pneumoniae} (also implicated in placentitis). Drugs were present for up to four hours in allantoic fluid but at concentrations lower than those in serum. Pentoxifylline was detected in allantoic fluid of experimentally-infected mares, but flunixin meglumine was not. The highly protein-bound nature of flunixin meglumine likely prevented passage of this drug through the microdialysis membrane, thus rendering results regarding placental passage of the drug inconclusive. However, flunixin meglumine is still used as an anti-inflammatory drug of choice in clinical cases of placentitis.

Foal viability after mares were treated with a variety of drug combinations has also been assessed. Long term administration of TMS and pentoxifylline tended (\textit{P} = 0.07)\textsuperscript{14} to extend gestational length in mares with placentitis when compared to infected, untreated mares. However, foal survival was not improved in treated animals (one live foal in each group). Interestingly, TMS and pentoxifylline were present in fetal and placental tissues. So, while TMS and pentoxifylline show good penetration of placental and fetal tissues, this drug combination was insufficient to prevent preterm delivery in this study.

Progestins (altrenogest; Regu-Mate\textsuperscript{®}, Intervet/Schering-Plough Animal Health, Summit, NJ) have also been combined with TMS and pentoxifylline to treat mares with induced placentitis.\textsuperscript{15} Progestins are postulated to promote uterine quiescence through reduction in myometrial gap junctions and oxytocin receptors.\textsuperscript{16,17} Administration of progestins in women with high risk pregnancies has shown to reduce the incidence of preterm labor, and this treatment has become standard practice.\textsuperscript{18} When mares with induced placentitis were administered TMS, pentoxifylline and altrenogest, 10 of 12 (83\%) delivered viable
foals.\textsuperscript{15} All five untreated, infected mares aborted or delivered non-viable foals. Most live foals had negative blood cultures at birth and normal parameters for complete blood count, serum chemistry, cortisol and IgG. It was concluded, from these data, that mares with placentitis benefited from treatment using an antimicrobial, anti-inflammatory agent and progestin. The authors of this study were careful to note that early initiation of treatment after experimental infection (within 96 hours) likely contributed to the high number of live foals in this study.\textsuperscript{15}

Recently, workers from Mississippi used an evidence-based approach to evaluate different treatment protocols in mares with induced placentitis. Mares were administered TMS, alone, or combined with anti-inflammatory agents (dexamethasone and aspirin), and/or with progestins (altrenogest + aspirin).\textsuperscript{19} Interestingly, mares administered TMS, alone, were as likely to deliver viable foals (4/6; 63\%) as mares administered TMS in combination with dexamethasone, aspirin and altrenogest (13/18; 72\%). These data prompt the question of whether anti-inflammatory agents are important to treatment of placentitis, or whether antibiotics (TMS) are sufficient to treat the disease. Interestingly, work in non-equine species suggests that multifaceted therapy is warranted for prevention of preterm delivery. Using a non-human primate model of placentitis, workers examined the effects of anti-inflammatory agents (indomethacin\textsuperscript{20}, dexamethasone and interleukin-10\textsuperscript{21}) to stop preterm delivery. In all experiments, treated monkeys had lower amniotic fluid prostaglandin concentrations and uterine contractions than untreated controls. None of the agents effectively inhibited production of pro-inflammatory cytokines. Administration of dexamethasone prevented preterm delivery of fetuses. The effect of antibiotic, alone, was also tested in the primate model. Monkeys inoculated with group B streptococci (in the amniotic cavity) were administered ampicillin, alone, or in combination with dexamethasone and indomethacin.\textsuperscript{22} Ampicillin effectively eradicated bacteria from the amniotic fluid of infected animals. However, amniotic fluid cytokines, prostaglandins and uterine contractions persisted in the face of maternal antibiotic treatment. When dexamethasone and indomethacin were added to ampicillin, cytokines and prostaglandins were suppressed as were uterine contractions. From these studies, one can speculate whether antimicrobials, alone, are more effective early after infection and anti-inflammatory treatment becomes important in more chronic disease. Unfortunately, in a practical setting, it is often difficult to predict the onset of placentitis and treatment must be initiated quickly. In these cases, it can be difficult to select a conservative treatment approach.

Limitations in antimicrobial choices are also problematic for the practitioner treating mares with placentitis. Oral administration of drugs is ideal in a field setting. However, TMS-based therapy does not consistently result in delivery of a live foal. Additionally, over 50\% of uterine cultures obtained immediately postpartum from mares with induced placentitis were positive for \textit{S. zooepidemicus} despite prolonged administration of TMS.\textsuperscript{15} This is in contrast to negative uterine cultures obtained from normal foaling mares.\textsuperscript{23} Studies have shown that TMS is not consistently effective in eradicating \textit{S. zooepidemicus}, \textit{in vivo}, despite \textit{in vitro} susceptibility of pathogens and high concentrations of TMS at the site of infection.\textsuperscript{24} However, few alternative oral preparations of antimicrobials are available, as are parenterally administered drug choices that can be used in field conditions.

Ceftiofur, a third generation cephalosporin, has excellent bactericidal activity against streptococcal organisms as well as many gram negative aerobes and some anaerobes.\textsuperscript{25-27} Ceftiofur penetrates body fluids, the endometrium, joints and pulmonary sites of infection with concentrations that equal or rival ampicillin or potentiated sulfonamides.\textsuperscript{28,29} Ceftiofur sodium, marketed as Naxcel\textsuperscript{\textregistered}, is a commonly used antimicrobial in equine practice. While not as convenient as orally administered TMS, once daily, intramuscular injection of ceftiofur sodium provides a practical method of administering a parenteral drug. However, the effectiveness of ceftiofur sodium for treating mares with placentitis is unknown.

In 2010 Pfizer Animal Health (New York, NY) received Federal Drug Administration approval for the use of long-acting ceftiofur crystalline free acid (CCFA; Excede\textsuperscript{\textregistered}) for treatment of horses. Excede\textsuperscript{\textregistered} has broad appeal for the equine practitioner because it provides therapeutic drug levels in horses for 10 days when administered at four day intervals. Additionally, CCFA is a potent antimicrobial against \textit{S. zooepidemicus}. In many ways, this exciting new drug would appear to be the perfect
antimicrobial treatment for mares with placentitis. Consequently, Excede® was recently tested in mares to
determine the ability of the drug to penetrate fetal membranes and the effectiveness of the drug for
preventing abortion in mares with induced placentitis. Mares were administered Excede®, alone (n=3) or
in combination with pentoxifylline and altrenogest (n=6). Three mares served as infected, untreated
controls. Concentrations of ceftiofur metabolites were measured as an indicator of drug distribution in
mares, foals and placental tissues using high performance liquid chromatography (HPLC; University of
CA Davis).

Serum concentrations of ceftiofur metabolites in mares were consistent with expected profiles
after administration of this drug.* However, drug concentrations measured in fetal and placental tissues
were considerably below therapeutic concentrations indicating low penetration of ceftiofur metabolites
across fetal membranes. Further, foal survival was poor after treatment with this drug ( live foals = 0/3
after Excede® alone, and 2/6 after combination treatment). Bacterial eradication using this antibiotic was
not achieved in uterine or foal samples from animals with confirmed bacterial infections after inoculation.
It is likely that much higher serum concentrations of ceftiofur metabolites would be necessary in order to
achieve therapeutic concentrations in placental and fetal tissue. However, since, Excede® is slowly
released from the site of injection it does not tend to provide very high serum concentrations even with
higher dose administrations. Therefore, ongoing work is investigating the ability of ceftiofur sodium to
pass through fetal membranes and attain therapeutic concentrations in fetal fluids and tissues.

In summary, conscientious treatment of equine placentitis is challenging. Data regarding
treatment are sometimes conflicting, and results after treatment in a clinical setting can be disappointing.
Yet, salvaging a pregnancy can be enormously rewarding. Ongoing efforts by several investigators are
focusing on earlier diagnostic methods, allowing for more rapid initiation of treatment, and hopefully,
more consistent effects of treatment.

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