Placental pathology: where does it all start?

Dr Stefania Bucca
Qatar Racing and Equestrian Club
POBox7559
Doha, Qatar

Introduction

Placental pathology represents the most common cause of preterm delivery, fetal death, stillbirth and neonatal disease worldwide in the horse [1].Inflammatory, degenerative, toxic and purely vascular conditions may affect placental tissues and function with variable outcomes. Some pathologies maybe inconsequential for the normal development of the foal, while many are fatal and lead to abortion or stillbirth. In between there is a spectrum of less severe pathologies that can result in the birth of a live foal, but the disease process, or its effects, may continue into the post-natal period and beyond. Challenging gestational conditions activate the close interaction between the three pregnancy compartments (maternal, fetal and placental) with resulting compensatory mechanisms, ultimately aiming at maintaining pregnancy. Under these circumstances, identifying the primary insult and pathogenesis can be rather difficult, prompting the question: where does it all start?

Incidence

The incidence of placental pathology is currently based on survey studies of equine abortion. These studies give some indication of general trends and geographical variation on the causes of abortion and foal death. However, direct comparison between studies of different causes of abortion is difficult due to the use of different classifications of disease, different levels of diagnostic investigation and the inclusion or not of neonatal death as well as abortion. Nowadays, umbilical cord torsion, often associated with a long umbilical cord, has been reported as the most common cause of abortion in the UK [2], but in US surveys, bacterial infectious placentitis represents the most common cause of abortion [3].It is not clear if these differences relate to different diagnostic procedures and interpretation or to climatic/environmental or management differences, influencing the risk of placentitis or risk factors affecting cord length and a predisposition to torsion. A more comprehensive assessment of the real incidence of placental pathology should include those conditions affecting the placental functional area, leading to intrauterine growth restriction and a group of placental disorders loosely termed as “placentopathies”, associated with premature placental separation. Improving diagnostic techniques may enable us, in the near future, to detect and monitor dynamically placental pathological conditions in order to implement preventive treatment and long-term follow up studies. However, at present we have to rely on placental examination to give historical insight on life in utero.

Pathogenesis

The pathogenesis of a dysfunctional placenta may recognize multiple contributing factors, originating from the fetal or maternal compartments, or more specifically, from a direct insult to the placental tissues. In particular, toxin insult to placental function can potentially take many forms. Key biological components of placental development and function, susceptible to toxic insult, may induce profound changes in placental metabolism. Such changes may result in altered placental development, direct cytotoxic effects on maternal and fetal placental tissue, induction of apoptotic cell death, endocrine disrupters, vasoactive effects on

either the maternal or fetal cardiovascular system, altered placental responsiveness to normal physiologic demands (altered homeostasis) and loss of immune-modulation enabling maternal rejection. And the question arises again: where does it all start?...
A large number of infective agents has been implicated in the pathogenesis of placentitis, many being opportunistic or environmental invaders [4]. Bacterial agents commonly associated with the occurrence of placentitis include Streptococcus equi subspecies zooepidemicus, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa as well as Leptospira spp and Nocardioform bacteria (Crossiella equi, Amycolatopsis spp and others). Annual variations in numbers and types of placentitis reported in different geographical areas suggest the possible role of environmental factors in the incidence of the condition (i.e: MRLS in Kentucky 2001-2002).

Placentitis
Placentitis refers to inflammation of the chorioallantois, often caused or complicated by infective agents and frequently extending to the amnion (amnionitis) and the umbilical cord (funisitis). The inflammatory response may vary in intensity from slight to severe and show a variable distribution from localized to diffuse. In general, the location of placentitis reflects the route by which the infection entered the uterus [4]. Four different types of equine placentitis have been described according to the morphological lesions and suggested pathogenesis, namely ascending, focal mucoid (nocardioform), diffuse (haematogenous) and, less commonly, multifocal. Overall, ascending placentitis is the most prevalent type of placentitis.

Lesions Distribution
Ascending Placentitis
Ascending placentitis in mares is reported to be most commonly caused by microrganisms ascending through the vagina and breaching the cervical barrier. An active role of the cervix in the pathogenesis of the condition is therefore implicit. If there are bacteria and/or fungi on the cervix and the cervical seal is compromised, they can enter the uterus and cause placentitis. Anatomical, hormonal or even neurological factors contributing to cervical incompetence and/or enhanced perineal or vaginal contamination will increase the risk of ascending placentits. Cervical inefficiency due to critical cervical shortening in mid gestation has been extensively described in women as a leading cause of preterm delivery, with no convincing evidence as to the possible cause. Progesterone administration and cervical cerclage have been used as effective means to correct the condition in the absence of infection [5]. A similar condition has been recently reported in pregnant mares and a comparable therapeutic approach appears to be highly beneficial [6]. Ascending placentitis tends to recur in some mares, where regular monitoring of US parameters of the cervix and cervical pole CTUP throughout gestation allows timely implementation of preventive strategies.
Ascending placentitis generally develops and progresses slowly during the course of weeks or months before clinical signs become apparent. The more chronic the infection the more extensive or pronounced the lesions of chorionic thickening and fetal growth restriction are likely to be. Depletion of chorionic villi, thickening and discoloration are commonly observed at the cervical pole of the affected placenta, often associated with a fibro-necrotic exudate. Thickening at the cervical star can prevent it rupturing at birth or abortion, so that the chorion tears across the rostral body. In about 12% of cases, infection will rapidly spread to the fetus causing septicaemia and abortion, before placentitis has become grossly evident. A variety of bacteria can be associated with ascending

placentitis, but most commonly Streptococcus equi subspecies zooepidemicus and Escherichia coli.

Diffuse or Multifocal Placentitis
Less commonly diagnosed, is associated with haematogenous spread of microorganisms to the uterus of the mare with subsequent infection of the placenta. Occasionally mares may show pyrexia and signs of septicemia prior to abortion. This form is usually associated with infection by viral agents (EHV, EVA) and some bacterial microorganisms in the genera Salmonella, Histoplasma and Candida. In several countries an increasingly recognised example of abortion and stillbirth due to a diffuse placental villitis is that caused by a number of different leptospiral serovars.

Focal Mucoid Placentits.
Also known as nocardioform placentitis, a chronic-active placentitis that occurs at the base of one or both uterine horns or rostral body. Gram-positive" nocardioform" filamentous branching microorganisms (Crossiella equi/ Amycolatopsis spp/Streptomyces spp) have been associated with the distinctive lesions, where sites with villous loss are often coated in brownish, muddy, mucoid exudates. The infection, although limited to the chorionic surface of the placenta, causes late abortion, stillbirths or premature births and has emerged as the most commonly diagnosed type of placentitis during recent years. The pathogenesis of this form of placentitis is presently unknown, and an experimental model to reproduce the disease recently proposed by Canisso et al (2015), failed to induce nocardioform placentitis in challenged mares.

Diagnosis
Diagnosis of placentitis during gestation is often difficult, as most mares show no outward signs of infection. Effective treatment of placentitis requires early diagnosis, ideally prior to the appearance of clinical signs (premature mammary development and lactation and vaginal discharge). Currently, ultrasound evaluation of the placenta is used to detect early cases of placentitis [9] and to implement treatment to prevent abortion and delay premature labor. While this practice has allowed more effective treatment and has improved the outcome in many cases, it is often impractical to ultrasound every mare repeatedly during mid-late gestation. In addition, early stages of placentitis can be missed during ultrasound examination and the technique is also prone to false positive diagnosis, resulting in unnecessary treatment, with long term risk of developing widespread bacterial resistance against antibiotics and the development of "super bugs".

Endocrine monitoring of affected mares can be a useful method to identify those individuals at risk for abortion or premature delivery, since the placenta synthesizes/metabolizes a wide variety of hormonal substances, critical for pregnancy maintenance and well-being. Repeated measurements are required. In addition, measurement of acute phase proteins has recently emerged as a useful biomarker in mares with experimentally placentitis. Serum amyloid A (SAA) has been reported to have a rapid and dramatic elevation, as early as 2 days post intracervical inoculation. Although SAA appears to be a very sensitive indicator for acute bacterial placentitis, it is a very non specific indicator, as many other acute inflammatory conditions may result in its elevation. It appears likely that more than one biomarker maybe required for accurate and early detection of placentitis in the mare. Following delivery/birth, gross examination and histopathology of fetal membranes should be carried out to confirm diagnosis.

Outcome

Placentitis results in several outcomes. In addition to abortion, stillbirth and pre-term birth, the mare may produce small weak foals, small normal and normal foals. Small, weak neonates represent a special management and medical challenge, as they carry an increased risk of developing sepsis and orthopaedic problems and suffer a degree of prematurity. Small normal neonates usually result from mares displaying clinical signs for quite sometimes. These foals usually do well, as they have completed their fetal maturation stage in preparation of birth [10]. They still carry a risk for sepsis and orthopaedic complications.

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