Mare Reproductive Loss Syndrome

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**ABSTRACT:** Mare reproductive loss syndrome (MRLS), an epidemic of equine abortion that occurred in Central Kentucky during spring 2001, affected mares both in early and late gestation. In addition to reproductive abnormalities, fibrinous pericarditis and unilateral uveitis were common. Although the syndrome recurred with significantly less intensity in spring 2002, the estimated economic losses associated with MRLS approached $500 million. Clinically, the abortions and stillbirths were explosive and often associated with premature placental separation. Microbiologic and pathologic characteristics included frequent fetal isolation of nonhemolytic *Streptococcus* and *Actinobacillus* spp, fetal pneumonia, placentitis, and funisitis. Epidemiologic surveys during 2001 identified high numbers of Eastern tent caterpillars in the mares’ environment as one of the risk factors. Subsequent investigations confirmed that these caterpillars caused MRLS, although the abortigenic factor(s) in these caterpillars remains unidentified.

In spring 2001, an epidemic of equine abortions occurred in Central Kentucky. Abortions occurred in either early or late gestation and were called *early fetal loss* and *late fetal loss*, respectively.1,2 Although the abortions were heavily concentrated in Central Kentucky, a similar syndrome occurred in southern Ohio, West Virginia, and Tennessee. The syndrome was later called *mare reproductive loss syndrome* (MRLS) and recurred with significantly less intensity in spring 2002.1-5 Several breeds were involved, but Thoroughbreds were affected the most. The combined economic losses in the 2 years were approximately $500 million.5 Epidemiologic investigations conducted during this period documented extremely high numbers of Eastern tent caterpillars in the farms affected by MRLS.5,6

**CLINICAL SYNDROME**

**Early Fetal Loss**

Early fetal losses were first noted during routine reproductive ultrasonographic examinations,7,9,10 with the majority of more than 1,500 fetal losses occurring between 48 and 171 days of gestation.11 Vulvar discharge and/or protrusion of
fetal membranes occurred occasionally; however, a lack of clinical signs was the norm. Ultrasonographic findings included lack of a heartbeat, a slow heartbeat, and/or reduced or absent movement of the fetus. Allantoic and amniotic fluids were highly echogenic, with amniotic fluid being more echogenic than allantoic fluid.

Late Fetal Loss
Epidemiologic surveys indicated approximately 1,216 abortions or loss of late-term fetuses during the 2001 season. More than 500 of these late-term aborted fetuses were submitted to the University of Kentucky Livestock Disease Diagnostic Center during a 5-week period from April through May; this was a 32% increase over the same period the previous year. Abortions occurred during the last trimester, usually during the last month of gestation, with the fetuses being aborted near or at term. A high percentage (32%) of these submissions were diagnosed with premature placental separation; dystocia (11%) was also commonly diagnosed. During the 2002 season, 164 late-term fetuses were submitted.

Typical clinical signs of late fetal loss included dystocia, foaling while standing, premature placental separation, and an overall description of explosive parturition. Foals delivered at term were stillborn or typically in cardiovascular collapse with clinical signs of asphyxia. These foals frequently died shortly after birth despite attempts at resuscitation and intensive care. An unusual finding in many of these sick foals was bilateral hyphema. Blood cultures were rarely positive; alpha Streptococcus and Actinobacillus spp were cultured most frequently.

In 2001, an unusually high number of mares with fibrinous pericarditis and unilateral uveitis were seen in Central Kentucky; not all of these mares were pregnant. For example, over a 2-month period coinciding with the reproductive losses, 38 cases of fibrinous pericarditis were diagnosed in Central Kentucky. Before 2001, only one or two cases repetitions were diagnosed per year in this area. The clinical signs associated with fibrinous pericarditis included marked mufﬁling of heart sounds, tachycardia, jugular vein distention, and peripheral edema. Pericardial fluid collected from affected mares was classified as a sterile exudate. Actinobacillus spp were the principal isolates from eight of 10 untreated, terminally affected horses and three of 10 clinically affected horses. Some patients responded to antibiotic and long-term steroidal therapy. In 2002, fewer than 15 cases of pericarditis were reported in the area.

At the same time that the number of cases of fibrinous pericarditis was increasing during the MRLS outbreak in 2001, approximately 40 cases of unilateral uveitis were reported in the same area. There was no age, breed, or sex predilection associated with the development of this condition, which occurred percutely with profound exudative ophtalmmitis. The ophthalmologic findings included corneal edema and exudate in the anterior and posterior chambers. The affected eyes were refractory to treatment, and blindness ensued. Fewer cases of unilateral uveitis were reported in 2002.

ASSOCIATED PATHOLOGIC FINDINGS
The typical pathologic lesion associated with early fetal loss was bacterial placentitis. The consistent state of autolysis of fetal submissions precluded specific anatomic localization of the inflammatory changes. Gross lesions associated with late fetal loss included a pale brown placenta, an intact cervical star, a yellow edematous umbilical cord, hyphema, placental thickening, and edema. Histopathologic changes included placentitis, funisitis (i.e., inflammation of the umbilical cord), and fetal pneumonia. A characteristic lesion of funisitis was identified in fetuses aborted in the later stages of gestation. Funisitis was consistently confined to the amniotic portion of the umbilical cord. The umbilical cord lesion consisted of neutrophil and bacterial aggregates, which were typically confined to the coelomic space in the subchorionic stroma. Placental inflammation was vascular or perivascular. The placentitis of MRLS was distinguishable from the typical ascending placentitis originating at the cervical star or from hematogenous placentitis with involvement of chorionic villi. There was no single pathognomonic lesion identified in cases of MRLS. Bacteriologic isolation found 10 different species from fetuses that were aborted in late gestation. Most bacterial isolates were non-β-hemolytic Streptococcus (51%) and Actinobacillus (13%) spp.
INITIAL INVESTIGATION INTO POSSIBLE CAUSES

Although it was initially thought that there might be an infectious cause of MRLS, this was rapidly discounted because there were no clinical signs noted in the aborting mares and the classical point source outbreak suggested an environmental source toxin. Subsequently, a variety of potential toxins were considered and most of these were eliminated (Table 1).

In 2001, Eastern tent caterpillars were spatially and temporally related to the outbreak of MRLS. Because Eastern tent caterpillars are commonly found on wild black cherry tree leaves that contain cyanogenic compounds and these caterpillars can convert the compounds to cyanide, a popular theory was that cyanide caused MRLS. This theory was intensively investigated but was discounted because administration of high levels of cyanide to pregnant mares failed to cause abortion.

EXPERIMENTAL INDUCTION OF THE SYNDROME

In 2002, MRLS was reproduced in small pasture plots by exposing 10 pregnant mares to Eastern tent caterpillars or their frass (i.e., excrement); seven of 10 mares aborted. In a group of nine mares exposed to Eastern tent caterpillar frass, seven aborted. Although three of 10 pregnant mares on control pasture plots aborted, it was noted that some migration of the Eastern tent caterpillars occurred across the control pasture plots. The results of these studies provided the first experimental evidence that exposure of mares to Eastern tent caterpillars can cause MRLS. This study was repeated with improved control of Eastern tent caterpillars, and only mares exposed to the caterpillars aborted.

In a second study, five early-term mares were gavaged with either Eastern tent caterpillars or frass, and an additional five control mares received water by the same route. All mares were treated for 10 days and maintained in stalls (to prevent exposure to grass). Four of five mares treated with 50 g of Eastern tent caterpillars aborted within 8 to 13 days, whereas no mares in the control group aborted. The results of this study were consistent with a causal role of Eastern tent caterpillars in cases of MRLS and ruled out involvement of Kentucky hay or pasture grasses.

In a third study, six late-term mares were gavaged with 50 g of Eastern tent caterpillars collected from the upper peninsula of Michigan. Five mares served as controls. All six of the mares gavaged with the Eastern tent caterpillars from Michigan aborted, whereas none of the control mares aborted. The results of this study showed that Eastern tent caterpillars from states other than Kentucky can cause fetal loss in late-term mares.

A series of additional studies have been conducted to determine whether other types of caterpillars can induce abortion, which component of Eastern tent caterpillars is responsible for inducing abortion, and the effects of freezing the caterpillars on induction of MRLS. The results of these studies (Table 2) indicate that Eastern tent caterpillars, but not forest tent or gypsy moth caterpillars, induce abortion in mares; that the abortifacient factor is in the exoskeleton of Eastern tent caterpillars; and that irradiation but not freezing reduces the ability of Eastern tent caterpillars to induce abortion.
DISCUSSION

The MRLS epidemic that struck Central Kentucky during spring 2001, followed by additional cases in spring 2002, was a previously unreported disease process that had several unique features:

- An association with ingestion of or exposure to Eastern tent caterpillars
- A unique clinical pattern and presentation of reproductive loss and, to a lesser extent, pericarditis and uveitis
- Lack of premonitory signs before the reproductive loss
- The explosive nature of the abortion, with premature placental separation
- Clinical signs of illness in the foals, including hyphema and progressive asphyxia
- Distinctive microbiologic findings
- Distinctive pathologic/histopathologic findings

The initial epidemiologic surveys conducted in Central Kentucky suggested that Eastern tent caterpillars might be involved in the pathogenesis of MRLS. The explosive nature of the Eastern tent caterpillar population in 2001 and, to a lesser degree, in 2002 coincided with unprecedented losses in the Kentucky horse population. Although associations between Eastern tent caterpillars and fetal losses had not been previously reported, the results of subsequent studies have confirmed a causal relationship between Eastern tent caterpillars and MRLS. The precise factor in Eastern tent caterpillars that initiates MRLS has not been elucidated; however, the factor appears to be contained in the cuticle or integument of the caterpillar. Filtration of Eastern tent caterpillars to particles smaller than 45 microns and irradiation reduce but do not totally ameliorate the abortifacient nature of the caterpillars. The following do not cause abortion: cyanide or related compounds, a related “hirsute” caterpillar, or the closely related laboratory-raised forest tent caterpillar (Table 2). Current theories regarding initiation of MRLS include the possibility that the setae of Eastern tent caterpillars serve as carriers of a toxin, enteric bacteria, other integumentary toxins, or possibly a product released by integumentary glands of the caterpillars. The role of bacteria in MRLS remains controversial because it is not clear whether the bacteria identified with abortions are primary or secondary.

The nature of the abortions experienced during the MRLS outbreaks was unique in the lack of premonitory signs in affected mares. Mares that aborted in late gestation occasionally exhibited mild colic or restlessness before abortion. In addition, the abortions were explosive unless the foal was late term and dystocia ensued. The sick foals appeared to have rapid-onset, short-term asphyxia. Hyphema, although not commonly identified otherwise, was a frequent clinical finding in the sick foals during the outbreaks.

Histopathologic features of the placentas of affected mares also appear to be unique to this syndrome. There was no evidence of an ascending or hematogenous route of bacterial entry into the placenta. Although the port of bacterial entry into the placenta in mares aborting during late gestation remains unclear, the microscopic lesions of the allantochorion were confined to the coelomic space in the subchorionic stroma and thus are closely associated with blood vessels. This finding suggests that there may be vascular involvement.

Bacterial culture of tissue in both early and late fetal losses indicated that *Actinobacillus* and *Streptococcus* spp were associated with the abortion or placentitis. This is
unique in that these organisms are rarely associated with these conditions in horses. These bacteria are likely normal inhabitants of the equine gastrointestinal tract and are a previously uncommon finding in equine abortion. The gross pathologic findings associated with early fetal losses were not specific, as indicated by autolysis of samples submitted. Although there was no evidence of funisitis in these fetuses, as occurred in fetuses aborted late in gestation, the microbiologic findings were similar to those identified with late fetal losses. No single pathologic finding was pathognomonic for MRLS or late fetal loss; however, funisitis was a characteristic lesion noted in fetuses lost in late gestation. The specific pathogenesis of the funisitis is unknown. It has been suggested that inflammatory cells may migrate from the umbilical cord vessels to the superficial layers of the umbilical cord. This migration of cells may be a result of chemotactic factors within the amniotic fluid. The placental characteristic of late fetal loss was clearly differentiated from ascending placentitis. In the placentas of horses with MRLS, histopathologic lesions were not observed on the chorionic surface, as occurs in ascending placentitis. The histopathologic lesions identified in the placentas of horses with MRLS are suggestive of vascular involvement, with the inflammatory lesions of the allantochorion found primarily in the coelomic, subchorionic stroma closely related to stromal blood vessels.

The fibrinous pericarditis and uveitis identified during spring 2001 were associated with the MRLS outbreak; however, these conditions were rarely identified in mares with either early or late fetal losses. Similarly, unilateral uveitis was not observed in mares with either early or late fetal losses. The incidence of pericarditis during the MRLS outbreak of 2001 was 30 times higher than the normal prevalence in Central Kentucky. The unilateral nature of the uveitis appears to be unique because there are no reports of unilateral uveitis epidemics in the medical literature. Neither unilateral uveitis nor fibrinous pericarditis was reproduced in the MRLS studies.

Although the syndrome recurred with significantly less intensity in spring 2002, the estimated economic losses associated with mare reproductive loss syndrome approached $500 million.

The initial popular theory that cyanide originating as a result of an interaction between Eastern tent caterpillars and cherry tree leaves caused MRLS was ruled out in summer and fall 2001. Subsequent studies determined that Eastern tent caterpillars with or without their frass were directly associated with induction of MRLS and that Eastern tent caterpillars, but not their...
frass, were a causal agent. The results of other studies indicated that Eastern tent caterpillars from regions other than Central Kentucky are abortigenic.

The suggestion that placental detachment might occur in utero (intact cervical stars) was introduced through an additional Eastern tent caterpillar feeding trial. The results of that study suggest a scenario involving placental detachment, hypoxia, fetal death, and abortion. This, in turn, suggests that the abortifacient acts at the uteroplacental interface.

Other studies using separated anatomic components of Eastern tent caterpillars found the integument of the caterpillar likely to contain the abortifacient because only mares administered the integument aborted. Thus a component or structural portion of the integument is involved in initiating MRLS. Autoclaved Eastern tent caterpillars did not cause abortions, suggesting that the abortifacient is heat labile and that bacteria associated with the caterpillars are not the cause of MRLS. The latter conclusion is supported by the fact that ethanol-treated Eastern tent caterpillars remained capable of inducing abortion. Although the role of a virus was not ruled out by either of these studies, the results of a study using irradiated Eastern tent caterpillars determined that an Eastern tent caterpillar virus is not involved in MRLS. Another Malacosoma sp (i.e., forest tent caterpillar) in Kentucky did not cause abortion in mares. However, these forest tent caterpillars were raised in the laboratory on a commercial diet, whereas the Eastern tent caterpillars used in all studies were caught in the wild.

Currently, two hypotheses are considered to be plausible as investigations continue into the cause of MRLS:

- Bacteremia or septicemia is induced by penetration of the mucosa of the gastrointestinal tract by the caterpillar setae (i.e., hairs)
- A toxin carried or deposited in the environment by the caterpillar initiates the syndrome

REFERENCES


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1. MRLS is caused by exposure to caterpillars.
   a. Western tent d. cecropia moth
   b. fall webworm e. gypsy moth
   c. Eastern tent

2. Which was not a component of MRLS?
   a. early fetal loss d. unilateral uveitis
   b. late fetal loss e. metritis
   c. fibrinous pericarditis

3. An important feature of early fetal loss in cases of MRLS was
   a. metritis. d. colitis.
   b. hyperechoic allantoic and amniotic fluid. e. uveitis.
   c. endometritis.

4. A common clinical feature of late fetal loss in cases of MRLS was
   a. premature placental separation. d. hepatitis.
   b. enteritis. e. colitis.
   c. metritis.

5. In cases of MRLS, the common bacteria isolated from aborted fetuses were
   a. Staphylococcus and Pseudomonas spp.
   b. Escherichia coli and Enterococcus spp.

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c. Streptococcus and Actinobacillus spp.
d. Campylobacter spp and E. coli.
e. Klebsiella and Enterococcus spp.

6. The most common bacteria isolated from horses with fibrinous pericarditis were
   b. Streptococcus spp.    e. Pseudomonas spp.
   c. E. coli.

7. The ophthalmologic findings associated with cases of MRLS were
   a. corneal edema and exudate in the posterior and anterior chambers.
   b. corneal ulceration.
   c. conjunctivitis and corneal ulceration.
   d. optic neuritis and corneal ulceration.
   e. conjunctivitis and optic neuritis.

8. Histopathologic changes associated with late fetal loss in cases of MRLS did not include
   a. fetal pneumonia.    d. hepatitis.
   b. placentitis.        e. amnionitis.
   c. funisitis.

9. Funisitis is inflammation of the
   a. umbilical cord.    d. cervical star.
   b. allantoic membrane. e. chorionic membrane.
   c. amniotic membrane.

10. _______________ did not cause abortion in studies of MRLS.
    a. Ethanol-treated Eastern tent caterpillars
    b. The integument of Eastern tent caterpillars
    c. Irradiated Eastern tent caterpillars
    d. Eastern tent caterpillars stored at –94°F (–70°C)
    e. Gypsy moth caterpillars