Management of the High Risk Mare

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Managing the equine high risk pregnancy relies on many of the same premises as those employed for women. Determining the root cause of a condition affecting the late pregnant mare is central to proper management. Serial monitoring of the condition is critical to assess health and effects of treatment. Often, an acute insult begins the disease process but the symptoms become chronic. Management approaches must be modified to meet the needs of the mare and developing fetus. In all cases, the end goal is to facilitate adequate gestational length for fetal maturation and delivery of a healthy foal.

Serial Monitoring of the High Risk Mare

Serial monitoring of the mare and fetus is useful to determine the progression of disease as well as response to treatment. Physical examination findings are often the strongest indicator of a mare's response to treatment. Once or twice daily physical examinations can reveal aberrations in heart and respiratory rates, body temperature, mucus membranes, gastrointestinal sounds, digital pulses and ambulation. Appetite and alertness provide information about the overall status of the mare. Premature mammary development and production of secretions can indicate stimulation of the hypothalamic-pituitary-adrenal axis and initiation of parturition/fetal expulsion.[1] Changes in mammary secretion electrolytes can be monitored to predict impending parturition or response to treatment. [1-3] Vulvar discharge is identified in mares having ascending bacterial placentitis or vaginitis and may also change with treatment. Abdominal enlargement due to hydropic conditions or muscular defects can be monitored for changes so that treatment decisions are implemented.

Integrating physical examination findings with results of diagnostic tests provides full assessment of the mare. Baseline laboratory data obtained at admission should include complete blood count, serum chemistry and lactate. Additional tests that are often useful include progesterone and serum amyloid A assays. More recent information suggests that estrogen assays may provide additional useful information when monitoring the high risk pregnancy.[4] Systemic health is often not compromised with conditions affecting late pregnant mares, however, data obtained at admission may differentiate conditions affecting the gastrointestinal or musculoskeletal tract from others. Additionally, laboratory values may shift over time, positively or negatively, thus prompting therapeutic changes.

Serial transrectal and transabdominal ultrasound examinations provide real-time information regarding placental integrity and fetal health. Transrectal ultrasonography in late gestation is a useful tool for evaluating placental integrity (at the cervical star), fetal activity and fetal fluid character. [5] The caudal aspect

of the allantochorion at the cervical star is the most frequently affected area in mares with placentitis due to an ascending route of infection. Thorough examination of this area using transrectal ultrasonography is critical when diagnosing placentitis. In the normal pregnant mare, the combined uterine and placental (chorioallantoic) unit is measured. Values of the combined thickness of the uterus and placenta (CTUP) for mares with normal pregnancies have been established (Table 1).[5] Mares with placental infection or inflammation will have an increase in CTUP measures or separation of the membranes with presence of purulent material.[6] Serial transrectal monitoring (every other day or twice weekly) reveals increased or decreased CTUP measures either in response to infection or treatment, respectively. While placental separation is not expected to improve over time, serial examinations will demonstrate if separation becomes more profound.

Fetal health is best assessed through transabdominal ultrasonographic measures of fetal heart rate, tone, activity and size. [7, 8] Placental integrity and fluid character provide information about possible infectious processes. A thorough ultrasonographic examination at admission provides baseline information that can be used for comparison in subsequent examinations. For accurate evaluation of the fetus, the mare should not be sedated prior to ultrasonographic examination. When possible, every other day to once daily transabdominal ultrasonographic assessments are performed in high-risk mares for real-time assessment of fetal well-being. Not only do regular examinations provide assessment of fetal viability parameters, but importantly, they allow timely recognition of fetal death. This point is particularly important for mares administered drugs that might prevent naturally-occurring pregnancy termination with a dead fetus, such as progestins or anti-inflammatories.

The simplest indicator of fetal well-being is fetal heart rate. The average heart rate in a fetus greater than 300 days gestation is cited as 75 ± 7 bpm, but significant individual variation in heart rates occurs.[7] Fetal heart rate slows by approximately 10 bpm at greater than 330 days gestation. Activity level can affect fetal heart rate throughout late gestation. Consistently low (less than 55 bpm) or high fetal heart rates (> 120 bpm) are associated with fetal stress and warrant re-examination and possible intervention.[7]

Fetal activity level and tone are easily determined while examining a fetus for heart rate. [7, 8] Activity and tone provide additional parameters for assessing fetal well-being. 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 viable fetus. A live fetus has excellent “tone” in that it is active and it flexes and extends the torso, neck and limbs.[7] An atonic fetus is flaccid and lies passively within the uterus and may be folded in upon itself. This is often an indicator of a dead fetus. Therefore, clearly identifying

the atonic/dead fetus can be difficult as traditional landmarks, such as a beating heart, are not easily identified and may be obscured by flaccid, folded limbs.

The character of the fetal fluids is also evaluated using transabdominal ultrasonography. Ideally, ultrasonographic examination of pregnancy, including fetal fluids, is performed in the quiet mare and not immediately after transport or exercise. Allantoic fluid is generally anechoic (black) to slightly echogenic in the late-term mare. Echogenic particles (snowfall appearance) can be noted after maternal or fetal activity, but will resolve over time. The amniotic fluid is mildly to moderately echogenic (light gray) in a normal pregnancy. Fluids that are highly echogenic or consistently have flocculent material present may indicate infection. In mares with ascending bacterial placentitis, the echogenicity of the amniotic fluid often increases long before echogenic changes occur in the allantoic compartment. Interestingly, in mares with nocardia-form placentitis, the amniotic fluid remains normal but the allantoic fluid becomes highly echogenic. Fluid character can also change in response to effective treatment.

While transabdominal ultrasonographic examination of late term pregnant mares is often performed under hospital conditions, the field veterinarian can easily incorporate routine transabdominal examinations into practice. Workers from Hungary demonstrated reliable identification of compromised fetuses using three readily attainable parameters: fetal heart rate, fetal aortic diameter and CTUP.[9] Serial measurements of these parameters were compared to a more extensive equine fetal biophysical profile that included fetal heart rate, fetal aortic diameter, maximal fluid depth, uteroplacental contact, uteroplacental thickness and fetal activity. [7] Significant interchangeability was determined between a modified, rapid fetal examination (5-15 min) and a more extensive (25-40 min) fetal examination when identifying fetuses as risk. The take home message is that fetal ultrasonographic evaluation can, and should, be performed in mares deemed “at risk” for preterm delivery.

Treatment Strategies for the High Risk Mare

Treatment of the late pregnant mare is directed at; 1) resolving/reducing the insult; 2) systemically supporting the mare and fetus 3) preventing early delivery. Often, treatment is palliative. Diagnosis of the primary insult is essential to effective treatment. However, accurate diagnosis of a condition can be elusive so empirical treatment is often elected based on clinical signs. A simple rule of thumb is to treat the mare to save the foal.

Supportive therapy is the mainstay for all conditions affecting the late pregnant mare. Fundamental to maintenance of a healthy pregnancy is adequate nutrition, adequate perfusion and musculoskeletal stability. These goals can conflict at times, for instance with a laminitic mare, so finding balance is essential.

Fetal growth increases by approximately one pound a day in the last trimester.[10] Furthermore, lactation poses the greatest energy demand for all

horses with the exception of the intensely training athlete. Therefore, the mare's caloric intake at the end of gestation and early in lactation must meet the needs of these energy drains. A general approach is to have the mare at ideal body weight, and at an increasing plane of nutrition, as she moves into her final trimester. Nutritional needs increase in the first months of lactation. The mare's body condition should be carefully monitored to facilitate dietary adjustments and prevent weight loss. Several dietary calculators are available online such as: https://www.purinamills.com/horse-feed/tools/horse-feed-calculator.

Integral to ideal body condition is the mare's ability to ambulate freely and without pain. A mare with a musculoskeletal condition poses a significant challenge in late pregnancy. Not only may she be unable to access feed freely, debilitating, chronic pain can drastically impair caloric intake and increase feed metabolism. Intense dietary management is critical for these mares. Generally, a well-balanced, highly digestible concentrate ration should be combined with free access to high quality forage. Rarely are supplements necessary. For mares at a decreasing plane of nutrition during pregnancy, corn oil has been suggested as a means of efficiently increasing caloric intake. Beet pulp is a highly digestible fiber and simple carbohydrate that can be used as an additional source of energy or to promote gut transit.

The conundrum exists for pregnant mares with musculoskeletal aberrations such as laminitis, hydrops or body wall defects. A general approach for managing horses with laminitis/musculoskeletal conditions is to maintain a low-moderate body condition to reduce stress on the laminae and preserve hoof integrity. While this goal is achievable in early/mid gestation, it becomes challenging in the end of gestation and early lactation. Constant monitoring of the mare's body weight and pain level is required so that dietary adjustments are made to meet the energy demands during this time. Adequate pain control must be instituted to ensure maintenance of appetite and attitude. Intensive efforts to manage the underlying conditions for these mares are critical throughout gestation.

Medications in the Pregnant Mare

Little is known about drug metabolism and safety in pregnant mares. Most drug dosing and safety studies for horses have been conducted in geldings. Safety data for commonly used equine therapeutic drugs (antimicrobials, anti-inflammatory drugs, sedatives etc) are virturally non-existent. The concerns when administering a drug to a pregnant mare are the risks to the developing fetus, as well as risks to the mare. The fetus is particularly vulnerable given its poor ability to metabolize and eliminate most foreign compounds. Too little is known about placental metabolism of drugs in horses to expect that the placenta provides a barrier to the developing fetus. On the contrary, the presence of placental transport systems suggests that the gateway for molecules to access the fetus is significant. A growing body of work has been published in recent years regarding drugs that are commonly used to treat mares with placentitis.[11-16] As a part of these trials, placental transfer data of antimicrobial and anti-inflammatory drugs

have been established (Table 2). Penicillin and trimethoprim sulfamethoxazole (TMS) achieved minimum inhibitory concentrations (MIC) against *S. zooepidemicus* in allantoic fluid of mares with induced placentitis, while gentamicin was detectable at concentrations effective to treat *Escherichia coli* and *Klebsiella pneumoniae* (also implicated in placentitis).[12, 13] Pentoxifylline was detected in allantoic fluid of experimentally-infected mares, but flunixin meglumine was not. Ceftiofur sodium and ceftiofur crystalline free acid were also not detected in fetal fluids or placental and fetal tissues.[15] Firocoxib, a potent Cox-2 specific prostaglandin inhibitor has recently been shown to achieve concentrations in fetal fluids as well as fetal and placental tissues after administration to normal mares (Macpherson, unpublished data). It is not clear what prevented passage of specific drugs across the fetal membranes, but caution should be exercised when using unproven drugs in pregnant mares.

Placentitis is the most common reason for medicating pregnant mares in North America. Treatment strategies for mares with placentitis have been directed at addressing infection (antimicrobials), inflammation (anti-inflammatory) and uterine contractility (progestins). Several drugs that are commonly used in mares with placentitis are listed in Table 3. Data examining drug combinations that improve fetal survival suggest that curbing inflammation can be as important as treating infection. This treatment strategy likely applies to all infectious conditions.

Delayed delivery and improved foal survival are important endpoints when treating mares with conditions threatening pregnancy. Foal viability after mares were treated with some drug combinations has been assessed using a model of ascending placentitis. Long term administration of TMS and pentoxifylline tended ($P = 0.07$) to extend gestational length in mares with placentitis when compared to infected, untreated mares.[17] However, foal survival was not improved in treated animals. When progestins (altrenogest; Regumate™) were added to the TMS and pentoxifylline treatment regimen, 10 of 12 (83%) mares delivered viable foals.[18] All five untreated, infected mares aborted or delivered non-viable foals. This treatment regimen has been broadly adopted in clinical practice with varying results. One explanation for variations in efficacy when treating mares for placentitis is the time interval from infection to initiation of treatment. In experimental studies, treatment protocols are implemented immediately after clinical signs are identified in carefully monitored mares. This approach is difficult to adopt in a clinical setting and subtle changes are often missed. Work by Carrick, et al.[19] demonstrated the usefulness of early, aggressive ultrasonographic monitoring of mares in an “at risk” population and subsequent early initiation of treatment. Mares were examined starting at day 150 to 180 of gestation and were examined at least every 28 days. Treatment using TMS and altrenogest was begun at the first sign of ultrasonographic or physical abnormalities (vulvar discharge, mammary development). Live foal delivery rate in this clinical population improved from approximately 25% to over 80% using this approach.

Limitations exist with this treatment approach. While oral administration of TMS is convenient, increasing microbial resistance to this drug is concerning. Studies have shown that TMS is not consistently effective in eradicating *S. zooepidemicus, in vivo*, despite *in vitro* susceptibility of pathogens and high concentrations of TMS at the site of infection.[20] In a placentitis model, over half of the mares administered TMS had residual bacteria recovered from the uterus when cultured within 3 hours of delivery.[18] In contrast, uterine swabs obtained from normal foaling mares were negative.[21] While oral administration is a clear advantage for TMS, the inconsistent *in vivo* efficacy against streptococcal organisms is a detractor for using this antibiotic when treating placentitis. More recent information regarding uterine isolates from mares with metritis show low efficacy for this drug against predominant microbes (*E. coli, Klebsiella spp, S. zooepidemicus*).[22] With the increasing incidence of multi-drug resistant organisms, administration of an antimicrobial based on ease of use is not prudent. Unfortunately, the options for effective antimicrobials that are safe for pregnant mares and are easy to administer are limited. Parenterally administered drugs such as penicillin and gentamicin are ideal antimicrobial choices for the typical bacteria in placentitis, but frequent dosing, expense and/or intravenous administration limit their usefulness. In some cases, it may be prudent to initiate aggressive treatment with intravenously administered drugs for a shorter period (ie, two-three weeks) and continue long-term treatment with orally administered drugs (Macpherson, personal opinion). However, while long-term therapy proved to be beneficial in experimental placentitis, this treatment approach should also be investigated. Exposure of microbes to antimicrobials for long periods of time is a cause for microbial resistance to drugs.

Conclusion

Managing mares for conditions in late pregnancy is not recipe-driven. The challenge of determining the root cause of the problem, providing therapies that are effective and supportive/protecting the health of the mare and fetus is significant for the equine veterinarian. Treatments are often empirical. Administration of therapeutic drugs to pregnant mares must be considered carefully and judiciously. Often, the equine veterinarian faces the dilemma of a mare that suffers a life-threatening condition which, ultimately, will threaten the life of the fetus/foal. However, caution must prevail when the teratogenic and fetal risks of administering drugs to pregnant mares is unknown. Treatment plans for mares requiring pharmacologic intervention should be formulated with good sense and sound judgement. When possible, medications with few to no known adverse effects on a developing fetus should be used. The United States Food and Drug Administration (FDA) provides guidelines for drug use in pregnant women through categorization of drugs into Risk Categories. An adaptation (reprinted, Dr. Steeve Giguere, ACVMIM 2014) of the FDA guidelines, with some equine drugs included, is provided in Table 4. Furthermore, minimum treatment times, that effectively address the condition affecting the mare, should be adhered to. Finally, consistent monitoring of the mare and fetus is necessary so

that therapeutic choices can be modified as needed. As is frequently the case, clear client communication is an essential component as outcome for either the mare or foal is often difficult to predict.

Table 1. Normal values for ultrasound measurement of the Combined Thickness of the Uterus and Placenta (CTUP)[5]

Gestational Day	**CTUP (mm)**
Day 271-300	< 8 mm
Day 301-330	< 10 mm
> Day 330	< 12 mm

Table 2. Distribution of commonly used equine therapeutics after administration at recommended doses and intervals to pregnant mares.

DRUG	DRUG TYPE	DOSE/ROUTE OF ADMIN	[PLASMA]	[PLACENTAL FLUIDS]	[FETUS]
POTASSIUM PENICILLIN	Antimicrobial	22,000 IU/kg, IV q 6 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Not tested
GENTAMICIN	Antimicrobial	6.6 mg/kg, IV q 24 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Not tested
TRIMETHOPRIM SULFAMETHOXAZOLE	Antimicrobial	30 mg/kg, PO q 12 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Yes
CEFTIOFUR SODIUM	Antimicrobial	4.4 mg/kg, IM q 24 hours	Equivalent to non-pregnant horses	**Not detected or very low levels (allantocentesis**)	No
CEFTIOFUR CRYSTALLINE FREE ACID	Antimicrobial	6.6 mg.kg, IM q 96 hours	Equivalent to non-pregnant horses	**Not detected or very low levels (allantocentesis**)	No
ENROFLOXACIN	Antimicrobial	5 mg/kg, IV 7.5 mg/kg, PO q 24 hours	Equal/higher non-pregnant horses	N/A	**Fetal Cartilage effects not known**
DOXYCYCLINE	Antimicrobial	10 mg/kg, PO Q 12 hours	N/A	Present in allantoic > amniotic fluid	**Detected in foal plasma and joints**
PENTOXIFYLLINE	Anti-cytokine, Vasoactive, xanthine deriv.	8.5 mg/kg, PO q 12 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Yes
FLUNIXIN MEGLUMINE	Non-steroidal anti-inflammatory	1.1 mg/kg, IV q 12 hours	Equivalent to non-pregnant horses	Not detected (microdialysis)	Not tested but unlikely
FIROCOXIB	Non-steroidal anti-inflammatory	0.1 mg/kg PO q 24 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Not tested
PHENYLBUTAZONE	Non-steroidal anti-inflammatory	4.4 mg/kg, PO q 12 hours	Equivalent to non-pregnant horses	Therapeutic concentrations	Not tested

Table 3: Common therapies used to treat mares with placentitis

Drug	**Dosage**	**Mechanism of action**
Potassium penicillin	22,000 U/kg, IV, q 6 h	Antimicrobial
Procaine penicillin	22,000 U/kg, IM, q 12 h	Antimicrobial
Gentamicin sulfate	6.6 mg/kg, IV or IM, q 24 h	Antimicrobial
Trimethoprim sulfamethoxazole	15 – 30 mg/kg, PO, q 12 h	Antimicrobial
Trimethoprim sulfadiazine	242 mg/kg, PO, q 12 h	Antimicrobial
Flunixin meglumine	1.1 mg/kg, IV or PO, q 12-24 h	Anti-inflammatory/anti-prostaglandin (mixed Cox-1 and 2)
Phenylbutazone	2.2 – 4.4 mg/kg, PO, q 12-24 h	Anti-inflammatory
Firocoxib	Administered on a per body weight basis	Cox-2 selective anti-inflammatory
Pentoxifylline	8.5 mg/kg, PO, q 12 h	Anti-cytokine/anti-inflammatory
Altrenogest	0.088 mg/kg, PO, q 24 h	Anti-prostaglandin/tocolytic
Acetylsalicylic acid	50 mg/kg, PO, q 12 h	Anti-inflammatory/anti-platelet

Table 4. FDA Pregnancy Risk Categories with selected examples of drugs commonly used in horses (Reprinted and adapted, S. Giguére, ACVIM 2014 Proceedings)[23]

CATEGORY	DEFINITION	EXAMPLES OF EQUINE DRUGS*
CATEGORY A	Adequate and well-controlled studies have failed to demonstrate risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters)	
CATEGORY B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women	Azithromycin, erythromycin, penicillins, cephalosporins, Metronidazole, amphotericin B, omeprazole, cimetidine, ranitidine
CATEGORY C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks	Clarithromycin, imipenem, gentamicin, fluoroquinolones, TMS, rifampin, fluconazole, itraconazole, ketoconazole, some NSAIDs, butorphanol, dexamethasone, prednisolone, fluticasone, albuterol
CATEGORY D	There is positive evidence from human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant the use of the drug in pregnant women despite potential risks	Tetracyclines, aminoglycosides (except gentamicin), some NSAIDs, ACE inhibitors, diazepam, phenobarbitol
CATEGORY E	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits	Misoprostol

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