MESSAGE FROM THE GRAYSON-JOCKEY CLUB RESEARCH FOUNDATION

PLACENTITIS, 20 YEARS LATER... WHAT HAVE WE LEARNED?

Grayson-Jockey Club Research Foundation

BY DR. MARGO MACPHERSON

IN 1999 THE LATE DR. MICHELLE LEBLANC was awarded a grant by the Grayson-Jockey Club Research Foundation to investigate factors contributing to the disease process of ascending, equine placentitis.

Using ambitious methodology, Le Blanc's research team established a working model of induced placentitis using a transcervically-placed inoculum of clinically isolated *Steptococcus equi* subspecies *zooepidemicus*. While some would argue the model does not realistically represent the clinical condition, the information gained from this model has positively improved the outcome of many mares affected with placentitis. The question is: what exactly have we learned about equine placentitis?

Placentitis in mares is most commonly caused by bacteria ascending through the vagina. The pathogen most commonly implicated in equine placentitis is *Streptococcus equi* subspecies *zooepidemicus*. Led by LeBlanc, workers from the University of Florida conducted several coordinated studies that provided formative information regarding the pathophysiology of this disease.

Important information gained from these studies revealed that after bacteria migrated through the mare's cervix, infection and inflammation of the placenta followed. Uterine contractions occurred earlier, and with greater strength, in infected mares, thus causing early delivery of premature foals. Some, but not all, aborted fetuses had bacterial infections. Some foals were delivered prematurely and survived. From these, and studies in other species, it is thought that some foals from infected mares are prompted to mature more quickly, in utero, due to the indirect production and secretion of cortisol.

Ultimately, treatment strategies have been directed at resolving bacterial infection, reducing inflammation and maintaining pregnancy long enough so that fetal maturation occurs and the foal survives.

Several studies that have been funded by the GJCRF have investigated diagnostic and treatment protocols for mares with placentitis to improve foal survival. Physical and ultrasonographic examination findings in mares "at risk" for placentitis remain the mainstay for initial diagnosis of disease. However, clinical findings often lag well behind the disease process and treatment. Ongoing studies supported by the GJCRF are investigating metabolomics, or the use of small metabolites found in cells, biofluids or tissues, for earlier diagnosis of placentitis.

Therapeutic agents that are used clinically have also been tested for placental passage and improved foal viability in normal pregnant mares and mares affected with placentitis. Commonly used drugs such as penicillin and trimethoprim sulfamethoxazole have been shown to achieve effective concentrations against *S. zooepidemicus* in allantoic fluid of mares with induced placentitis. Similarly, gentamicin was detectable at concentrations effective to treat *Escherichia coli* and *Klebsiella pneumoniae* (also implicated in placentitis) in mare allantoic fluid.

Based on drug concentrations, these antimicrobial drugs may be appropriate for treating placentitis. Ceftiofur sodium and ceftiofur crystalline free acid were not detected in fetal fluids or placental and fetal tissues, but did have a pharmacologic profile in pregnant mares that was similar to non-pregnant animals. Thus, cetioufur-based drugs are not good antimicrobial drugs for treating mares with placentitis but can be useful for treating other disease (i.e. respiratory) in pregnant mares.

Anti-inflammatory drugs are an important part of placentitis treatment protocols. Pentoxifylline was detected in allantoic fluid of experimentally-infected mares, but flunixin meglumine was not. Firocoxib, a potent anti-inflammatory drug has recently been shown to achieve concentrations in fetal fluids as well as fetal and placental tissues after administration to normal mares. GJCRF studies are ongoing to determine whether firocoxib, physiologically, impacts the placentitis disease process. These studies hope to provide evidence to support the use of firocoxib in mares with placentitis.

Delayed delivery and improved foal survival are important end points when treating mares with placentitis. Long term administration of TMS, pentoxifylline, and progestins (altrenogest; Regumate™) to mares with induced placentitis resulted in the majority of mares (10/12; 83%) delivering live foals.

Untreated, infected mares aborted or delivered non-viable foals. This treatment regimen has been broadly adopted in clinical practice with varying results. More recently, a group of seven mares with placentitis were administered TMS, firocoxib, and altrenogest. All seven mares delivered live foals. While results from this small study do not suggest a "silver bullet" treatment for mares with placentitis, they do encourage further investigation of this drug regimen in a large population of mares.

In summary, equine placentitis is a challenge both diagnostically and therapeutically. Yet, salvaging a pregnancy can be enormously rewarding. Ongoing efforts by several investigators are focusing on methods for earlier diagnosis of disease, allowing for more rapid initiation of effective treatments and delivery of more viable foals. BH

Dr. Margo MacPherson is a reproduction professor at the University of Florida and a Grayson-Jockey Club Research Foundation-funded researcher.