

SHINING A LIGHT ON THE BLACK BOX OF EARLY PREGNANCY LOSS

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This study will determine how common genetic disorders of the early equine embryo occur as well as identify how they present to veterinarians and key factors that increase their risk.



While progress has been made over the last two decades in getting more mares pregnant, owners and veterinarians still face a significant challenge in preventing pregnancy loss, particularly in the first two months after conception. This lack of progress is significantly hampered by our lack of understanding of the reason a pregnancy fails making treatment and management approaches close to impossible.

Previous research has focused on the possible role of the mare's uterus in providing a suitable environment for the developing embryo, but in contrast, a significant gap exists in understanding all other causes of early pregnancy loss (EPL) which account for around 60-80% of cases.

Our lab has been investigating novel reasons why a pregnancy may fail and have approached this by working alongside vets, to pioneer new methods to obtain clinical cases of EPL and determine if their genetic composition is compatible with life. Veterinarians submit tissue from clinical cases of EPL to our laboratory for assessment. In our first analysis of these failed conceptuses, we found that 20% of clinical cases were associated with a genetic disorder termed aneuploidy, that is, the loss or gain of a whole chromosome compared with the normal number.

This condition is very well described in the human literature as a common cause of miscarriage in women but it was the first description of this disorder in cases of pregnancy loss in the mare. An abnormal number of chromosomes results in significant disruption to the genome usually incompatible with continuation of the pregnancy in any mammalian species. It represents the most common single cause of EPL described to date in intensively managed mares finally providing us with a new target to interrogate. We know the genome can be modified from its normal state in many other ways.

Exactly if and how these other genetic variations in the genome lead to pregnancy loss in the mare remains unknown. Furthermore, we know very little about the clinical features of genetically abnormal pregnancies, key to vets being able to identify which pregnancies should be maintained, which are better off being terminated and the mare rebred.

This project will investigate two types of genetic disorders termed triploidy and aneuploidy. Instead of a single whole chromosome being duplicated or lost, as is the case of aneuploidy, in triploidy an individual has an extra copy of all the chromosomes resulting in three full sets as opposed to the usual two sets. The project will characterize how these embryos ended up with an abnormal number of chromosomes. We predict this will be very common (30-50% of cases) and it primarily due to a combination of (i) genetic errors in the egg and (ii) an error of the egg that allows two sperm to fertilize the egg, as opposed to the usual one sperm.

Studies in women have shown that the source of the genetic defect impacts multiple clinical features of the pregnancy, which is incredibly useful for early detection and clinical management by the veterinarian. Therefore, will also ask the questions: What risks factors (exposures) increase the chance of these genetic disorders occurring? How do these pregnancies present clinically so that they can be detected and managed appropriately by the veterinarian? Ultimately this will empower veterinarians with new knowledge that we predict will lead to new diagnostic tests, treatment approaches and ultimately reduce the occurrence of this common but frustrating condition.

The team is uniquely placed to investigate genetic causes of EPL in the mare with a large tissue bank and clear ways to expand these in 2024/2025 achieved through established and strong partnerships with multiple collaborating veterinarians and a track record in reproduction, genomics, epidemiology and Thoroughbred research. An established collaboration with an international leader in equine genomics is also in place for consultation on genomic methodologies.

Importance to the Equine Industry: The ultimate goal of owners of breeding mares is to produce a viable and healthy foal each year she is bred. One of the greatest impediments to achieving this goal is the loss of her pregnancy in the first two months following conception, referred to here as early pregnancy loss (EPL). T

his condition is incredibly frustrating for the veterinarian and owner alike as it results in increased veterinary interventions and associated welfare implications for the mare, much higher costs for owners, and can be emotionally distressing for owners striving to produce that elusive foal. It can also mean a mare fails to produce a foal that season as a result of poor fertility related to endometrial cup formation, or indirectly due to drifting of the conception date so late in the season that it is no longer viable to breed her in the subsequent year. The first question owners often ask when the veterinarian finds a failed pregnancy is: why did it fail?

Unfortunately, we know so little about the underlying causes of EPL that the answer is usually 'I don't know'. Scientific studies have shown that in around 60-80% of clinical cases of EPL the underlying cause is not identified using currently available knowledge. In the absence of specific diagnoses of the cause of EPL, stud farm veterinarians have very few options available to them to manage EPL. Generic treatments such as progesterone supplementation is sometimes used in a hope of preventing EPL, although low progesterone is usually not the reason that the pregnancy was lost and therefore in most cases

it is ineffective. Further, pregnancies with genetic errors incompatible with life that are treated with progesterone are unnecessarily prolonged, and as a result, the mare may miss the opportunity to be rebred that season. Essential to overcoming these challenges is identification of new explanations as to why EPL occurs informing novel diagnostic tests, therapeutics and management approaches can be implemented in the future.

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