Open Veterinary Journal, (2022), Vol. 12(6): 903–909
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)
Review Article
DOI: *10.5455/OVJ.2022.v12.i6.16*

Submitted: 26/07/2022 Accepted: 01/11/2022 Published: 01/12/2022

Early embryonic death in equines and camelids

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Abstract

This paper includes the study of early embryonic death (EED), predisposing factors of EED and treatment. EED refers to the fetal mortality which varies in mare and camelids but most probably not later than 50 days of gestation. This duration may be divided into very early mortality, early mortality and late embryonic mortality. This also varies in mare and camelids. There are different embryonic, maternal, environmental/external, and infectious and noninfectious factors which lead to early embryonic loss. Diagnosis is very difficult as in most of the cases resorption of fetus occurs but it is done by the use of ultrasound. Unfortunately, there is no treatment to avoid early embryonic mortality. However, new reproductive technologies have increased the service rate in a herd, and efforts are still being made to determine the rate and frequency of camel embryonic loss.

Keywords: Mortality, Economic losses, Mares, Progesterone, Corpus luteum.

Introduction

Researchers have worked a lot to determine the various external factors which may cause early embryonic mortality. There are certain factors which may include stress which may be related with season and environmental temperatures and the effect of male horses (Lesser and Kruse, 2004). All these factors affect the development of embryo in one way or another. Different kinds of stress which may be nutritional, physical, or disease in nature.

Camelids are a significant mean of animal production in many parts of the world there is always a question mark on reproductive efficiency of camel. Birthing rates of camels hardly go beyond 40% in nomadic herds and 70% in more concentrated flocks (Spencer, 2012). In addition to embryonic loss, there are also neonatal loses evident in camels (Nagy *et al.*, 2021). In South American Camelids, llamas, and alpacas, birth rates are much improved, however, greater rates of pregnancy loss and infertility are a big concern (Fowler, 2011). In alpacas, the mean annual fertility reported is 50%, however, in llamas, the average birth rate is 45.9%. In alpacas, 50%–57.8% embryonic mortality occurs in first 30 days of gestation (Tibary *et al.*, 2006).

Early embryonic death (EED) in mare

The term is usually defined as loss of *conceptus* during the first 42–50 days of fertilization (dpf). This is actually the time when differentiation is completed after conception and organ systems start to develop (Vanderwall, 2008). Different researches show that mares which are reproductively sound have shown over 90% abortion rate per cycle as compared to sub fertile mares which show 81% to 92% abortion ratio. Reproductive sound mares show embryonic mortality approximately 9% at a young age between the dpf and day 14, but in sub fertile mares it shows more than 60% mortality (Ball *et al.*, 1986; Brinsko *et al.*, 1994). Similarly, embryonic mortality between the first 40 and 50 days, in fertile mares' rate of embryonic loss is approximately 20% while it is more than 70% for sub fertile mares (Willmann *et al.*, 2011).

For the EED following classes may be formed:

- Very early mortality (0–7 dpf)
- Early mortality (7–24 days)
- Late embryonic mortality (24–50 days)

Causes of EED in mares

There can be different causes of EED such as of maternal, embryonic, and external in origin.

Maternal factors

There are different factors within the mare which affect pregnancy, usually termed as maternal factors for pregnancy maintenance. These maternal factors may include; age of mother, uterine and oviductal environment, changes in serum progesterone levels, and postpartum breeding. These all either directly or indirectly may cause EED (Wilmut *et al.*, 1986; Zama and Uzumcu, 2010). Serum progesterone level is the most important factor in maintaining pregnancy which should be monitored throughout the gestation period at different intervals in order to find the particular etiologic factor. Although it will not tell the actual causative age of EED, it will show that the maternal progesterone level is not sufficient for maintenance of pregnancy (di Renzo *et al.*, 2016).

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Role of progesterone in early embryonic mortality

The drop in progesterone levels in mares who died early in their embryonic development (Volkmann *et al.*, 2008). Serum progesterone plays a vital role in sustaining uterine quiescence during pregnancy in several animals. It decreases contractility by hyperpolarizing the myometrium and decreasing the amount of gap junctions and contractile agent receptors in the myometrium (Thorburn, 1993; Silver, 1994). Corpus luteum is the only source for maintaining early pregnancy, but when luteolysis occurs the level of serum progesterone is decreased which indicates that its production from corpus luteum is not enough (Allen, 2001). There are several factors which cause the initiation of luteolysis. Consequently, during early pregnancy decrease in peripheral level of serum progesterone ends pregnancy in mares. The production of prostaglandins by slight inflammatory reagents in the uterus induces luteolysis and ends pregnancy (Krakowski *et al.*, 2010). The size of an embryo is important in maternal recognition of pregnancy and hence to prevent luteolysis which should be adequate on day 16 in order to produce sufficient interferon-tau (Mann and Lamming, 2001; Robinson *et al.*, 2006). The secretion of maternal progesterone also affects the development of the production of interferon-tau by embryo (Mann *et al.*, 2006). Low serum progesterone levels and early embryonic mortality could result if the maternal recognition system for gestation fails (Allen, 2001).

Maternal age

Older mares have a higher rate of early pregnancy loss. Vanderwall says that "Overall, decreased oocyte quality appears to be the most age-related factor driving an increase in pregnancy loss in older mares" (Vanderwall, 2008). Oocytes from older mares reached metaphase II at a substantially smaller rate than oocytes from younger mares in an *in vitro* study, with more oocytes from older mares halting during metaphase I (Brinsko *et al.*, 1995). This shows that oocytes from older mares are more likely to have aberrant meiotic division. In a report by Carnevale and Ginther (1995), oocytes were harvested from both young and older mares and transferred into the uterine tubes of young recipient mares using gamete intraoviductal transfer investigations (Carnevale and Ginther, 1995). After being transferred to the uterine tube of a young recipient mare, oocytes from elderly mares resulted in much fewer pregnancies than those from young mares, according to the findings of this study. Mitochondria from *in vitro* developed oocytes from older mares also showed increased ultrastructural defects, implying that it could be a key underlying cause in oocyte quality reduction (Torner *et al.*, 2007).

The increase of follicle-stimulating hormone and luteinizing hormone is linked to a prolonged follicular phase in older mares, and this extended follicular growth is linked to a greater risk of defective oocytes (Carnevale *et al.*, 1994). Various studies have found that aging of the egg after ovulation causes a decrease in pregnancy rates, a delay in embryonic growth, and probably a greater risk of eventual embryonic death in mares (Woods *et al.*, 1990; Satué and Gardon, 2016).

Disturbance of embryo–maternal interaction

The contact between the *conceptus* and the uterine environment leads to early *conceptus* development and implantation, which is recognized by the mother. It is also used to describe the physiological process that extends the corpus luteum lifespan. An increase in prostaglandin release can be seen 14 days after ovulation during the estrus cycle, which promotes corpus luteum lysis (Sharp *et al.*, 1997). The pregnancy identification signal has to be present on or before day 14 of pregnancy (Ababneh *et al.*, 2000). EED can result from breakdown of the corpus luteum linked with lack of maternal detection of pregnancy (Daels *et al.*, 1991; McDowell *et al.*, 2003). In mares with embryonic loss prior to day 20, failure of the embryo to inhibit luteolysis was discovered, which was defined by the existence of embryonic vesicles that were too tiny for days of age and fixation failure. Serum progesterone levels were decreased in these mares on days 12, 15, and 18 (Bergfelt *et al.*, 1992).

Embryonic factors

After fertilization, the fetus after implantation in uterus is required to signal to the mother for its presence (Barnea, 2014). However, if communication between mother and fetus is not appropriate, then prostaglandin-F2 alpha (a hormone which causes lysis of corpus luteum, produced within the uterus), results in the lysis of the corpus luteum. Consequently, progesterone (which maintains pregnancy) level is reduced. From days 6 to 16 of gestation, the fetus keeps moving throughout the uterus continuously which helps to communicate with the mother (Allen and Wilsher, 2009). However, the mechanism is not fully understood; it is thought that the uterus or the fetus releases chemicals (proteins) that aid in the recognition of each other. Another factor which helps in maternal recognition of pregnancy is the Estradiol which is formed from an early staged embryo. So, any disturbance in these movements may cause release of prostaglandins, consequently causing early embryonic loss (Meyer *et al.*, 2019).

External factors

Cortisol is released if mare is given stress such as transport during early pregnancy days, as a result of which progesterone level is reduced (Nagel *et al.*, 2019). However, transport has shown no significant role in early embryonic loss. Still, proper care should be done. These days, there is a strong link between poor physical health and greater pregnancy loss. Effect of season on early embryonic loss is of great importance. Several researches have shown an increase in the EED in early spring as compared to the warmer months. Another researcher proposed that dilating the cervix was caused by early spring circumstances or improved pasture quality richness (Radostits *et* *al.*, 2006). Bacterial placentitis would take place as a result of cervical dilatation, resulting in pregnancy loss (Fernandes *et al.*, 2020).

The consequences of extended exposure to increased ambient temperatures on the early pregnant mare have long been a source of worry, but little research has been done on the subject (Jauchem, 1997). Infections in the uterus can cause embryonic death. Complications from a variety of diseases can employ a variety of avenues to cause harm (Vaala and Sertich, 1994). Endotoxemia is a typical side effect of illness. Endotoxins are released into the circulation when the gut wall is compromised. The body reacts by generating prostaglandins, which cause luteolysis and the embryo's demise (Canisso *et al.*, 2020).

- Flunixin meglumine (banamine) can inhibit prostaglandin release and avert embryo loss if given within 48 hours after the commencement of endotoxemia (Graham *et al.*, 1995).

If a stallion passes on a venereal illness, he might be the causative factor of embryonic loss. Furthermore, studies have shown that when females are mated to sub fertile males, the likelihood of pregnancy loss increases (Snider, 2015) (Very little data).

Diagnosis

EED is studied using ultrasound examination. The embryonic vesicle has an irregular form. The embryo is smaller than usual and there is no embryonic heartbeat. There are visible endometrial folds, the vesicle continues to move, there is fluid buildup within the uterus, and there is vesicle dislodgment and fluid loss (Griffin and Ginther, 1992).

Treatment methods

Unluckily, till now not even a single method of prevention and treatment of EED is in practice beyond several cases of embryonic loss (Lefebvre, 2015). Sometimes progesterone supplements are given as a probable treatment to treat affected endogenous progesterone level Regumate, a progesterone analog, has been shown to keep ovariectomized mares pregnant (Beyer *et al.*, 2019).

Progesterone therapy can begin as early as 5 days after ovulation and last for up to 150 days. The placenta also becomes a cause of progesterone around days 50–70.

By days 120–150, the natural decline of progesterone levels has begun. As a result, Regumate administration can be gradually and safely discontinued at this time.

NSAIDs like flunixin meglumine (banamine) are also considered as a remedy. In circumstances when endotoxemia is suspected, banamine has been employed (Kallings, 1993). Long-term use of banamine in pregnant mares is unidentified regarding the safety of animals. For this reason, the use of banamine in practice is limited (Rose *et al.*, 2018).

- Retaining sufficient nutritional care, as well as limiting infectious illness and other environmental pressures, can help to lower the incidence of EED (Padalino, 2015).

When we compare the reproductive capability of the mare against the financial loss to the breeding business as a result of EED, we find that it needs a significance importance and research. The betterment or reduction of early embryonic losses can affect industry by increasing its efficiency (Scoggin, 2015).

EED in camels

The loss is considered early pregnancy loss if it occurs before 50 days of gestation (Nagy *et al.*, 2021). Usually, there are no generalized or obvious signs of loss but when pregnancy is beyond or up to 35 days small amount of fleshy tissue and fluid can be recognized nearby the manure mass (Khan *et al.*, 2003). In a number of cases, the owner even does not recognize pregnancy and consider the female is open because she may show signs of reception when there are mating animals or by the presence of any male in the zone, sometimes female do not develop abdominal distention or cush in late gestation (Letaief and Bedhiaf-Romdhani, 2022). And when the owner suspects pregnancy or its loss becomes too late to carry any research and reach a specific diagnosis for the cause of animal loss (Pearson *et al.*, 2014). Therefore, proper pregnancy diagnosis should be carried out within first 60–90 days through several examinations. The pregnancy diagnosis should be carried out at 14, 25 to 30, and 45–60 days (Dholpuria *et al.*, 2012). The females that have history of pregnancy loss, endometritis, or infertility, a diagnosis is also recommended at somewhere between 80 and 90 days (Runcan and da Silva, 2022). If this schedule is followed properly and as per recommendations animal is not allowed to move out of farm during this period, the fetal loss as well as its signs and symptoms can be recognized to reach a specific diagnosis.

Causes of EED in camel

In a generalized clinical survey study, almost 355 embryonic death was reported in dromedary camels (Tibary and Anouassi, 2001). Basic factors attributed to EED in Camelidae are;

- Genetic causes
- CL insufficiency
- Unreceptive uterine environment; nevertheless, no factor can be changed to promote embryo sustainability (MacKay *et al.*, 2022).

Heat stress, chromosomal abnormalities, or genetic factors (such as lethal genes, segregation, mutation, structural abnormality, aneuploidy, e.g., monosomy, trisomy, polyploidy, multiple numbers of haploid chromosomes, polyspermia, etc.), nutritional factors (such as a lack of proteins, vitamins, microminerals, the effect of toxins and nitrate poisoning, etc.), abnormal hormonal situations/endocrine factors (such as low progesterone), energy balance (an important factor in retaining pregnancy), genital infections (which may be specific or nonspecific), venereal diseases (such as Trichomiasis, Brucellosis, Trypanosomiasis, etc.), uterine environment, immunological factors (normally immune suppressors produced by mothers, if not produced, cause fetus rejection), effect of palpation (improper timing of palpation), improper timing of Artificial insemination (late AI aged embryo), twin pregnancy, effect of the male (such as lethal genes, abnormal chromosomes, venereal diseases, etc.), infectious causes, and other proper causes, such as older animals, are among the causes of EED in camels (Ali *et al.*, 2018; Abdelnour *et al.*, 2020).

Yagil (1985) claimed that one of the basic causes of fetal death is inbreeding of herds. Rate of abortion due to infections vary from 10% to more than 70% in some areas of the world (Abo-Aziza *et al.*, 2017). In llamas and alpacas, the most common reasons for abortion are leptospirosis, chlamydiosis, and toxoplasmosis (Al Khalifa *et al.*, 2018). Whereas, in camels of Middle East and Africa brucellosis and trypanosomiasis are considered as major causes of infectious abortion (Khalafalla *et al.*, 2017).

Maternal factors

Hormonal imbalance

Progesterone is required to keep a pregnancy going. EED has been linked to a progesterone shortage produced by primary luteal insufficiency, but this is unlikely to be a common occurrence (Pratap *et al.*, 2012).

Disturbance of the embryo–maternal interactions

Embryonic loss can occur when the embryo–maternal connections are disrupted (Vettical *et al.*, 2019). Signals from the embryo are required for maternal pregnancy identification prior to implantation (Abdoon *et al.*, 2017). This initiates the hormonal alterations required to provoke the uterine modifications for embedding.

Age of dam

Activity of follicles and quality of oocytes are reduced in aged animals, resulting in a loss in embryo developmental ability (Abdelnour *et al.*, 2020). Furthermore, as animals become older, the quality of their endometrium deteriorates (Jarrar and Faye, 2013).

Inbreeding

The reason of EED has been linked to inbreeding (Dubey, 1999). It is also been discovered that the rate of early embryonic mortality differs by breed (Nagy *et al.*, 2021).

External factors

High environmental temperature

Extreme temperature in the course of initial months of pregnancy might also be harmful to the embryo. Extreme uterine temperature has been shown to have a direct detrimental effect on the embryo, as well as the pushing of blood away from the uterus to the outside to maintain body temperature, result in a decreased nutrients load (Perry and Smith, 2015).

Specific nutritional deficiencies or malnutrition

The embryo can be harmed by certain nutrient deficits or starvation (Hogan and Phillips, 2016). EED can be caused by a significant deficit of vitamins (vitamin A) or other nutrients (Cu, Zn, and I) that function as metabolic supervisors (Gupta and Solanki, 2012). Poor nutrition or a serious negative energy balance might impact follicular growth, oocyte quality, and oviduct secretory and motile activity, which is where the fertilization process takes place (Schjenken and Robertson, 2020). Butler and Smith (1989), and Foxcroft (1997) found that nutrition has an impact on the very early phases of conception (Qazi *et al.*, 2018).

Stress

Stress has a negative impact on animal reproductive performance (Padalino *et al.*, 2015). Stress-causing factors (such as transportation, mechanical trauma, isolation, pain, blood pressure alteration, etc.) impact reproductive function by acting on the hypothalamus (GnRH) or ovarian levels (progesterone) (Al-Suhaimi and Khan, 2022).

Environmental toxicant, teratogenic compounds, and mycotoxins

When taken during critical early stages of gestation, toxins in the environment, cancer-causing chemicals, and fungal toxins can have devastating consequences on embryo life (Darwish *et al.*, 2014).

In severe cases, acute endometritis has a direct influence on the embryonic environment following mating or artificial insemination and, in severe cases, is accompanied by the synthesis of luteolytic chemicals such as prostaglandins (Donovan *et al.*, 2012). Endometrial glands are surrounded by layers of fibrous tissue, resulting in a lack of functional glands, depriving the embryo of protein-rich exocrine secretion (Weaver and Prentice, 2003).

Noninfectious causes

In animals, primary reason for failure of a pregnancy in its early stages is chromosomal abnormalities (Ali *et al.*, 2019). According to King *et al*. (1990), chromosomal abnormalities account for around 20% of overall embryonic and fetal loss (Gherissi *et al.*, 2019).

Treatment

Till now, there is no practical procedure to reduce the risk of embryonic loss in camels (Nagy *et al.*, 2021). However, new reproductive technologies have increased the service rate in a herd, and efforts are still being made to determine the rate and frequency of camel embryonic loss (Pratap *et al.*, 2012).

Conclusion

Keeping in view the economic importance of mares and camels, it is important to know the early embryonic loss in these animals. The first 42–50 days of pregnancy are critical in both of these animals. Studies have shown that early pregnancy loss is more common in older animals. If the maternal recognition mechanism for gestation fails, low progesterone levels and early embryonic mortality may follow.

In mares, the aging of the egg after ovulation results in lower pregnancy rates, a delay in embryonic growth, and a higher chance of eventual embryonic death. On or before day 14 of pregnancy, the pregnancy identification signal must be present. A clear correlation exists between poor physical health and a higher rate of pregnancy loss. Seasonal effects on early embryonic loss are quite important. The growing embryo of an animal can be harmed by complications from a range of disorders.

In camels, within the first 60–90 days, a proper pregnancy diagnosis should be made through a series of tests. Heat stress, chromosomal abnormalities, or genetic variables (e.g., lethal genes, segregation, mutation, structural abnormality, aneuploidy, etc.), infections, immunological factors, and other suitable causes can all cause camel embryo loss.

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