EQUINE PLACENTITIS: DIAGNOSIS AND TREATMENT OPTIONS

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INTRODUCTION

Placentitis remains a leading cause of abortion and stillbirths in the equine industry and can account for almost 1/3 of all late term abortions and neonatal mortality. This presents significant economic losses with the loss of a foal and the loss of a breeding season. Therefore, prompt diagnosis and treatment is vital in order to save a pregnancy.

PATHOPHYSIOLOGY

Ascending infection through the cervix is by far the most common route of infection in most cases. Infectious organisms often enter through the cervix and infect the chorioallantois. This causes an increase in inflammatory cytokines which leads to a release in prostaglandins. This inflammatory response initiates the foaling cascade that ends in premature delivery of the fetus. With an ascending infection, the cervical star of the placenta is the most affected as the infection begins here and then moves cranially into the body of the uterus. Common pathogens include *Streptococcus zooepidemicus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia, Staphylococcus species* or fungal (*Candida species* or *Aspergillus species*)

A notable exception to this traditional route is nocardioform placentitis. Eighty-five percent of nocardioform placentitis were caused by *Amycolatopsis* spp. and *Crossiella. equi*, which are gram positive branching actinomycetes. The route of infection is currently unknown, but the lesions are located not at the cervical star, but at the bifurcation of the uterus. These bacteria cause a thick tan exudate and often go undiagnosed because the cervical star area remains normal.

CLINICAL SIGNS

Clinical signs often are not observed until well into the disease process making successful treatment even more difficult. Mares tend to be aged mutiparous mares and often have poor perineal conformation. The most common clinical sign associated with placentitis is premature udder development well before the mare's due date. This mammary development occurs as a response to the initiation of the foaling cascade and is in preparation for the imminent delivery of the fetus. The second most common clinical sign is vulvar discharge. This is not a consistent finding as the amount of discharge produced varies. When examining a mare for premature udder development, the underside of her tail should be examined closely for matting of tail hairs caused by vulvar discharge. The presence of vulvar discharge may help differentiate placentitis from the other major cause of premature udder development, twins.

DIAGNOSIS

Ultrasound

A complete physical examination of the mare should be performed. They are rarely systemically ill or febrile with placentitis alone. A thorough examination of the pregnancy should then be performed. A transrectal palpation should assess fetal viability by movement of the fetus as well as cervical integrity. Transrectal ultrasound of the caudal reproductive tract has become one of the most used diagnostics for placentitis. Assessing the placenta at the area of the cervical star allows for detection of placental abnormalities such as thickness or areas of detachment. By placing the ultrasound probe rectally and just off midline (either left or right depending on location of the fetus), the uterine artery can be found. The combined thickness of the uterus and placenta (CTUP) can be measured between the artery and allantoic fluid (figure 1). Several measurements should be taken, averaging thick and thin areas to get and accurate assessment. Measurements should be within the following guidelines:

151-270d: <7mm 271-300d: <8mm 301-330d: <10mm 331-delivery: <12mm

Transrectal ultrasound also allows assessment of the fetal fluids surrounding the cervical star. The fluids should be anechoic early in gestation, but will become slightly more flocculent as the due date approaches. Placental

detachment typically occurs surrounding the cervical star area first. Often, a fluid pocket can be seen between the uterus and the chorioallantois indicating separation.

Transabdominal ultrasound is the best way to evaluate fetal health. Locating the fetal heartbeat is important to assess the overall stress of the fetus. The ultrasound probe should be placed on the ventral midline near the sternum in a late term pregnant mare and moved caudally until rib shadows are observed. If none are seen, move the probe laterally and try again. Once the fetal rib shadows are seen, rotate the prove to find the heartbeat. The fetal heartrate can be taken manually or using M mode. The heart rate of the fetus may vary with activity, but should be around 75-120 beats per minute (bpm). If the heart rate is consistently low (60 bpm) or high (150 bpm), fetal stress is likely. Recheck the heart rate every 30-60 min to assess trends. The fetal fluids and placenta can also be examined transabdominally. The CTUP is less reliable transabdominally, but can be measured to show trends.

Endocrine Analysis

Progesterone is the main hormone of pregnancy early in gestation. Starting at 60 days and complete by 150-180 days gestation, the fetal-placental unit (FPU) begins to take over the maintenance of pregnancy. Progesterone is broken down into metabolites (progestins) at the placenta and the actual hormone, progesterone, is virtually undetectable by gestation day 180. Measuring total progestins during pregnancy will give an idea of fetal stress. An elevated total progestin indicates that the fetus is compromised and under stress. A low total progestins is a poor prognostic indicator and is often followed by delivery of the fetus. Total progestins should range between 4-10ng/mL until gestation day 320. Progestins then increase the last 15-21 days before foaling and then drop 24-48 hours before foaling. In one study using mares with experimentally induced placentitis, 14 of 15 mares showed a change in plasma progestins. Plasma progestins decreased dramatically in mares that aborted within 7 days of inoculation and increased in mares that carried the fetus over 15 days from inoculation. Therefore, if total progestins change (high or low), fetal stress should be highly suspected.

Estrogen concentration in the mare's serum follows gonadal development in the fetus. The fetal gonads provide the precursors for estrogen formation by the placenta. Therefore, estrogens can also be a marker for fetal health and well-being. Total estrogens in a normal pregnancy should remain greater than 1000 pg/mL from gestational day 150-320 before decreasing gradually as foaling approaches. Treatment with supplemental estrogens (ECP) in cases of placentitis and when total estrogens are low has been reported to be beneficial in the delivery of a viable foal in cases of experimentally induced placentitis⁴.

Serum Amyloid A (SAA) is an acute phase protein that increases in conditions such as infection, inflammation, stress, etc. However, SAA decreases rapidly when the inflammatory process has resolved. SAA was shown to be elevated in the aborted fetus in mares that aborted due to placentitis or other inflammatory condition. In the mare, SAA was shown to be elevated in mares with experimentally induced placentitis starting 2-3 days after inoculation. Therefore, SAA may be an additional tool in the diagnosis of placentitis⁵.

Alpha-fetoprotein (AFP) has been shown to increase in mares with experimentally induced placentitis. AFP was detected in the fetal fluids of all pregnant mares, but elevations were detected in the plasma of affected mares when compared to controls⁶.

Other

If placentitis is suspected, a vaginal speculum exam should be performed to assess the cervix and acquire a sample of any discharge. A cervical exam in the pregnant mare should be performed with caution and only when the benefits outweigh the risks of the exam. Risks include the entry of environmental bacteria and contaminants into the cranial vaginal vault and through the cervix, causing a placentitis. In cases of placentitis, the external cervical os should be cultured to determine what bacteria is present. This is best accomplished by using a double guarded swab through a disposable vaginal speculum. A cytology of the discharge can also be obtained.

TREATMENT

The goals in treatment of placentitis are to inhibit or eliminate bacterial growth, maintain uterine quiescence by decreasing uterine contractions, increasing cervical tone, and increasing blood flow to the uterus and placenta. Because inflammatory cytokines initiate the foaling cascade, blocking the release of cytokines and prostaglandins by counteracting the sequellae of endotoxemia is also critical.

Antimicrobials

Antimicrobials used must be broad spectrum until the causative agent is identified, and, must have the ability to penetrate the uterus and placenta. Studies evaluating placental drug transfer were performed by either serial allantocentesis or placing a microdialysis device into the allantoic cavity in late term pregnant mares ^{1,2}. Trimethoprim sulphamethoxazole showed similar concentrations in the serum and allantoic fluid, whereas potassium penicillin and gentamicin were 20% lower in the allantoic fluid than in serum. It should be noted that the rate of clearance of potassium penicillin was slower than in the serum indicating that dosing regimen may need to be adjusted when treating placentitis. Recently, ceftiofur (Excede) has been evaluated in normal mares and mares with induced placentitis. Drug concentrations in the fetal fluids, placental tissue, and foal serum were below the minimum inhibitory concentration necessary for successful treatment. Therefore, it is not recommended in cases of placentitis³.

Length of treatment with antibiotics depends largely on response to therapy. Typically, treating for 10-14 days is recommended with frequent assessment of the fetal well-being and placental thickness.

Progestins

Treatment with altrenogest is a standard recommendation in cases of placentitis. Progesterone promotes uterine quiescence and was shown to improve outcome when combined with trimethoprim sulfa and pentoxifylline. A dose of 0.088mg/kg is recommended. Duration of treatment is varied from a few weeks to deliver of the foal. This author recommends discontinuing treatment between 320-330 days gestation.

Nonsteroidal Anti-Inflammatories (NSAIDS)

A nonsteroidal anti-inflammatory agent is key to blocking the inflammatory cytokines that initiate the foaling cascade. Flunixin meglumine is the most commonly used NSAID at a dose of 1.1mg/kg IV or orally twice daily. Other NSAIDS have not been evaluated for efficacy in cases of placentitis. Duration of treatment will depend on response to therapy, but is typically 5-7 days. Care should be taken if treatment continues longer term to prevent GI complications.

Other Treatments

Pentoxifylline improved blood flow to the uterus by decreasing the viscosity of the blood and making the red blood cells more malleable. It also has anti-inflammatory properties. The recommended dose for placentitis is 8.5 mg/kg, orally, twice daily.

Clenbuterol can be added as a tocolytic agent. Research has shown contradicting results using the oral form that is available in the United States. It has not been shown to prolong gestation length in late term mares, but may have some tocolytic effects in cases of placentitis. Clenbuterol has a narrow spectrum of safety and should be used with caution, but can be added to the drug protocol in selected cases.

MONITORING

Mares diagnosed with active placentitis should be monitored frequently (daily to every other day) using transabdominal and transrectal ultrasound. The fetus and placenta should be evaluated with each examination. If treatment is effective, the CTUP should normalize, the vaginal discharge and mammary development should improve, and the fetal heart rate remain stable. Weekly serum samples monitoring progestins and estrogens may also help guide response to treatment.

MANAGEMENT AFTER DELIVERY

Owners should be made aware that placentitis places their foal at risk of premature delivery and sepsis which could affect the desired athletic outcome of the foal. Once the foal is delivered, a complete placental evaluation should be performed. This assessment will provide a guide for continued treatment of the mare and foal. Cultures of the mare's uterus may also provide a sample of the causative agent and can be correlated to a blood culture taken from the foal at birth. Supportive care for the foal should be performed and include antimicrobial therapy. Foals are often compromised and foaling at a full care facility should be considered.

Few studies are available to determine the best treatment of the mare's uterus following a placentitis delivery. In most cases, several days of uterine lavage of the postpartum mare is indicated as well as intrauterine antibiotics once the lavage fluid is clear. A complete breeding soundness examination including uterine culture and cytology should be performed prior to re-breeding. If a cause could be identified (poor perineal conformation), treatment should be initiated to prevent recurrence.

CONCLUSION

Diagnosis of placentitis is still reliant on clinical signs. Effective treatment plans are multimodal and antiinflammatories, tocolytics, and antibiotic therapies all show effectiveness in delaying premature parturition.



Figure 1

Transrectal ultrasound of the combined thickness of the uterus and placenta (CTUP). The bladder can be seen on the right of the picture and the allantoic cavity is on the left side. The CTUP is measured by identifying the uterine artery (white arrow) adjacent to the cervix (white arrow).

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