

A clinical approach to managing the mare with placentitis

M.L. Macpherson*, C.S. Bailey

Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL, USA

Abstract

Placental infections in the mare are a diagnostic and therapeutic challenge. The following article will review techniques for identifying placental infections, approaches for treating placentitis, and methods for managing these mares after foaling.

© 2008 Elsevier Inc. All rights reserved.

Keywords: Pregnancy; Placentitis; Placental infection; Placenta; Mare

1. Introduction

Ascending placentitis in mares has generated a great deal of attention in recent years. This disease is not new to equine medicine. However, significant financial losses caused by placentitis have stimulated interest in improved diagnostic and treatment tools for affected mares. The disease, most frequently caused by an ascending bacterial infection, can be insidious in nature. Clinical signs frequently do not occur until well into the disease process; at that time, it may be difficult to salvage the pregnancy. The following review will focus on a clinical approach to diagnosing and managing mares with placentitis prior to foaling, as well as in the postpartum interval.

2. Mare profile

Anecdotally, mares suffering from ascending placentitis are multiparous and middle-aged to aged.

Affected mares often have poor perineal conformation or defects. No breed predilection has been identified. At the University of Florida, Thoroughbreds are heavily represented, due to the local horse population, and an interest in breeding aged mares.

3. Clinical signs

The most common clinical presentation for the mare with placentitis is premature udder development, with or without vulvar discharge. The mammary gland of a pregnant mare develops in preparation for imminent delivery of the fetus. In the normal foaling mare, the mammary gland develops approximately 1–2 wk prior to parturition. This phenomenon is affected by parity and season. Precocious mammary gland development is most frequently attributed to twin pregnancies or placental abnormality. Although early diagnosis and management of twin pregnancies have substantially reduced the incidence of twins carried to term, twin pregnancy should always be considered a cause of precocious udder development.

Vulvar discharge is a very inconsistent clinical finding in mares with bacterial placentitis. It is likely that discharge is often present in affected mares, but it may be produced in such scant quantities that it is

* Corresponding author at: Department of Large Animal Clinical Sciences, College of Veterinary Medicine, University of Florida, PO Box 100136, Gainesville, FL 32610, USA. Tel.: +1 352 392 4700; fax: +1 352 392 8289.

E-mail address: macphersonm@vetmed.ufl.edu (M.L. Macpherson).

difficult to see without careful scrutiny. Furthermore, small amounts of vulvar discharge can easily be removed from the vulva by the tail.

Mares in an experimental model of placentitis more frequently had vulvar discharge than mares with field cases of placentitis. Study mares were inoculated (transcervically) with *Streptococcus equi* subspecies *zooepidemicus* and then examined every 12 h for evidence of mammary gland development or vulvar discharge. Although precocious mammary development was evident in only one of 17 infected mares, vulvar discharge was the primary clinical sign in all 17 infected mares. Factors that may have contributed to the higher incidence of vulvar discharge in experimentally infected mares include a high dose of bacterial inoculum and extremely vigilant monitoring of the perineal area. Notwithstanding, we concluded that mares “at risk” for bacterial placentitis should have thorough monitoring of the vulva, tail hairs, and hind legs for evidence of discharge originating from the caudal reproductive tract. In that regard, early identification of clinical signs of placentitis facilitates prompt initiation of treatment, with a potentially better pregnancy outcome.

4. Ultrasonographic tools

4.1. Transrectal ultrasonography

Transrectal ultrasonographic examination of the caudal reproductive tract has become a commonplace diagnostic tool for placentitis. This method enables direct examination of the cervical star region, the area most often afflicted with placentitis. It also allows for evaluation of fetal activity, fetal fluid character, fetal orbit measures, and subjective amniotic evaluation.

In the normal pregnant mare, the area visualized in the region of the cervical star is the combined uterine and placental (chorioallantoic) unit. Renaudin and co-workers [1,2] developed the technique for evaluation of the combined thickness of the uterus and placenta (CTUP) and established normal values in light-horse mares throughout gestation. For 271 to 300, 301 to 330, and >330 d of gestation, normal concentrations for CUTP were <8, <10, and <12 mm, respectively [2,23]. However, mares with placental infection or inflammation have increased (thicker) CTUP measures, or separation of the membranes from the endometrium. Furthermore, purulent material (hyperechoic) may accumulate in pockets between the chorioallantois and the endometrium. Thickening of the amnion may also indicate inflammation.

Allantoic fluid throughout most of gestation is hypoechoic (black), whereas amniotic fluid is slightly more echodense (light gray). However, fetal activity can agitate cellular material and change the characteristics of either fluid compartment. Fluids that persistently have increased echodensity likely have increased cellularity due to infection or inflammation. Serial ultrasound examinations are essential to determine if fluid character changes are iatrogenic or pathologic.

4.2. Transabdominal ultrasonography

Transabdominal ultrasonography is an excellent tool for evaluating the fetus and placenta in mares [3–5]. Fetal well-being can be assessed with transabdominal ultrasonographic assessment of fetal heart rate, tone, activity, and size. Locating a fetus (es) is most easily achieved by identifying the fetal thorax; it is visualized as several linear, hypoechoic shadows (intercostal spaces), interdigitated with linear, hyperechoic ribs. The active fetal heart is easily identified at the cranial-most aspect of the fetal thorax (the end that narrows into the cervical spine). The average heart rate in a fetus at >300 d gestation is 75 ± 7 bpm [3]. Fetal heart rate slows by approximately 10 bpm at >330 d gestation, but can vary with activity levels. Consistently low or high fetal heart rates are indicative of fetal stress.

Placental membrane integrity and thickness and fetal fluid character are also evaluated using this technique. Again, the chorioallantois is intimately associated with the endometrium and cannot be easily identified as a separate structure from the transabdominal approach. Mares with normal pregnancies should have a minimum CTUP of 7.1 ± 1.6 mm, and a maximal CTUP of 11.5 ± 2.4 mm [3]. Evaluation of the caudal allanto-chorion is not accurate using the transabdominal approach. However, transabdominal evaluation of fetal membranes is very useful for identifying placental abnormalities in mares with hematogenously-induced or nocardia-form placentitis. Mares infected with the nocardia-form bacteria will often have placental separation and purulent material at the base of the gravid horn and the junction of the uterine body [6].

Transabdominal ultrasonography is the most accurate method to diagnose twins in late gestation. Confirmation of twins is generally made by identifying two fetal thoraces, and/or beating hearts. Measurements of fetal thoraces can be used to confirm the presence of twins, if thoracic size differs between fetuses. Additionally, the orientation of the thorax can be used to verify the presence of twin fetuses.

Fetal activity level and tone are easily determined while examining a fetus for heart rate. Fetal activity can vary during the examination period, as fetuses have periods of sleep and wakefulness. In response to the ultrasound beam, the normal fetus commonly becomes very active during the examination period. Fetal “tone” is a subjective term describing the viability of the fetus. A live fetus has excellent “tone” in that it is active and it flexes and extends the torso, neck and limbs [3,7]. Conversely, a fetus without “tone” is often dead or in the terminal stages of life. An atonic fetus is flaccid and lies passively within the uterus and may be folded in upon itself. Clearly identifying the atonic fetus can be difficult, as traditional landmarks, e.g. a beating heart, may be obscured by the limbs of the flaccid fetus.

Serial examinations should be performed to verify fetal well-being or distress. Transabdominal ultrasonographic assessments are commonly performed at least once daily in high-risk mares, whereas fetuses experiencing distress are often evaluated several times a day to assess heart rate and activity level.

5. Progesterin concentrations

Measurement of blood progesterin concentrations has been advocated as a means of diagnosing placental pathology [8,9]. Maternal progesterone (P4), produced by the ovaries, supports pregnancy for approximately the first 150 d of gestation. Thereafter, pregnancy is maintained by progestins (including P4) produced by the fetoplacental unit [10]. Progesterin concentrations remain stable in the second half of gestation. Prior to parturition (Day 315 forward), circulating progesterin concentrations rise significantly, with a dramatic decline in the last 24–48 h prior to foaling [10].

Actual measurable P4 concentrations in maternal serum are negligible in the latter half of gestation, as P4 is metabolized into several other progestins. Unfortunately, assays for specific progestins produced by the fetoplacental unit are not readily available. However, some commercial P4 radioimmunoassays and ELISA's are known to have cross-reactivity with fetoplacental progestins [24]. Therefore, these assays can be used to monitor changes in total progestins produced by the fetoplacental unit that might indicate a compromised pregnancy, potential premature delivery, or response to treatment in the mare with placentitis. Recent work by Morris et al. [8] described two patterns of progesterin profiles in mares with experimentally-induced placentitis. Mares with imminently impending abortion (within 7 d of inoculation) had decreased plasma progesterin concentrations, whereas those maintaining

pregnancy (despite chronic placental infection) had a rise in plasma progesterin concentrations. This group also reported increased sensitivity of plasma progesterin assays for identifying fetoplacental compromise when combined with ultrasonographic examination of the caudal chorioallantois [1,8].

6. Mammary secretion electrolyte concentrations

Mammary gland development and presence of colostral secretions are accurate indicators of fetal readiness for extrauterine life in the normal mare [11]. Mammary gland secretion electrolytes (calcium, potassium and sodium) can be monitored using commercial serum chemistry analyzers (after dilution) or stall-side tests to detect changes in electrolyte concentrations. The advantage of laboratory analysis of secretions is that quantitative figures for calcium, sodium and potassium can be obtained. Concentrations of at least 40 mg/dL calcium and inversion of sodium (decreases) and potassium (increases) are indicative of a mature foal [11]. Inversion of the sodium and potassium often occurs at approximately 30 mEq. Disadvantages for using a laboratory to analyze mammary secretions are turn-around time and expense. Stall-side tests are also available to monitor mammary secretion electrolytes (Predict-A-Foal™, Animal Healthcare, www.ahcpi.com; FoalWatch™ CHEMetrics, www.chemetrics.com). These tests are semi-quantitative and measure calcium and magnesium, but not sodium or potassium. Based on calcium concentrations in secretions, a prediction is made regarding impending parturition in the mare. However, these assays are not foolproof, and there are inherent risks in predicting delivery time of a foal. Furthermore, pathologic conditions, such as placentitis, can cause changes in electrolyte concentrations, resulting in erroneous conclusions [12].

7. Treatment

Placentitis in mares is commonly caused by bacteria ascending through the vagina [6,13,14]. The most frequent bacterial pathogens implicated in equine placentitis are *Streptococcus equi* subspecies *zooepidemicus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [15]. Although bacterial infection initiates disease, based on recent work from an experimental model of ascending placentitis in pony mares, premature delivery may occur secondary to inflammation of the chorion rather than as a consequence of fetal infection [16,17]. These inflammatory

Table 1

Products commonly used to treat placentitis in the mare

Action	Product	Dose, route, and frequency
Antimicrobial	Potassium penicillin	22,000 units/kg, IV, QID
	Procaine penicillin	22,000 units/kg, IM, BID
	Ceftiofur (Naxcel)	2.2 mg/kg, IV or IM, BID
	Cefazolin	20 mg/kg, IV, QID
	Trimethoprim sulfa	15–30 mg/kg, PO, BID
Anti-inflammatory	Flunixin meglumine	1 mg/kg, IV, BID
	Phenylbutazone	2.2–4.4 mg/kg, PO, BID
	Pentoxifylline	8.5 mg/kg, PO, BID
Tocolytic/uterine quiescence	Altrenogest (Regumate)	0.088 mg/kg, PO, SID
	Isoxuprine	1 mg/kg, SID

processes increase production of prostaglandins (PGE₂ and PGF₂α) and stimulate myometrial contractility, thus resulting in pre-term delivery [18,19]. Therefore, therapies directed at resolving microbial invasion, inflammation, and uterine contractions are probably needed to effectively combat placental infections.

Several recent studies have contributed to elucidating appropriate therapy for mares with placentitis. Two studies from the University of Florida [20,21] employed *in vivo* microdialysis to determine if selected drugs attained therapeutic concentrations in allantoic fluid of normal pony mares and mares with experimentally-induced placentitis. Penicillin potassium G (22,000 units/kg, IV, q6h), gentamicin sulfate (6.6 mg/kg, IV, q24h), trimethoprim sulfamethoxazole (30 mg/kg, PO, q12h) and pentoxifylline (8.5 mg/kg, PO, q12h) were all detected in allantoic fluid of both normal and infected pony mares. Furthermore, concentrations of antimicrobials in allantoic fluid were sufficient to exert a short-term (approximately 4 h) effect. Both penicillin and trimethoprim sulfamethoxazole reached effective minimum inhibitory concentrations (MIC) against *Streptococcus equi subspecies zooepidemicus*, whereas gentamicin concentrations in allantoic fluid were adequate to be effective against *Escherichia coli* or *Klebsiella pneumoniae*. In a subsequent study [22], trimethoprim sulfamethoxazole and pentoxifylline were identified in fetal and placental tissues obtained from mares with experimentally-induced placentitis. Treating infected mares with these two drugs prolonged gestation, but did not result in more live-born foals. Recent work from the University of Florida (Bailey, 2006 unpublished data) has shown encouraging results when altrenogest (RegumateTM, 0.088 mg/kg, PO, SID) was added to the trimethoprim sulfa and pentoxifylline protocol. Ten of 12 mares with experimentally-induced placentitis delivered live foals after treatment with this protocol. The combined effects of the drugs may have

provided the necessary intervention for preterm delivery, by addressing microbial infection, inflammation and uterine contractility. Furthermore, early diagnosis of disease, and initiation of treatment, likely contributed to the positive outcome in this study. Results from this study also supported long-term therapy in affected mares (from the onset of clinical signs to delivery of the foal).

Not all drugs used in clinical practice for treatment of placentitis have been evaluated critically. Commonly used products and their protocols are summarized (Table 1).

8. Pregnancy management

Management practices for mares with placentitis include long-term therapy and vigilant monitoring. At the University of Florida, mares are evaluated using transabdominal ultrasonography on a daily basis to monitor fetal viability, fluid character and placental integrity. Changes in fetal heart rates suggesting fetal deterioration are used for prognostic information relayed to owners.

Transrectal ultrasonography is generally performed on a daily basis, starting early in the course of the disease, to assess progression of placental pathology or response to therapy. Once placental pathology appears to have stabilized, transrectal examinations are performed every second or third day.

9. Post-foaling diagnostic tests

9.1. Uterine culture

Uterine cultures are not routinely done in normal postpartum mares. However, in mares with placentitis, uterine cultures can provide useful information relative to treatment selection. In an experimental model of

placentitis, uterine cultures were obtained from mares within 2 h after foaling. *Streptococcus equi* subspecies *zooepidemicus*, the infective organism, was recovered from the uterus of the majority of infected mares, independent of prepartum treatment. This was true for animals that maintained pregnancy for an extended period (>20 to 30 d post-infection) and delivered healthy foals. Therefore, if cultures can be obtained from mares shortly after parturition, they may provide useful information for antibiotic selection. However, uterine cultures obtained 1 or 2 d after foaling are likely to reveal mixed bacterial organisms characteristic of the postpartum period in the normal, foaling mare.

9.2. Placental evaluation and culture

Evaluation of the placenta may provide critical clues to the health status of a foal or the cause of abortion. This may guide the clinician in treatment choices for both the dam and the foal. Ascending bacterial placentitis is typically seen as a thickening and discoloration of the caudal chorioallantois around the cervical star, which may radiate cranially. Histologically, infected placentas are characterized by supportive, necrotizing placentitis and funisitis [17]. Usually the placenta is grossly contaminated at the time of examination, and culture may or may not be useful. However a fresh placenta with obvious gross lesions may be cultured to develop appropriate treatment plans for the dam or foal.

9.3. Neonatal blood culture

Neonatal septicemia is a highly detrimental sequella of placentitis. Antimicrobial therapy is indicated in foals delivered from mares having placentitis. Blood cultures can be taken from neonates as a means of directing antimicrobial choice. However, blood cultures may not always implicate an organism. In one study (Bailey, unpublished) blood cultures were done in foals delivered from mares with experimentally induced placentitis. Foals delivered from mares treated with antibiotics and pentoxifylline during pregnancy had negative blood cultures. However, five of seven non-viable foals in this study had positive blood cultures, independent of mare treatment. These findings supported the efficacy of drug treatment in mares with placentitis in combating foal disease. However, on a practical basis, negative blood cultures would not preclude treating foals delivered from mares known to have placental disease.

10. Treatment of the postpartum mare after placentitis

Treatment protocols for postpartum mares experiencing placentitis have not been critically evaluated. Treatments are empirical and generally consist of a combination of uterine lavage, antimicrobial, and anti-inflammatory therapies. Uterine lavage is done to augment removal of uterine debris and residual microbes. Experimentally-infected mares retained microbial organisms, despite long-term antimicrobial therapies (Bailey, unpublished data). In general, uterine lavage is done for 2 or 3 d postpartum in mares with placentitis. In addition, mares are administered broad-spectrum antimicrobial therapy for an additional 5–7 d after foaling, and anti-inflammatory therapy for 3–5 d after foaling. Using this approach in an experimental model of placentitis, all mares remained systemically healthy and had negative uterine cultures 14 d after cessation of systemic antimicrobial therapy.

11. Conclusions

Placentitis in the mare is a complex set of events; this complexity hinders rapid diagnosis and initiation of treatment. Presently, clinical signs are the best diagnostic indicators of disease. Success of therapy is largely determined by rapid initiation of a multi-pronged therapeutic approach.

References

- [1] Renaudin CD, Troedsson MHT, Gillis CL. Transrectal ultrasonographic evaluation of the normal equine placenta. *Equine Vet Educ* 1999;11:75–6.
- [2] Renaudin CD, Troedsson MHT, Gillis CL, King VL, Bodena A. Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare. *Theriogenology* 1997;47:559.
- [3] Reef VB, Vaala WE, Worth LT, Sertich PL, Spencer PA. Ultrasonographic assessment of fetal well-being during late gestation: Development of an equine biophysical profile. *Equine Vet J* 1996;28:200–8.
- [4] Adams-Brendemuehl C, Pipers FS. Antepartum evaluation of the equine fetus. *J Reprod Fertil Suppl* 1987;35:565–73.
- [5] Vaala WE, Sertich PL. Management strategies for mares at risk for periparturient complications. *Vet Clin North Am Equine Pract* 1994;10:237–65.
- [6] Hong CB, Donahue JM, Giles RC, Petritesmurphy MB, Poonacha KB, Roberts AW, et al. Etiology and pathology of equine placentitis. *J Vet Diag Investigation* 1993;5:56–63.
- [7] Reef VB, Vaala WE, Worth LT, Spencer PA, Hammett B. Ultrasonographic evaluation of the fetus and intrauterine environment in healthy mares during late-gestation. *Vet Radiol Ultras* 1995;36:533–41.

- [8] Morris S, Kelleman AA, Stawicki RJ, Hansen PJ, Sheerin PC, Sheerin BR, et al. Transrectal ultrasonography and plasma progesterone profiles identifies feto-placental compromise in mares with experimentally induced placentitis. *Theriogenology* 2007;67:681–91.
- [9] Ousey JC, Houghton E, Grainger L, Rosedale PD, Fowden AL. Progesterone profiles during the last trimester of gestation in thoroughbred mares with normal or compromised pregnancies. *Theriogenology* 2005;63:1844–56.
- [10] Holtan DW, Houghton E, Silver M, Fowden AL, Ousey J, Rosedale PD. Plasma progesterone in the mare, fetus and newborn foal. *J Reprod Fertil Suppl* 1991;44:517–28.
- [11] Ousey JC, Dudan F, Rosedale PD. Preliminary studies of mammary secretions in the mare to assess fetal readiness for birth. *Equine Vet J* 1984;16:259–63.
- [12] Rosedale PD, Ousey JC, Cottrill CM, Chavatte P, Allen WR, McGladdery AJ. Effects of placental pathology on maternal plasma progesterone and mammary secretion calcium concentrations and on neonatal adrenocortical function in the horse. *J Reprod Fertil* 1991;579–90.
- [13] Platt H. Infection of the horse fetus. *J Reprod Fertil Suppl* 1975;23:605–10.
- [14] Whitwell K. *Equine infectious diseases V*, 5th ed., Lexington: University of Kentucky Press; 1988.
- [15] Acland HM. Abortion. In: McKinnon AO, Voss JL, editors. *Equine reproduction*. Philadelphia: Lea & Febiger; 1993 p. 554–61.
- [16] Leblanc MM, Giguere S, Brauer K, Paccamonti DL, Horohov DW, Lester GD, et al. Premature delivery in ascending placentitis is associated with increased expression of placental cytokines and allantoic fluid prostaglandins E-2 and F-2 alpha. *Theriogenology* 2002;58:841–4.
- [17] Mays MBC, Leblanc MM, Paccamonti D. Route of fetal infection in a model of ascending placentitis. *Theriogenology* 2002;58:791–2.
- [18] Pollard JK, Mitchell MD. Intrauterine infection and the effects of inflammatory mediators on prostaglandin production by myometrial cells from pregnant women. *Am J Obstet Gynec* 1996;174:682–6.
- [19] Dudley DJ, Trautman MS. Infection, inflammation, and contractions – the role of cytokines in the pathophysiology of preterm labor. *Sem Reprod Endocrin* 1994;12:263–72.
- [20] Murchie TA, Macpherson ML, Leblanc MM, Luznar S, Vickroy TW. Continuous monitoring of penicillin G and gentamicin in allantoic fluid of pregnant pony mares by in vivo microdialysis. *Equine Vet J* 2006;38:520–5.
- [21] Rebello SA, Macpherson ML, Murchie TA, Leblanc MM, Vickroy TW. Placental transfer of trimethoprim sulfamethoxazole and pentoxifylline in pony mares. *Anim Reprod Sci* 2006;94:432–3.
- [22] Graczyk J, Macpherson ML, Pozor MA, Troedsson MHT, Eichelberger AC, Leblanc MM, et al. Treatment efficacy of trimethoprim sulfamethoxazole and pentoxifylline in equine placentitis. *Anim Reprod Sci* 2006;94:434–5.
- [23] Renaudin CD, Liu IKM, Troedsson MHT. Transrectal ultrasonographic diagnosis of ascending placentitis in the mare: a report of two cases. *Equine Vet Education* 1999;11(2): 69–74.
- [24] Sheerin PC, Morris S, Kelleman AA, Stawicki R, Sheerin BR, LeBlanc MM. Diagnostic efficiency of transrectal ultrasonography and plasma progesterone profiles in identifying mares at risk for preterm delivery. *Focus in Reproduction: Am Assoc of Equine Practitioners* 2003;1:22–3.