Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 158 (2021) 59-71 EISSN 2392-2192

Fertilization failure and early embryonic mortality as a major cause of reproductive failure in cattle: A review

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ABSTRACT

Reproductive failure in lactating dairy cows is a significant limitation to the dairy industry. Fertilization failure, Embryonic or fetal losses are major contributors to that limitation. The objective of this review was to determine cause of fertilization failure and early embryonic mortality in cattle. Fertilization failure and embryo mortality is a major cause of economic loss in dairy production systems. Direct effects of fertilization failure and embryo mortality are reflected in reduced conception rates with consequent effects on efficiency, production and profitability. Embryonic loss can be early or late .The major component of embryo loss occurs before day 16 following breeding with emerging evidence of greater losses before day 8 in high producing dairy cows. Late embryo loss causes serious economic losses because it is often recognized too late to rebreed females. Various factors can be a cause for fertilization failure and embryonic mortality. The major cause includes genetic, environmental, endocrine, infectious nutritional factors. More balanced breeding strategies with greater emphasis on fertility, feed intake and energy must be developed. There is a range of easily adoptable management factors that can either directly increase in embryo survival or ameliorate the consequences of low embryo survival rates. The correction of minor deficits in several areas can have a substantial overall effect on herd reproductive performance.

Keywords: Bovine; Embryo mortality, Fertilization failure, Reproductive failure

(Received 04 May 2021; Accepted 25 May 2021; Date of Publication 26 May 2021)

1. INTRODUCTION

Reproductive failure in lactating dairy cows is a significant limitation to the dairy industry. Fertilization failure, Embryonic or fetal losses are major contributors to that limitation. Embryo mortality and fertilization failure is a major cause of economic loss in dairy production systems through repeat breeding (reduced conception rates) and increased cost of artificial insemination. Early embryonic death (EED) also leads to extended calving intervals and prolonged dry period resulting in reduced life time milk production and reduced net calf production. It is generally accepted that embryonic mortality is associated with fertilization failure, genetic defects, impaired embryonic, diet components and its specific nutrients, heat stress.

2. CHALLENGES IN EARLY EMBRYO DEVELOPMENT IN CATTLE

Sartori et al. (2010) and Wiltbank et al. (2016) reports shows that, fertilization seems normal for most cows as a fertilization rate is above 80% has been commonly observed in a range of independent studies.

However, Growing evidence demonstrates 30-50% embryos are lost during the first week after insemination which is a critical phase of development between fertilization and the blastocyst stage (Bajaj et al., 2018; Diskin et al., 2011; Wiltbank et al., 2016). Similarly; the second peak time for embryo loss occurs during peri-implantation development that is, concurrent with trophoblast elongation and the secretion of IFNT (Sartori et al., 2010; Wiltbank et al., 2016; Raktim et al., 2019; Eze, et al., 2018; Habtie, 2019; Gwaza & Monoh, 2016).

In practice, early embryo loss during the first month after insemination has been a significant challenge in dairy cattle as it accounts for approximately 60% of total embryo/conceptus loss during pregnancy which is a major contributing factor that results in poor fertility in dairy cows (Wiltbank et al., 2016). It has been observed that the calving rate is only 35-40% after a single insemination in modern dairy cows and it is even lower in high yielding dairy cattle due to various reason (Wiltbank et al., 2016).

Table 1. Distribution of Pregnancy Failures in Cattle.

Timing or Cause		**Percentage of losses**
Fertilization failure		
	Male factors	10
	Delayed ovulation, ovum transport, etc	8
Embryonic		57
Lethal gene		5
Rebred by mistake		1

Placentation		
	Early	4
	Late	12
Fetal		3

Source: From Inskeep and Dailey (2005).

3. CAUSE OF FERTILIZATION FAILURE

Repeat breeding (RB), defined as a cow fail to conceive from 3 or 4 regularly spaced services in the absence of detectable abnormalities, is a costly problem for the dairy producer. The repeat breeding (failure of fertilization or conception post fertilization) causes great economic losses for dairy farmers. The costs of herds management and rearing are increased by increment of expenses of unsuccessful frequent artificial insemination (AI), extended length of the days open (DO) as well as culling and replacement of those cows that can't conceive (Ahmadi and Dehghan, 2007). The potential cause of the fertilization failure mainly include pathological endometritis, nutritional deficiency, specially trance minerals and vitamin A, age of the dam, improper heat detection, and endocrine dysfunction, oocyte quality, oocyte maturation and other related factor (Ahmed., 2009).

3. 1. Abnormalities in Ovulation

Ovulation is critically dependent on the timing, frequency and amplitude of the hormonal changes. Inappropriate pattern of hormones could lead to atresia or to undue persistence of the dominant follicle (with detrimental effects on the quality of the oocyte). The crucial hormonal event that initiates the Ovulatory process is the switch from negative feedback by progesterone and oestrogen to positive feedback by estrogen. A longer estrus-ovulation interval usually appears and premature insemination is then carried out. The LH release pattern is modified and follicle does not get the stimulus for ovulation to occur. Irregular and delayed ovulations have been associated with asynchrony between estrus and ovulation, asynchrony of LH peak and ovulation, or incapacity for LH release. The LH peak characteristics are altered in repeated breeder cows and estrous signs are less intense than in normal cows (Perez-Marin and Espana, 2007).

3. 2. Anatomical defect of the genital tract / Oviduct obstruction

The reproductive tract of cow provides a suitable environment for oocyte growth, as well as for sperm transport, fertilization and implantation. Anatomical or functional changes of these structures can drive to gestational failure and infertility (Kessy and Noakes, 1985). Cows having tubular abnormalities may show repeat breeding of known or obscure etiology which requires to be confirmed by patency testing. Abnormities of the fallopian tubes have been attributed as one of the most important causes of fertilization failure. The major causes of oviduct obstruction include Salpingitis which is inflammation of the fallopian tubes due to some infectious cause. Hydrosalpinx is also an affection in which the fallopian tube is filled with inflammatory fluid and is the end result of pelvic infection. Pyosalpinx refers to presence of pus in one fallopian

tube. When both tubes are affected with the accumulation of pus inside, the term used is pyosalpinges. Pyosalpinx is a consequence of pelvic inflammatory diseases (PID) which may be caused by streptococcus and staphylococcus infection. Infections may start from vagina and progress up to the cervix, uterus and to one or both fallopian tubes (Shrestha et al., 2004).

3. 3. Genetic or Acquired defects of ova

A superior oocyte quality is of paramount importance for successful embryogenesis, especially when dealing with assisted reproduction. A competent oocyte is able to maintain embryonic development to term (Gandolfi and Gandolfi, 2001). Although the culture conditions can impact on the developmental potential of the early embryo, the intrinsic quality of oocyte is the key factor determining the proportion of oocytes developing to the blastocyst stage. Generally oocyte quality is determined by the Oocyte's nuclear and cytoplasmic maturation which is attained during its growth in the follicle. Oocyte quality is still a poorly defined characteristic but exposure of oocytes to an unfavorable environment (including heat stress, NEB and disease) up to 3 months before ovulation may have a negative effect on the ability of the oocyte to be fertilized and develop into an embryo (Fair, 2010; Sayid et al., 2021).

3. 4. Follicle and oocyte quality

During pre-implantation development, particularly for the first couple of days after insemination, the embryos are substantially dependent on maternally stored factors derived from the oocyte (Zhang and Smith, 2015). Oocyte quality, also termed oocyte competence, denotes the ability of an oocyte to complete meiosis, fertilization and cleavage, to proceed to early embryonic development, and eventually give rise to a healthy offspring (Sirard et al., 2006). Oocytes from the larger, older follicles were fertilizable, but early development was retarded, and embryonic death usually occurred before the 16-cell stage. Several authors have found that premature ovulation of follicles is probably as detrimental to fertility as ovulation of aged or persistent follicles. Again, as with delayed ovulation, development to the blastocyst stage was compromised (Mermillod et al., 1999). Currently, poor oocyte quality is one leading factors associated with reproductive failures in dairy cattle .It seems that oocyte quality could be disrupted by lactation in high yield dairy cattle, which may suggest there is a negative genetic correlation between fertility traits and milk yield traits (Berry et al., 2016).

3. 5. Abnormalities related to male/Semen

Any Abnormalities Related to Semen spermatozoon has been considered abnormal. Genetic Defect and Aging of Spermatozoa; All cells undergo senescence. Spermatozoa, however, are especially susceptible to aging. Their highly concentrated nucleic DNA and reduced cytoplasm may result in DNA damage that is more likely to accumulate without repair. Furthermore, their high metabolic activity results in substantial exposure to oxidative stress, leading to extensive cellular damage over time. Negative consequence of the functional decline of aging sperm has effect on different aspects of reproduction, such as sperm motility, fertilization potential or embryonic survival (Tarin et al., 2000).

The population (concentration) of sperm reaching the site of fertilization (oviductal ampullary-isthmus junction) is enriched in both viability and normal morphology over that inseminated. Although morphologically head, tail and chromosomal abnormal sperm have been associated with sub-fertility and sterility for many years, it is now known that sperm with

classically misshapen heads do not traverse the barriers of the female reproductive tract or participate in fertilization based upon accessory sperm data from ova and embryos (Saacke et al., 1998).

4. CAUSE OF EMBRYONIC MORTALITY IN CATTLE

Embryonic mortality refers to the losses which occur in the period between fertilization and the completion of the stage of differentiation at approximately day 45 or embryonic death or mortality denotes the death of fertilized ova and embryo up to the end of implantation. Thus, embryonic loss could be classified into early (from fertilization to day 27) and late (from day 28 to 42) embryonic losses. Embryonic/fetal loss occurs throughout pregnancy in cattle; however, it is concentrated mainly in the first 42 d after breeding. Approximately 30 percent of all embryos and fetuses will not survive to birth. About 80 percent of this loss occurs before day 17, 10-15 percent between day 17 and 42 and 5 percent after day 42 (Humbolt, 2001; Macklon et al., 2002; Sartori et al., 2003).

It is well known that, the establishment of pregnancy results from the interaction between the embryo and the dam and is the culmination of a series of events initiated with development of the follicle and gametes. However the main factors implicated in embryonic or fetal loss are, physiological, genetic, immunological and endocrine origin (Bajaj, 2001) including nutrition, temperature and heat stress, time of insemination, genital infection, uterine environment and asynchrony, maternal age and genetic factors (Bajaj, 2006).

4. 1. Genetic Cause

Genetic causes of embryonic death include chromosomal defects, individual genes and genetic interactions. Chromosomal abnormalities are known to be a cause of embryo mortality. One research summary estimated an average of 10 percent embryos had gross chromosomal abnormalities. Most of these embryos were lost before day 12. Unfortunately, this problem cannot be controlled through management. A range of misalliances can occur during the pairing of the haploid parental chromosomal sets at the time of fertilization, which are subsequently lethal to the embryo. Chromosomal abnormalities may also originate by penetration of ovum by more than one sperm cell, polyspermia (Van Raden and Miller, 2006).

Apart from these genetic causes, several reproductive traits are adversely affected by inbreeding. Another factor is the age of the animal which is responsible for fluctuations in conception and embryo survival rate. In heifers, conception rate is maximum at 15 to 16 months of age and breeding heifers at 26 months of age or older result in a 13% reduction in conception rate, presumably due to a lower embryo survival rate (Kuhn et al., 2006).

4. 2. Nutritional causes

4. 2. 1. Diet energy and / or protein contents

Nutritional factors have been shown to contribute to low conception rates resulting from embryonic mortality. Research studies have shown that cows with severe change in body condition score (greater than 1 point loss on a scale of 1 to 5) during the first five weeks postpartum had an extended interval to first service and a very low conception rate compared to herd mates with only a minor or moderate change in body condition.

Whether this is due to an abnormal hormonal situation such as reduced progesterone secretion or ovulation of a defective oocyte has not been determined. Several reports showed that feeding excess crude protein, excess degradable intake protein or low levels of fermentable carbohydrate and the various combinations of these nutrients can cause low conception rates. Such situations can produce excessive levels of ammonia in the blood and uteri of cows.

Some researchers believe this could be toxic to the gametes and the developing embryo. The excess ammonia that is not utilized by the rumen microbes must be converted to urea at a significant energy cost which can further adversely impact conception rate. Mycotoxins and exposure to toxic substances and toxic plants have also been implicated as a cause of embryonic mortality.

Extremes of nutrition in early pregnancy are detrimental to the growth and survival of the embryos. A positive relationship between high plane of nutrition or increased feed intake and embryo death was reported in dairy cows (Wathes et al., 2003). This relationship was mainly ascribed to the rapid clearness of circulating P4 during early pregnancy which is related to increase liver blood flow .Excess protein level increase peripheral level of ammonia and urea, toxic to sperm, oocyte and embryo (Sangsritavong et al., 2002). Deficiency of protein can cause increase basal level of LH and cause endocrine disturbance as well as influence basal progesterone level which allow for persistence of CL and anestrus.

On the other hands, occurrence of negative energy balance (NEB), particularly in high-milk producing animals, at the last three weeks of gestation to the first three weeks post-partum has been found to affect embryo survival (Butler, 2005). Negative energy balance induces several metabolic disorders mainly due to mobilization of body fat reserve which increases concentrations of blood non-esterified fatty acid and β-hydroxybutyrate and decreases glucose concentrations. Accumulation of such metabolites in follicular fluid can affect oocyte competence leading to production of embryo with less developmental capacity and to form less functional CL (Butler, 2005; Leroy et al., 2008).

Deficiencies of a wide range of specific nutrients have been implicated in poor reproductive performance through affecting embryo survival. Of specific nutrients, amino acids have been confirmed to affect embryo survival via implicating in different physiological events. Many amino acids have positive effects on physiological processes independently of their effects on synthesis of proteins. These effects of amino acids are termed “functional effects”. The increase in specific amino acids in the uterus near the time of embryo elongation appears to be due to an induction of specific amino acid transporters in the uterine endometrial cells (Groebner et al., 2011).

The induction of these amino acid transporters is most likely induced by the protein interferon-tau (INFτ) that is secreted by the elongating embryo. Thus, there is likely a positive feedback system occurring during this critical time of embryo elongation with uterine amino acids being essential for rapid embryo growth and embryonic interferon-tau production; whereas, interferon-tau stimulates active amino acid transport through the uterine epithelial cells to increase amino acid supply to the elongating embryo.

4. 2. 2. Plant secondary metabolites

In ruminants, feeding estrogenic diets, goitrogenic cruciferous crops and cottonseed gossypol can affect embryo survival. Long term consumption of isoflavones increases number of inseminations, infertility rates and early embryonic loss (Hashem and Soltan, 2016; Piotrowska et al., 2006). Phytoestrogens (mainly isoflavones) and their active metabolites

evoke PGF2α synthesis by epithelial and stromal cells of bovine endometrium, decrease luteal P4 synthesis, stimulate PGF2α synthesis by luteal cells, and decrease LH pulse-frequency. These hormonal alterations drive to increase the risk of early embryonic loss (Woclawek-Potocka et al., 2013). Cottonseed contains gossypol that can be toxic to mammalian cells. High plasma gossypol concentrations (>5 μg/ml) reduced embryo quality and development, and conception rates. Cows fed high gossypol diets experienced more fetal losses, and reduced conception rates and fetal survival were associated with higher plasma gossypol concentrations (Santos et al., 2003).

4. 2. 3. Infectious Cause

Infectious agents can cause uterine infection or directly affect the embryo causing death. Infection of the uterine and oviductal environment can be caused by specific and non-specific uterine pathogens. Specific uterine infections are caused by a number of viruses, bacteria, Fungi and protozoa. The major organisms adversely affecting reproduction are : Corynebacterium pyogenes, Campylobacter fetus (Vibriosis), Haemophilius somnus, Leptospirosis, Neospora and the viruses bovine virus diarrhea (BVD), infectious bovine rhinotracheitis (IBR) and to a lesser extent Urea plasma and Mycoplasma.

4. 2. 4. Inflammatory diseases

Inflammatory diseases are prevalent in cattle and impair fertility. Cows affected by inflammatory disease from parturition to the day before breeding have reduced fertilization of oocytes, reduced survival of zygotes to the morula stage, impaired development to early stages of conceptus elongation, reduced secretion of interferon during the period of pregnancy recognition, altered transcriptome of preimplantation conceptus cells, and increased pregnancy loss. Consequently, these cows have reduced pregnancy and calving per breeding. Reduced oocyte competence is a likely reason for the carryover effects of diseases on developmental biology, but impaired uterine environment is also involved

4. 2. 5. Environmental Causes

- **Heat stress**

The environmental factor like heat stress seems to have the greatest impact on embryo survival (Sartori et al., 2002). There are several possible mechanisms by which heat stress can prevent the growth of oocytes and embryonic loss. The foremost is the reduction on the synthesis of pre-Ovulatory surge in luteinizing hormone and estradiol. Hence, there is poor follicle. Elevation of maternal body temperature affects various aspects related to pregnancy such as secretion of reproductive hormones, oocyte quality, success of fertilization, and embryo development (Sartori et al., 2002; De Rensis et al., 2017).

The direct effects of heat stress on the embryo appear at its early developmental stages immediately after the onset of estrus and early during the pre-implantation period. Most of the detrimental effects of heat stress could be due to the oxidative stress (production of excessive free radicals) originating from the elevation of temperature. Free radicals could damage organelles or DNA and alter gene expression of dams and/or preimplantation embryos.

This is because oocytes, zygotes, and early stage embryos have low potential for scavenging free radicals mediated by heat stress due to lack of gene activation in these developmental stages (Sakatani, 2017).

4. 2. 6. Endocrine cause of embryonic mortality

Hormonal patterns or imbalances associated with embryonic mortality have been identified. The challenge for researchers is to develop synchronization programs and treatments that provide high progesterone, maintain low estrogen, and lead to a highly functional corpus luteum to maintain pregnancy. Hormonal patterns or imbalances associated with embryonic mortality have been identified. The challenge for researchers is to develop synchronization programs and treatments that provide high progesterone, maintain low estrogen, and lead to a highly functional corpus luteum to maintain pregnancy.

The relationship between progesterone and estradiol in circulation during the first two week post insemination play a crucial role in the maintenance of luteal function and therefore pregnancy itself. A new wave of ovarian follicles grows during the luteal phase, even if fertilization has been successful. If estradiol production of these growing luteal phase follicles is not diminished early enough, luteolysis is triggered and corpus luteum resolved.

There major reasons for a lack of progesterone includes, (i) Corpora Lutea has a short lifespan (6 to 12 days) with optimal progesterone secretion. Thus, luteolysis occurs before the embryo has time to signal its presence through secreting bTP-1 and (ii) CLs that have a normal lifespan (more than 14 days) but secrete low levels of progesterone, which does not suppress the luteolytic effects of the prostaglandin or Corpora Lutea may has a short lifespan with sub optimal progesterone secretion (**Figure 1**).

In cattle, sub-luteal concentrations of P4 during the estrous cycle prior to the insemination increase frequency of LH-pulses which increase the risk of formation of persistent dominant follicle (Geary et al., 2013) and evoke secretion of estradiol-17β that might induce alteration in endometrial morphology (Diskin et al., 2006). Ovulation of such follicles results in oocytes that are at a more advanced stage of maturation at time of ovulation, due to its exposure to high detrimental amounts of estrogen. However, this oocyte is highly fertilizable; it yields embryo die before reaching 16-cell stage (Ahmad et al., 1995).

The main source of P4 during early pregnancy is CL, thus CL dysfunction resulting in low P4 concentration during early pregnancy seem to be the most important reason for the occurrence of early embryonic loss in most mammals. In cattle, days from 14 to 17 post mating are the critical period for maternal recognition of pregnancy, which coincides with the beginning of regression of the CL and decreased P4 levels. Actually, P4 is required through days 4 to 9 post-mating, when excessive secretion of PGF2α can be both embryo toxic and luteolytic, through the period of maternal recognition of pregnancy, days 14 to 17, when lower pregnancy rates have been associated with low P4 and high estradiol-17β, and through the late embryonic period, days 28 to 42, when placentation and attachment are in progress (Inskeep, 2004).

- **Inadequate CL function/Luteal deficiency**

The importance of sufficient P4 synthesis by luteal cells is more determinable for pregnancy establishment in some luteal-dependent species, not only pending placenta formation but also during the whole pregnancy term (Hashem and Aboel-ezz., 2018). Therefore, short luteal phase with sub-optimal P4 level, short luteal phase with optimum P4 level and normal luteal phase with sub- optimal P4 level (Figure 1), increase the opportunity of early embryonic loss in most farm animals Hashem et al (2015).

As reported by Vasconcelos et al (2001), ovulation of very small follicles in lactating cows resulted in smaller CL, lower serum progesterone concentrations and lower conception

rates, compared with ovulation of larger follicles. The reduction in conception rate might have been due to a reduction in IFN-τ production by the conceptuses since maternal progesterone concentrations were positively correlated with IFN-τ production (Kerbler et al. 1997).

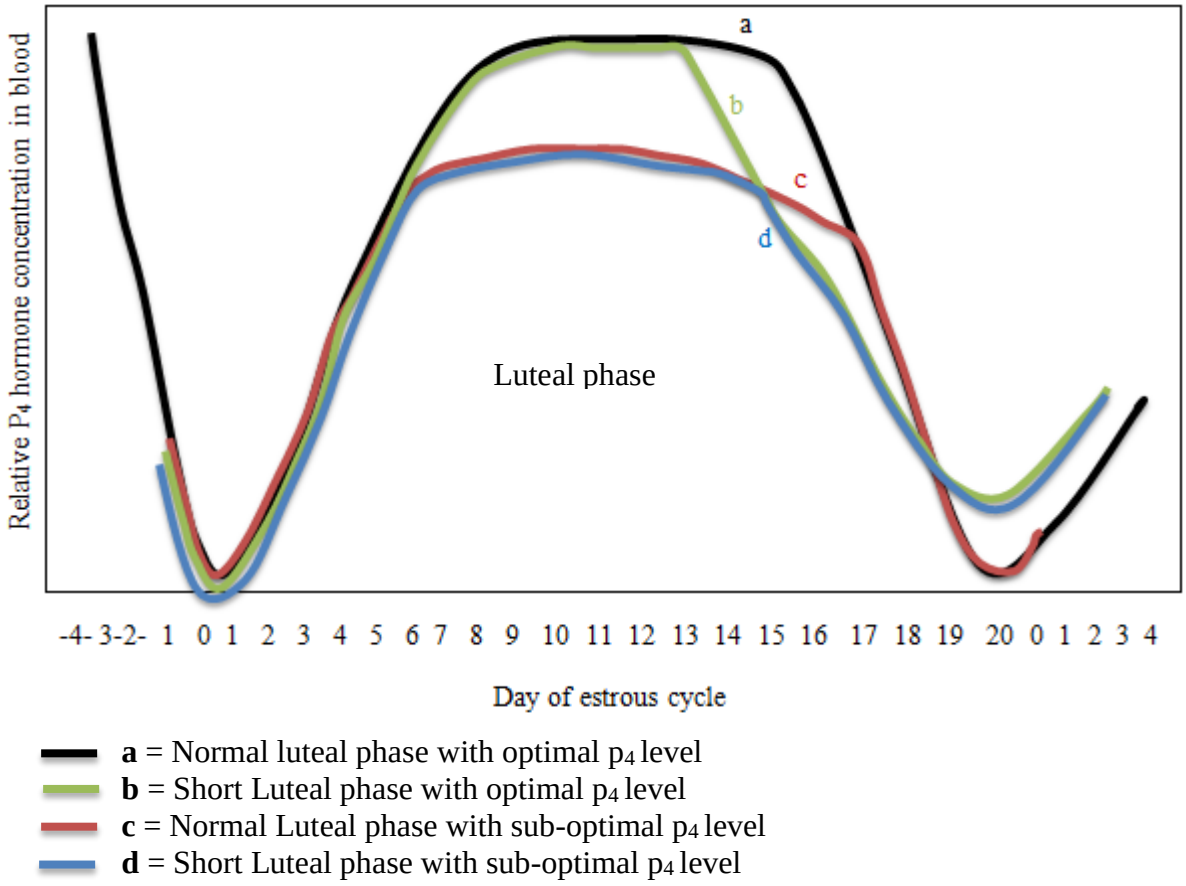

Figure 1. Schematic representation of relative level of progesterone secreted versus lifespan of luteal phase

4. 2. 7. Embryonic Role

Success pregnancy is equally contributed by both maternal and embryonic sides. In the vast majority of species, maternal-pregnancy recognition, implantation and decidualization of the endometrial stromal compartment are triggered by signals sent from the implanting embryo.

During pre-implantation period, early developing embryos synthesize different molecules such as human chorionic gonadotropin (hCG) in human, equine chorionic gonadotropin (eCG) in equines, E2 in pigs, interferon-tau in cattle and gonadotropin-like substance in rabbit signaling their presence to the dam (Herrler et al., 2002).

Gonadotropins released by an embryo have an endocrine action via rescue of the CL from luteolysis subsequent P4 release during pregnancy. Also, they have paracrine actions on the endometrium affecting decidualization, angiogenesis, immune-modulation and matrix remodeling, preparing for embryonic implantation (Peng et al., 2000).

A significant proportion of the losses are likely associated with defects in the process of conceptus elongation during which. Appropriate communication between the developing conceptus and the maternal endometrium is essential for the establishment and maintenance of pregnancy in all mammals. While different strategies exist for maternal pregnancy recognition depending on the species the basic principle is the same across species—prevention of the mechanisms that bring about luteolysis in order to maintain progesterone concentrations and endometrial function to facilitate implantation and fetal development. Spatial and temporal changes in the endometrial transcriptome and histotroph composition are necessary to establish uterine receptivity to implantation and, in turn, are pivotal to the success of pregnancy. These modifications are regulated by the corpus luteum-derived steroid progesterone (P4) as well as conceptus-derived IFNT in ruminants. Low circulating P4 leads to an altered endometrial transcriptome and retarded conceptus elongation which in turn leads to reduced interferon-tau production (Mann & Lamming, 2001) and lower fertility.

5. CONCLUSION AND RECOMMENDATION

Fertilization failure and embryonic loss represents one of the major reproductive failure causes in in livestock sectors. Embryonic loss could be occurred early following fertilization until day 45 of gestation (late embryonic loss). Overwhelmingly, in different farm animals, most embryonic loss takes place between days 8 and 16 after insemination (around implantation time). The risk of this type of reproductive failure lies in its difficulty to detect as the only sign could be observed on animal is repeated insemination with longer estrous cycle. During early pregnancy, embryo survival is preliminary affected by the success of maternal-embryonic communication which depends on maternal conditions and embryo quality, in addition to the effects of environmental and genetic factors. Similarly, inadequate environmental conditions such as heat stress and unbalancing nutrition can directly affect embryo survival or indirectly evoke negative physiological consequences, leading to increase the risk of embryonic loss.

Therefore, based on the above conclusion the following recommendations are forwarded:

- Efforts should be made to provide appropriate protection against high or low temperatures, to overcome heat stress effect
- Effective vaccination, clean environment and proper timing of insemination should be undertaken
- The use of highly fertile semen, appropriate semen thawing techniques and good semen handling and placement should be considered to overcome problem related with semen side
- Herd nutrition and health management should be improved to overcome problem arising from nutrition ,endocrinological and infectious side and to optimize fertility and to reduce embryonic mortality

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