Chapter 16

Pregnancy Loss in Mares

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Additional information is available at the end of the chapter

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Abstract

The reasons concerning losses during the first months of pregnancy has special importance in equine reproduction. Most of these losses occur early in pregnancy and around 15-20% of mares that conceive will lose the embryo before day 50. Early pregnancy loss is generally characterized by the sudden disappearance of the embryonic vesicle and is due to different reasons. Several etiologies factors involving both the mother and the embryo as, inflammatory and non-inflammatory endometrial disease, progesterone insufficiency, maternal age, lactation, site of intrauterine fixation of the embryonic vesicle, stress, plane of nutrition, season or climate, chromosome abnormalities or oocyte quality are some of the factor listed. Abortion occurs from the first month of pregnancy to full term and may be have an infectious or not origin. Causes of abortion include viral or bacterial infections, ingestion of mycotoxins, stress, gene mutations, Mare Reproductive Loss Syndrome, lack of sufficient nutrients and umbilical cord abnormalities. Some mares will show signs of impending abortion but other mares will abort without warning. Premature labor, discomfort, unusual activity or having a vulvar discharge of the mare require immediate attention. Pregnancy failure in mares represents a serious economic damages, expectations, and potential genetic improvement. Therefore is absolutely important that all losses are assessed for giving an appropriate treatment, and for preventing current and future losses.

Keywords: equine, mare, pregnancy, fetal loss, abortion

1. Introduction

1.1. Pregnancy loss in mares

In equine normal pregnancy, parameters include a gestation length of 330–340 days, an umbilical cord with a length of 36–84 cm and a placental weight (thoroughbred) of 5.7 ± 0.08 kg, or 11% of the foal's body weight. The fail of fertilized eggs to result in a live foal about 11 months later is one of the more frustrating aspects of horse breeding [1, 2].

In mares, abortion is defined as the failure of the fetus before it reaches the 300-day gestation period. A dead foal, either during or at the end of the pregnancy, may result from a diversity of reasons. Infectious agents, such as bacteria, viruses or fungi, or other "causes", can attack the fetus or fetus membranes, causing fetal death and expulsion. These "causes" are attributable to the mare, fetus, or external factors, including twinning, hormonal deficiencies, congenital anomalies, ergot alkaloid toxicity, or ingestion of tent caterpillar setae [3, 4].

Most of the losses occur in the first 35 days of pregnancy and the embryo is resorbed, after which the mare may come back into heat at a longer interval after the last estrus. In fact, around 20% of mares that conceive will lose the embryo before day 50. Older mares and mares with uterine inflammation have an increased risk of early embryonic loss. Stress and other diseases also may increase the rate of early embryonic loss. If the embryonic loss is detected, the mare can be served again later in the breeding season [5, 6].

If the abortion cause is bacterial, fungal, viral, hormonal, stress-induced, or the result of twinning, will appear to be spontaneous with symptoms of the contributing cause, which sometimes, do not have time to develop fully. Therefore, premature labor, discomfort, unusual activity, bagging up or having a vulvar discharge of the mare require immediate attention, and actions should be taken to safeguard the health of the mare and, if possible, the foal [7].

1.2. Early embryonic loss

In the mare, early pregnancy failure corresponds to the time of transition from the embryo stage to the fetal stage of conceptus development [6]. Early pregnancy loss is generally characterized by the sudden disappearance of the embryonic vesicle between ultrasound examinations. However, signs of impending embryonic loss can be detectable with transrectal ultrasonography. Usually, there are different signs which include the following: irregular shape of an embryonic vesicle, prolonged mobility of a vesicle beyond day 16, excessive endometrial edema, an undersized vesicle, loss of embryonic heartbeat, detachment of a vesicle with fluid loss, increased echogenicity of fluid within the conceptus, or abnormal development of the embryonic membranes [5].

Ultrasonography provided an early diagnosis of pregnancy (day 12th–14th postovulation) and important information about the development of embryo and embryonic death. Thus, under field conditions, this method allows direct assessment of the conceptus viability during approximately three-quarters of the interval when early embryonic loss occurs. The incidence of embryonic loss is generally in the range of 5–15%; however, foaling rates decline with maternal age after 14–16 years[8]. Thus, in mares over 18 years of age, the highest embryonic loss rates (20–30%) can be detected[9].

During the first stages of embryo development (fertilization to day 10th), several studies estimate that the embryonic loss rate were 9% for young mares compared to 60–70% for aged mares[10–12]. Thus, blastocysts recovered from the uterus of aged mares have more morphological defects, and fewer of them survive after embryo transfer to healthy recipient mares [13, 14].

The interval between day 2 and 4 might represent a critical period in pregnancy failure in aged mares. This finding indicates that pregnancy rates at day 2 were similar in young and aged mares; by 4 days after fertilization, there was a significant reduction in pregnancy rates in aged mares [10]. The equine embryo resides in the oviduct for 6 days and reaches morula or early blastocyst stage of development before entering the uterus. Therefore, there are a number of important events that occur during oviductal transit that could affect embryonic survival. During this time, early blastomeres cleavage progresses to further differentiation resulting in compaction, blastulation, and initial formation of the inner cell mass and trophoblast. Likewise, the embryonic genome is activated, and the transition from maternal to embryonic control of development has been proposed as a critical juncture in embryonic development [15]. Differences in proteins synthesized and secreted in vitro by explanted oviductal tissue have been reported and demonstrated that both qualitative and quantitative differences in the patterns of proteins from oviductal epithelium were detected between young and aged mares [16].

Several etiology factors have been described as responsible for early embryonic loss in mares. Vanderwall[9] discussed several etiology factors involving both the mother and the embryo. Thus, inflammatory and non-inflammatory endometrial disease, progesterone insufficiency, maternal age, lactation, site of intrauterine fixation of the embryonic vesicle, stress, plane of nutrition, season or climate, chromosome abnormalities, and oocyte quality are some of the factor listed.

Related to oocyte quality, mare age-related decline in oocyte quality is a major factor in the reduced fertility. In an in vitro studies [15], oocytes from aged mares reached metaphase II at a much lower rate than did oocytes from younger mares, with more oocytes from older mares arresting at metaphase I. This suggests that meiotic division of oocytes from older mares is more likely to be abnormal. In a report of Carnevale and Ginther[17], using gamete intrafallopian transfer studies, oocytes were collected from both young and aged mares and transferred into the uterine tube of young recipient mares. The results of this experiment inform that oocytes from aged mares resulted in significantly fewer pregnancies than those from young mares after transfer to the uterine tube of a young recipient mare. Mitochondria from in vitro matured oocytes from aged mares also demonstrated more ultrastructural abnormalities, suggesting that it may be an important underlying factor associated with reduced oocyte quality[18].

Prolongation of the follicular phase in aged mares is associated with an elevation of both Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH), and this prolonged follicular development is related with an increased incidence of abnormal oocytes[19]. Different reports show that in mares, aging of the oocyte subsequent to ovulation results in a decline in pregnancy rates, a delayed embryonic development, and possibly an increased rate of subsequent embryonic loss [20, 21].

Endocrine factors, such as progesterone, have also been cited as a potential factor contributing to reduced fertility or early embryonic loss in mares[16, 22, 23, 24]. Progesterone is the hormone whose function is to prepare the uterus for the reception and development of the fertilized egg. In most animals, this hormone is produced primarily by the corpus luteum of pregnancy. The corpus luteum is constituted of specialized cells (small and large cells) that produce progesterone. In the horse, in case of pregnancy, the corpus luteum produces enough

progesterone to maintain the gestation for only 40–50 days. Around this time, the "endometrial cups" develop in the uterus. These structures produce and secrete equine chorionic gonadotropin (eCG), a hormone that stimulates the production of additional progesterone by the ovary. These “extra” progesterone is required to maintain pregnancy into the fourth or fifth month of gestation[25]. Until day 40 of the embryonic period, progesterone is produced solely by the primary corpus luteum that is formed at the time of the initial ovulation. Minimal accepted concentrations of serum progesterone vary according to the laboratory or study reported; however, values between 2.0 and 4.0 ng/mL are typically used as the minimal serum progesterone concentration during early gestation [22, 26].

Maternal recognition of pregnancy involves an interaction between the conceptus and the uterine environment, which lead early conceptus development and implantation. Also is used to refer to the physiological process by which the lifespan of the corpus luteum is prolonged. During the estrus cycle, an increase in the secretion of prostaglandin can be observed 14 days after ovulation, which promotes lysis of the corpus luteum[27]. According to this, the pregnancy recognition signal has to be present on or before day 14 of pregnancy. In this regard, a study conducted with conceptuses collected 14 days after ovulation were placed in dialysis bags permeable for substances of different molecular weights and co-incubated with endometrial explants. These results indicate that prostaglandin inhibitory factor is a low molecular mass (3-10 kDa) proteinase K-resistant substance that may be adsorbed by dextran-coated charcoal [28].

Lysis of the corpus luteum associated with failure of maternal recognition of pregnancy can lead to early embryonic death[29, 30]. Failure of the embryo to block luteolysis has been identified in mares with embryonic loss prior to day 20 and was characterized by the presence of embryonic vesicles that were too small for days of age and by failure of fixation. In these mares, serum progesterone concentrations were lower at days 12, 15, and 18[31].

1.3. Abortions

Causes of abortion in mares include viral diseases, ingestion of poisonous plants, mycotoxins, bacterial infections, stress of either the mare or the fetus, gene mutations, mare reproductive loss syndrome (MRLS), and lack of sufficient nutrients to support the fetus, especially in the case of twins [32, 33].

Umbilical cord abnormalities also cause abortion. Those abnormal conditions of the cord, which can produce potentially lethal problems in the fetus, are usually associated with excessive length and include strangulation of the amniotic portion of the cord around parts of the fetus and excessive torsion of the amniotic part of the cord with urachal and vascular obstruction [34].

1.3.1. Infectious causes of abortion

Over the past 6 years, infectious abortions have accounted for approximately one-third of all abortions diagnosed. Equine herpesvirus (EHV-1) is the major infectious agent, accounting for 18% of all abortion diagnoses [35].

1.3.1.1. Viral abortion

Equine herpesviruses

Five, equid herpesviruses (EHV) have been identified and are known to infect the horse. Of these, equid herpesviruses 1 and 4 are the most important for horse industries worldwide based on their veterinary medical and economic consequence. Equid herpesvirus 1 (EHV-1) or abortion virus is most often related with abortions, whereas equid herpesvirus 4 (EHV-4) or rhinopneumonitis virus is associated with respiratory disease in colts. Beyond, both virus subtypes have the potential to cause respiratory disease and abortion [36].

Equid herpesvirus 3 is the cause of equine coital exanthema. This is contagious venereally transmissible disease affecting the external genitalia of the stallion and the mare, but there is no evidence implicating the virus in infertility or abortion in the mare [37, 38]. Equid herpesviruses 2 and 5 are gammaherpesviruses that have been associated with different clinical manifestations in the horse, such as upper and lower respiratory disease [39], keratoconjunctivitis[40], chronic follicular pharyngitis, and poor performance [41].

Equid herpesviruses 1 and 4 were originally considered subtypes of one virus EHV-1[42]. For both viruses, the natural host species is the horse and in this situation both are genetically stable[43]. However, EHV-1 can infect cattle, cervids, camelids, and laboratory mice [44, 45]. Likewise Equid herpesvirus 1 is considered as the principal cause of contagious abortion in mares in many countries [43]. Another clinical outcome of EHV-1 infection is a neurological syndrome, specifically a myeloencephalopathy[46] and also has been linked to a fatal non-neurological syndrome characterized by a multisystemic vasculitis, severe pulmonary edema, and a mild enterotyphocolitis[47].

Transmission of EHV-1 and EHV-4 takes place primarily by the respiratory route. This is consequence of direct or indirect contact with nasal or conjunctival secretions of infected animals, aborted fetuses, placental membranes, and fluids. Transplacental transmission may occur in the case of EHV-1 and not often for EHV-4. In the case that these type of transmission occurs, usually result in abortions in the last trimester of pregnancy [48].

Most abortions due to this virus occur between 8 and 11 months of gestation, although they may occur as early as 5 months. Once the virus reaches the pregnant uterus, it infects endothelial cells of the uterine vascular layer causing endometrial vasculitis. This causes the damage of the endometrium and the chorioallantoic membrane. At the same time, this leads to thrombosis of the affected vessels of the placenta[3, 49, 50].

The severity and the extent of thrombosis determine whether the abortion occurs or not. In those areas where thrombotic lesions are focal and not widespread, the virus is transmitted to the fetus by infected fetal leukocytes, causing widespread in many tissues necrotic lesions. At the same time, a local edema develops in the maternal-fetal interface, resulting in premature separation of the chorioallantoic membrane from the endometrium. The final result is abortion with the fetus and placenta positive for the virus. However, in cases of extensive thrombotic lesions, placental ischemia occurs rapidly with premature separation of the placenta and abortion. In such circumstances, the virus has not had enough time to invade the fetus and therefore the placenta, but not the fetus is positive for the virus[51].

Infected mares during early pregnancy, no induction of abortion before the fifth month of pregnancy is attributed to the fact that endometrial vascular changes and expression of viral antigen on endothelial cells, are significantly lower than those observed in mares infected later in pregnancy [52]. Mares exposed very late in pregnancy to EHV-1, may not abort, however, will give birth to a congenitally infected live foal. In some cases, the foal will be born alive at term and will die shortly after birth due to infection by the virus. The abortion rate may approach 100% in a herd of susceptible mares [36].

Abortion due to EHV-1 or EHV-4 has no adverse effect on the subsequent fertility of the mare. Viruses cannot be detected in the mare's uterus beyond 48 hours after abortion of an infected fetus. Mares rarely abort from virus in successive years but may abort later in their reproductive life if reinfected during pregnancy [53, 54].

The family of herpesviruses has the ability to persist in the body of its host in a latent state as a carrier no apparent after primary infection. In a time that can vary from months or years after primary infection, latent herpesvirus can manifest itself again with renewed replication and with the possibility of starting new outbreaks of the disease in their host, as well as stable mates susceptible. Consequently, it is the existence of these latently infected carrier horses, from which the virus is reactivated by stress-induced circumstances and provides the means to infect other individuals, which starts a new occurrence of this disease[36].

Equine arteritis virus

Equine viral arteritis (EVA) is an infectious disease of equids that is caused by equine arteritis virus (EAV). EVA occurs throughout much of the world, although the prevalence varies greatly between countries and among horses of different breeds [55]. EAV is the prototype virus in the family Arteriviridae, a grouping that also includes porcine reproductive and respiratory syndrome virus, simian hemorrhagic fever virus, and lactate dehydrogenase-elevating virus of mice [56, 57].

EAV was first isolated in 1953 from the lung of an aborted fetus after an extensive outbreak of respiratory disease and abortion on Standardbred mares. EVA was distinguished from equine influenza and equine herpesviruses type 1 and type 4 [58, 59]. EVA was identified as an etiologically distinct disease after isolation of the EAV and description of characteristic vascular lesions [60].

The majority of EAV infections are subclinical, but occasional are characterized by any combination of influenza-like illness in adult horses, abortion in pregnant mares, and interstitial pneumonia in young foals [35, 61]. Abortion after infection of pregnant mares EAV is the result of a lethal fetal infection. This is actually that leads to expulsion of the fetus, rather than myometritis or damage to the placenta that affects the synthesis of progesterone. Aborted fetus tissues contain high titers of virus than mares which aborted, indicating that substantial virus replication occurs in the fetus. Is thought to the stress that results from fetal infection is responsible for activating the hypothalamus-pituitary axis fetal, which induces abortion [62].

In pregnant mares, EAV-infected abortions are not preceded by premonitory signs and can occur late in the acute phase or early in the convalescent phase infection. In the past after

natural or experimental infection, abortions have been documented at 3 months to over 10 months of gestation [55, 59, 63, 64]. Abortion rates in outbreaks of EVA have varied from less than 10% to more than 60%. While the abortive potential of different strains of EAV has not been adequately compared, it appears that abortigenic strains differ in their potential as well as their virulence characteristics [55].

During acute infection, stallions may undergo a period of temporary infertility associated with decreased libido. Ejaculates may have decreased sperm motility, concentration, and percentage of morphologically normal cells. These changes can persist for 6–7 weeks after infection and considered to be the result of increased testicular temperature instead of any pathological effect induced by the virus. Semen quality is apparently normal in persistently infected stallions, despite active shedding of virus into the semen [55, 65].

Transmission of EAV between horses occurs through either respiratory or venereal routes[55, 66]. EAV can also be transmitted by aerosol from urine and other body secretions of acutely infected horses, infected respiratory tract secretions, aborted fetuses, and their membranes [67]. Another important route of natural transmission of the virus is in the semen of stallions that are either acutely or chronically infected. Persistently infected carrier stallions are the essential reservoir responsible for perpetuation and maintenance of EAV in equine populations [66, 68].

Mares that become infected following natural or artificial insemination with semen collected from shedding stallions can readily transmit the virus by the respiratory route to susceptible partners in close proximity [69]. Also it has been demonstrated that under experimental conditions, EAV can be transmitted to a recipient mares through embryo transfer from a donor mare inseminated with EAV infective semen[70]. In mares infected with EAV in late gestation, congenital infection of foals after transplacental transmission frequently develops a rapidly progressive, fulminating interstitial pneumonia, and fibronecrotic enteritis [71, 72].

EAV appears to be restricted to the reproductive tract during persistent infection of carrier stallions [55, 73]. Virus in semen is associated with the sperm-rich fraction and not with the pre-ejaculatory fluid, and the titers of virus in sequential ejaculates vary little from the same stallion. The mechanism of persistence of EAV in the male reproductive tract is not clear. However, persistence of EAV in stallions is testosterone-dependent.

It has been shown that carrier stallions are clearly responsible for the generation of genetic heterogeneity in field strains of EAV. Some reports indicate that sequence analyses of the variable gene of strains of EAV present in the semen of carrier stallions showed that the EAV acts as a population of genetically related viral variants during persistent infection. This involves both genetic and phenotypic divergence virus[66, 74].

1.3.1.2. Bacterial abortions

Several species of bacteria have been implicated as causative agents of abortion and infertility in mares. The most common causative agent of bacterial abortion in mares, belongs to the group of streptococci. However, we have identified other groups of bacteria from aborted fetuses, which include *Leptospira, Nocardia, Klebsiella,* and Staphylococcal species. Bacteria can

be introduced at breeding, ascend through the cervix. Cervical incompetence and/or pneumovagina can predispose the mare to an ascending bacterial infection and abortion. The bacterial infection may extent to the fetus itself and infect and damage a range of organs. Abortion occurs following fetal death either from septicemia or by progressive placentitis and subsequent placental insufficiency [75, 76].

As a consequence to bacterial abortion, retention of the placenta is often common as well as the infection of the uterus (endometritis and/or metritis). Before a successful breeding, treatment of the mare is often required. A good practice is to swab mares before breeding to determine whether dangerous bacteria are present in the uterus. The veterinarian can advise on the need to lavage the mare's uterus with or without an antibiotic [7].

Streptococcal infections

The streptococci are Gram-positive, catalase-negative, facultative anaerobic, coccoid, or ovoid bacteria. The numerous species of streptococci may be as α-hemolytic, β-hemolytic, and nonhemolytic species. From all of them, *Streptococcus equi* subsp. *zooepidemicus*, *S. equi* subsp. *equi,* and *S. dysgalactiae* subsp. *equisimilis* assume greater importance in equine medicine[77].

Streptococcus equi subsp. *equi* is the agent responsible for strangles, which is a highly contagious infection of the upper respiratory tract and associated lymph nodes [78]. This streptococci enter through the mouth or nose and attach to cells in the crypt of the tonsil and adjacent superficial lymphoid nodules. Nasal shedding usually begins after a latent period of 4–14 days and ceases between 3 and 6 weeks after the acute phase [79, 80]. Horses in the nearest postconvalescent phase are resistant to experimental challenge even with numbers of *S. equi* exceeding those required to produce the original infection[78]. Thus, almost 75% of horses develop a solid immunity to strangles following recovery from the disease [81].

Streptococcus equi subsp. *zooepidemicus* shares very high DNA homology (>98%) with its clonal derivative *S. equi* but differs in their biology and pathogenicity. Normally is a mucosal commensal that opportunistically produces disease in situations of virus infection, heat stress, or tissue injury. *S. zooepidemicus* is the most frequently isolated pathogen from the uterus of the mare[82]. The clitoral fossa, clitoral sinuses, and the vagina have been suggested as possible bacterial reservoirs [82, 83]. *S. zooepidemicus* is able to reach the uterus and pass the vulva, the vestibulovaginal sphincter, and the cervix. Poor anatomical conformation of the internal and external reproductive organs may impair these barriers and allow bacteria to ascend into the uterus. Consequently, endometritis is caused by an ascending infection in a random manner primarily governed by the uterine defense mechanisms of the mare [3, 84, 85]. Uterine infection has been described to depend on factors related to the uterine defense mechanisms as well as mare with advanced age, repeated history of unsuccessful foaling results also called "high-risk mares"[84, 86]. Virulence factors, such as fibronectin-binding proteins [87], hyaluronic capsule [88], M-like proteins [89], and Fc receptors, have also been identified [90].

A recent study of Rasmussen et al. [91] indicates that *S. zooepidemicus*-associated endometritis in mares belongs to a genetically distinct subpopulation. These findings add a new perspective to the pathogenesis of equine infectious endometritis. In this regard, it could not be caused by rather probable pathogenic strains of more specialized endometrium random contamination

S. zooepidemicus in the reproductive tract but flow. This indicates that not only the efficiency of uterine defense mechanisms to determine if *S. zooepidemicus* establish an infection, but rather to the interaction between strain of *S. zooepidemicus* and uterine defense mechanisms involved. Contamination of the uterus also takes place during live mounting, artificial insemination, or iatrogenically[86].

The normal habitat of *Streptococcus dysgalactia* subsp. *equisimilis* appears to be the skin and mucosal surfaces. Therefore, it was considered to be an infrequent bacterium isolated from horses and has been reported in horses from aborted placenta [75]. However, in a retrospective study Erol et al. (2012), repot that *Streptococcus equisimilis* was recovered, fetal tissues, umbilical cord and genital tracts of both foals and adult horses. These data comprise 74.8% of total sites isolated for *S. equisimilis*. This records strongly suggests that S. *equisimilis* is mostly a reproductive system agent. Also the results show that both *S. equisimilis* and *S. zooepidemicus* have an ability to invade sterile organs such as brain, kidney, and joints suggesting they have similar pathogenesis and tissue tropism.

Placentitis

Placentitis in mares is a potential threat because of the involvement of fetal and neonatal viability. This disease is normally caused by bacteria rising through the vagina. The most common pathogens implicated in equine placentitis are *Streptococcus equi* subspecies *zooepidemicus*, *Escherichia coli*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*[93]. *S. zooepidemicus* and *E. coli* are able to cause acute placentitis with bacteremia during early and midgestation in foals[34, 94].

Usually bacterial infection initiates disease; however, a work from an experimental model of placentitis in pony mares showed that premature delivery may happen secondary to inflammation of the chorion instead of as a consequence of fetal infection. It was suggested that these inflammatory processes result in PGE2 and PGF2α, production and stimulation of uterus contractility, resulting in premature delivery [95].

In some cases of placentitis (chronic cases), foals will suffer a faster fetal maturation. As a consequence, these foals will be delivered prematurely, but will be mature enough to survive. It has been demonstrated that, in humans, the indirect stimulation of the fetal HHG axis by proinflammatory cytokines is responsible for advanced fetal maturation [96]. If this assumption is true for equine fetuses, then the possibility of delaying preterm delivery sufficiently to allow fetal maturation can improve survival rates colt. To achieve this goal, it is necessary to diagnose and treat disease. Transrectal ultrasonographic examination of reproductive tract has become a routine diagnostic tool for placentitis. This method allows direct examination of the cervical region and also allows for evaluation of fetal activity, fetal fluid character, and subjective amniotic evaluation. In the normal pregnant mare, the area visualized in the region of the cervical is the combined uterine and placental unit.

Renaudin et al. [97, 98] developed the technique for evaluation of the combined thickness of the uterus and placenta (CTUP) and established normal values in light-horse mares throughout gestation. Thus, for 271–300, 301–330, and >330 days of gestation, normal concentrations for CUTP were <8, <10, and <12 mm, respectively. However, during placental infection or

inflammation, CTUP measures have increased, or membranes are separated from the endometrium. Additionally, purulent material may accumulate in pouches between the chorioallantois and the endometrium. Thickening of the amnion is also indicative of inflammation. Throughout the gestation, the allantoic fluid is hypoechoic, whereas amniotic fluid is slightly more echodense. Normal, fetal activity can shake cellular material and change the characteristics of the fluid. Fluids that persistently increased echodensity have increased cellularity due to infection or inflammation. For that reason, successive ultrasound examinations are essential to determine whether fluid character changes are pathologic or not [99].

Placental membrane integrity and thickness and fetal fluid are evaluated using transabdominal ultrasonography. Since the chorioallantois is intimately associated with the endometrium, it cannot be easily identified as a separate structure from the transabdominal procedure. Mares with normal pregnancies should have a minimum CTUP of 7.1±1.6 mm and a maximal CTUP of 11.5±2.4 mm[100]. Evaluation of the caudal allantochorion is inaccurate using the transabdominal approach. However, transabdominal assessment of fetal membranes is useful for recognizing placental abnormalities in mares with placentitis. Thus, mares infected with bacteria will often exhibit placental separation and purulent debris at the base of the gravid horn [101].

Ultrasound techniques, combined with endocrinological assays, provide additional tools for early diagnosing and progression of placentitis in mares. Pregnant mares with signs of placentitis should be treated with systemic broad spectrum antibiotics and anti-inflammatories. Different researchers [99, 102] informed that the administration of penicillin (22,000 IU/kg, q 6 hours), gentamicin (6.6 mg/kg, q 24 hours), and trimethoprim sulfamethoxazole (30 mg/kg, BID) resulted in inhibitory concentrations (MIC) of these drugs in allantoic fluid and placental tissue of pregnant pony mares. Similarly, another observation suggests that long-term therapy with a combination altrenogest (0.088 mg/kg), flunixin meglumine (1.1 mg/kg BID), and pentoxifylline (8.4 mg/kg BID) and antibiotics have a positive influence on pregnancy outcome with delivery of healthy foals [103].

Most placental lesions are observed by transrectal ultrasonography as over 90% of cases are caused by ascending infections. In cases of Nocardioform placentitis, changes in the placental unit may be seen transrectally or transabdominally by ultrasound, especially in the cervical region. The CTUP should be measured in the ventral portion of the uterus, just cranial to the cervix. The CTUP increases from a mean of 4.0 mm between 4 and 8 months of gestation to 1.0–1.2 cm at term [104]. A CTUP greater than 1.2 cm at 9 months of gestation or a CTUP greater than 1.5 cm at 11 months should be associated with placentitis[105, 106]. Usually, the fetal membranes may separate from the uterus and pus may be visualized swirling between the membranes and uterus [107]. In case that mares show premature udder development without a vaginal discharge should be evaluated by transabdominal ultrasonography for twins and Nocardioform placentitis. Uterine infections caused by Nocardioform bacteria, an organism that resides in the soil, frequently result in abortion or premature delivery [108].

Mares with placental pathology may have increased plasma concentrations of progestagens as a result of stress to the fetal placental unit. Fetal–placental progesterone is rapidly metabolized to 5α-pregnanes. Unfortunately, 5α-pregnanes are not readily assayed in a commercial setting, so diagnosis of placental disease using 5α-pregnane concentrations is not possible.

This progestins cross-react with the progesterone antibody used in commercial radioimmunoassay and enzyme-linked immunosorbent assays and can be measured in the maternal circulation in late gestation [109, 110]. Also, subnormal plasma relaxin concentrations were detected in mares with abnormal pregnancies [111]. Mares with clinical signs of placentitis and mares exhibiting signs of fescue toxicosis had suppressed plasma relaxin concentrations. Furthermore, sensitivity assays can be improved when combined with evidence of placental thickening as detected using transrectal ultrasonography [112].

Unfortunately, many mares do not exhibit classical signs of infection, premature udder development, and a vaginal discharge, so infections are commonly missed. Mares having vaginal discharge with or without udder development should be examined ultrasonographically[108]. A weak foal resulting for a premature delivery is devastating to horse owners. Most of these foals, if they live, never have productive performance, even if they receive the best neonatal care. The most important cause of premature delivery is placentitis due to it accounts for nearly a third of late-term abortions and fetal mortality during the first day after foal[113]. Placentitis affects approximately 3–7% of pregnant mares, the value of the foals, both economically and emotionally, makes this an important disease to study [108].

Mares most commonly afflicted are pluriparous. Many have anatomical defects of the caudal reproductive tract, such as pneumovagina, vestibule-vaginal reflux or cervical fibrosis, tears, or adhesions. Some, but not all mares, exhibit a vaginal discharge and develop an udder premature in response to placentitis. Management of mares at risk of abortion owing to placentitis is directed at prolonging pregnancy because chronic placentitis has been associated with accelerated fetal maturation. A foal may be born significantly premature and survive with limited neonatal care, if premature birth can be delayed for a few weeks after placentitis develops [107, 114].

Treatment protocols designed for prolonging gestation and for producing viable foals are currently being studied in experimental models [114, 115]. Induction of parturition prematurely with the expectation of delivering a mature foal is not an option because fetal maturation only occurs in the last 5 days of gestation and gestation length varies widely from 320 to 365 days. Removing the fetus from its dam's uterus before its final maturation will result in a premature foal that usually will not survive even with the best of neonatal care. So inducing precocious maturation of the fetus with corticosteroids has been considered a risk and not reliable in mares. Although data are limited, large doses (100 mg q 24 hours for 3 days) are necessary, and laminitis can be an important sequel [116].

Leptospira infections

Leptospirosis is a bacterial disease of worldwide distribution caused by spirochetes of the genus *Leptospira*. The first report of naturally occurring leptospirosis in horses was done in Russia by Lubashenko and Novikova in 1947. *Leptospira* infection in horses is manifested as either abortion or recurrent uveitis although sporadic cases of renal and hepatic disease have also been reported [117, 118].

Leptospires are motile bacteria called spirochetes. The order Spirochaetales includes two families of spiral bacteria, *Spirochaetaceae* and *Leptospiraceae*, which share unique morphologic and functional features. The genus *Leptospira* includes a large number of both pathogenic and

nonpathogenic bacteria. Morphologically, all the leptospires are flexible, tightly coiled, unicellular bacteria and can be are grouped into serogroups, serovars as well as genotypes based on DNA homology. The serovars *pomona, grippotyphosa, hardjo, bratislava, canicola*, and *icterohaemmorhagiae* are the ones we are most interested in. Leptospires are very common in domestic and wild animals and can also infect humans. Leptospirosis is maintained in nature by subclinically infected maintenance hosts, also known as reservoir hosts or definitive hosts, such as deer, raccoons, or rodents [119, 120]. Leptospires can invade the mucous membranes and/or damaged skin and migrate to various body organs of an incidental host[121].

Leptospirosis has been confirmed as a significant cause of abortion, stillbirth, and perinatal death in horses in locations worldwide [36, 122]. For most serovars of *Leptospira*, horses are incidental hosts. Although there are evidence suggesting that as in other farm animals (cattle and pigs), horses may be a maintenance host for *L. interrogans* serovar Bratislava [123].

Multiple serovars of *Leptospira* have been associated with abortion, with serovar Pomona type kennewicki being among the most common[124, 125]. In this regard, some reports indicate that the genotype kennewicki of the pomona serogroup was responsible for 86% of the abortions. However, the genotype grippotyphosa was responsible for only the 8% of abortion in mares [126]. The authors indicated that mammal of the raccoon family (Procyonidae) is the maintenance host for grippotyphosa, whereas the maintenance host for kennewicki has not been determined. Also mixed infections with multiple serovars have been reported[127].

Most leptospiral abortions occur between 6 and 9 months of gestation. The affected placenta is thick, edematous, hemorrhagic and could be covered with a brown mucoid material on the chorionic surface. However, occasionally, the affected placenta lacks detectable gross lesions. In some cases, a green discoloration or cystic adenomatous hyperplasia of the allantois is observed, and it has also been described funisitis or inflammation of the umbilical cord [119, 128]. Several serovars of *Leptospira* have been isolated from aborted equine fetuses. The fetus may present with mild to moderate icterus and liver enlargement. Fetal histopathologic lesions may include various degrees of nephritis and hepatitis[119, 129].

Clinical presentation of bacterial abortion is preceded by vaginal discharge and premature lactation. Mares with these symptoms should be considered high risk and should be required for detailed fetoplacental evaluations. The appearance of the placenta following a bacterial abortion can vary from minimal alterations in acute cases to a thickened, edematous placenta, either generally or in localized areas. The chorionic surface is often brown and covered in exudate [130].

1.4. Noninfectious abortion

1.4.1. Abortion due to twinning

In horse breeding, twins are not good news and are well known that the birth of healthy twin foals is unusual. The origin of equine twins is almost exclusively dizygotic originated from two separate fertilized oocytes with two different spermatozoa. A strong association between twinning rate and breed, age, reproductive status, season, use of drugs to control ovulation

has been reported. Twinning also appears to have a high degree of repeatability and heritability [131].

Compared with other breeds, more twins are diagnosed per cycle in Thoroughbreds mares [132]. Twinning rate is also more common in older mares than younger mares[133]. Similarly, fewer multiple ovulations are expected on the first postpartum estrus compared to other cycles [6]. As well as multiple pregnancies are more commonly detected when ovulation induction was used [134].

It is generally accepted that the inability of a mare to successfully carry twin foals to term is due to placental insufficiency. In twin pregnancies usually, one fetus develops more rapidly, progressively assuming the major portion of the maternal blood supply and causing the other fetus to die from lack of blood. In other words, insufficient fetal membranes are produced to accommodate and provide nutrition to two developing fetus. Therefore, the death of one fetus usually results in the abortion of both. Abortion due to twinning is most common between the 5th and 9th months [135].

Most twin pregnancies terminate in early fetal resorption or loss, late-term abortions, or the birth of small growth retarded foals. The mare is very efficient at reducing twins to a single pregnancy. In some cases, one twin dies and becomes mummified, allowing the other twin to continue to develop and be maintained to term. In case of resorption, the reduction is reached by a competitive absorption of nutrients that is related to size and position of the early pregnancy and later to orientation of the embryo proper within the developing conceptus[6]. However, the resolution of twins by the application of any nonintervention program depends on the age at identification, the orientation of the vesicles, and any disparity in size[136].

With the common use of ultrasound in equine practice, twin pregnancies are now commonly detected early and dealt with. Mares with a history of producing twins should have an ultrasound pregnancy test preferably between 14 and 16 days after the last service, and then one embryo can be destroyed so that the other can continue to develop normally. The mare is very efficient at reducing twins to a single pregnancy. Due to this, sometimes one twin will fail to develop and be resorbed without any veterinary intervention[6].

Mares aborting twins in late gestation frequently have foaling difficulties, damage their reproductive tracts, and are difficult to rebreed. Few twins can carry to term and survive. Complications that can arise with late-term abortion of twins or delivery of twins at term include dystocia, retained placenta, delayed uterine involution and metritis, and death of one or both twins [137]. If foals born alive, they are frequently small, demonstrate the effects of intrauterine growth retardation, and have a poor survival rate, with many needing expensive sophisticated critical care[93].

1.4.2. Umbilical cord torsion

Primary umbilical torsion is the most commonly diagnosed condition of the noninfectious causes of abortion [35]. Torsion, or strangulation of the umbilical cord, is said to be the cause of fetal deaths and abortions in the later stages of pregnancy. Excessive twisting or wrapping of cord around the limb of the fetus cause vascular obstruction in the umbilical cord resulting

in the death of the fetus. Equine fetuses are extraordinarily active and their movements can result in 360° twisting of the amniotic and/or the allantoic parts of the cord[138]. Umbilical torsion was observed in 19% of 515 cases submitted to the Animal Health Laboratory over six breeding seasons[35]. Statistical reviews from Ricketts et al.[139] showed that umbilical cord torsions resulting in vascular compromise and fetal death involved the 35.7% of abortion and neonatal deaths and 46.2% of pre-term abortions, respectively.

In equine fetuses, sudden vascular compression/cord torsions tended to occur before signs of urachal dilatation (urinary retention) developed at twist sites (5.5–7.5 months). Where urachal dilatations had developed the pregnancies tended to continue up to 6–10 months [34, 35]. Fetuses dying in utero due to vascular obstruction in the umbilical cord are not usually aborted immediately, so the tissues display variable degrees of autolysis when aborted. Cord lesions include local intimal or medial vascular wall tears and associated intramural and stromal hemorrhages, local edema even sufficient to cause 'stretch tears' at the amniotic surface, and small aneurysmal dilatations[34].

1.4.3. Fungal abortions

Fungal abortions are caused by fungi that produce mycotoxins in the class of chemicals called "ergot" or "ergopeptine alkaloids".

1.4.3.1. Ergot alkaloid toxicity in the late gestation

Different mycotoxins called ergot or ergopeptine alkaloids are produced for number of fungi, both saprophytic and endophytic. Among the different animal species, sensitive to ergopeptine alkaloids is dissimilar. While mares are sensitive to at levels as low as 50–100 ppb, cattle do not show visible signs until 1000–2000 ppb. These alkaloids have toxic effects on the reproductive tract and mammary gland of the mare, and also they have been associated with depression of serum prolactin (PR) and progestagens (P4), prolonged gestation, thickened edematous placenta, and agalactia. The ergopeptine interfere with the normal rise of P4 and PR in the last 40 days of gestation. The normal P4 levels increase from 300 days to birth (4.8 ± 1.5 to 22.7 ± 2.7 ng/mL). Foals born without the normal increases in progestagens suffer hypoadrenocortical function with the consequence of being born smaller, weak, or still-born[140].

1.4.3.2. Fescue toxicosis

Fescue toxicosis in horses is caused by an endophytic fungus infection of tall fescue grasses (*Festuca arundinacea*). Fescue toxicity is the form of ergot alkaloid toxicity by the endophytic fungus *Neotyphodium coenophialum* (formerly called Acremonium coenophialum). It lives inside the plant, between the cells, and produces ergot alkaloids, resulting in the disease condition called fescue toxicity [141].

Ergotism is the clinical syndrome of ergot poisoning caused by *Claviceps purpurea* fungus. It is a saprophytic fungus that infects cereals, using the plant's nutrients. *Claviceps purpurea* can live on a variety of hays and pasture grasses, including bluegrass, barley, and cereal rye [141]. It

has been demonstrated that three classes of alkaloids, including the ergovaline, lolines, and peramine, are produced by the fungus and play a potential role in affecting animal performance [142].

Signs commonly associated with mares consuming infected fescue are prolonged gestation, agalactia, increased foal and mare mortality, dystocia, tough and thickened placentas, weak and dysmature foals, reduced serum progesterone and prolactin, and increased serum estradiol-17β. These chemicals cause dystocia in mares and deaths of foals. An early study by Garrett et al. [143] shows the relative incidence of 38% prolonged gestation, 18% abortion, and 9% thickened placentas in mares with fescue toxicosis.

In cattle and horses, toxins have vasoconstrictive effects on the vascular system. The ergopeptine alkaloids are agonists of the dopamine D2 receptors. Thus, under the reproductive point of view, the consequence of dopamine is the inhibition of prolactin. Decreased prolactin concentrations are a main physiological aspect in the pathogenesis of the absence of milk production (agalactia) and decreased mammary gland development in mares [144].

Another effect of exposure of these toxins is the abnormal production by the placenta of P4 that becomes depressed during the last 30 or 40 days of gestation. It was suggested that the reason for this is lower placental production of P4, which inhibits adrenocorticotropic hormone (ACTH) secretion in the fetus[140].

Additional effects of fescue toxicity on placental function are related to vasoconstriction [145]. This effect is principally important due to the nature of the fetal and maternal placenta, of being an extensive vascular interface between them. Several placental lesions have been reported in fescue toxicity, including edema, fibrosis, and mucoid degeneration of arteries. The incidence of retained placentas is 62% in mares consuming fescue pasture grasses. The primary clinical signs of ergot alkaloid poisoning in the late gestation include an extended gestation length from 11 to 12 months; dystocia, with mares trying to foal for many hours; agalactia with poor quality colostrum; "red bag" placentas from premature separation; thick edematous placentas with weights that exceed normal; and weak or dead foals with aspiration pneumonia, as consequence of a thickening of the placenta [146].

1.4.4. Mare reproductive loss syndrome

Mare reproductive loss syndrome or MRS was identified in early fetal losses (40–100 day) plus late-term abortions and the birth of weak foals, many of which died, with no immediate explanation for the cause [147].

Based on pathological examination, the cause of MRLS is not always identifiable. However, a number of disease conditions can be eliminated as possible causes of the syndrome. The main pathological findings in MRLS fetuses were the inflammation of the umbilical cord (funisitis), pneumonia, bacterial infection, and hemorrhages. The bacterial infection in aborted fetuses represents an ante mortem event, and most of the pathological lesions could be attributed to this origin. According to the literature, it could not be determined whether the bacteria are the primary cause of abortion or just represent a secondary opportunistic infection[148].

Pericarditis is another pathological finding associated with MRLS. *Actinobacillus* spp. are the most commonly reported isolates from pericardial fluid of horses with bacterial pericarditis. In other reports unrelated to MRLS, *Streptococcus* spp., *Pasteurella multocida*, *Staphylococcus aureus*, *Pseudomonas* spp., *Acinetobacter*, and *Enterococcus faecalis* were isolated in some cases [149].

MRLS caused abortion in early pregnancy, and even though the abortion happened with 2 months remaining in the breeding season, only rarely were these mares able to get back in foal. The primary reason for these mares not becoming pregnant is due to the presence of eCG (equine chorionic gonadotrophin) in their circulation implying that mares not cycle normally. The eCG levels are maintained due to the presence of endometrial cups produced by the placenta before the pregnancy loss [150].

In case of parturition, the delivery was characterized as "red bag" in 32% of the cases, indicating that the allantochorion was presented and passed concurrently with the fetus. This high incidence of red bag delivery indicates a possible premature placental separation, suggesting placental injury or problem with placentation. There are no pathognomonic findings or individual diagnostic tests that allow diagnosis of abortion by MRLS. Diagnosis of abortion or stillbirth related to MRLS is based on a combination of several factors, such as history, time of year, bacteriologic results, and the above-described pathological findings[147].

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