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Different factors affecting the embryonic mortality in cattle

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Abstract

The aim of the present article is to give a review of the principal causes affecting embryonic mortality, and to emphasize more recent information relating to fertility losses in cattle. Based upon reviews by numerous authors, much of the loss potential offspring in cattle is concentrated in embryonic period and is more sensitive than other period in development of embryo. Moreover, it is well appreciated that the establishment and maintenance of pregnancy is a highly orchestrated process which integrates a multitude of events. Several pathogens enter the uterus by the haematogenous route or via the vagina during natural service or during insemination. Concerning the non infectious causes, chromosomal aberrations are a major cause of early embryonic mortality in animals. Heat stress is one of the environmental factors that can cause the most important decrease in reproduction performances. Some reports published which indicate an adverse effect of a high plane of nutrition or under nutrition on fertility in the bovine specie. Other important points, such as hormonal aspects, or genetic factors have been discussed in this synthesis paper.

Keywords: embryonic loss, factors, cattle

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Introduction

Embryo development begins on day 0, or the day of standing oestrus (Table 1.). This is the day the female is receptive to the male. Ovulation occurs on day 1 or about 30 hours after the first standing mount. After fertilization, the first cell division occurs on day 2 and by day 3 the embryo has reached the 8 cell stage. Between days 7-8, the zygote migrates into the uterine horn, and two distinct parts of the embryo can be observed: the inner cell mass which will form the foetus and the trophoblast which will form the placenta. On day 15 to 17, the embryo sends a signal (Farin et Farin, 1990; Mann et al., 2001) as a messenger for pregnancy initiation. The embryo starts attachment in the uterus on day 19, with a fully bound by day 42.

Embryonic mortality in cattle, as well as in the other domesticated farm animals, is the major source of economic loss for livestock producers. The magnitude of embryonic loss in the domestic species (30 to 40 %) has been known for over a century, as reported by Hammond (1914) and Robinson (1921). It is well demonstrated that the establishment and maintenance of pregnancy is a highly orchestrated process which integrates a multitude of morphological, physiological, endocrinological, and immunological events. Prenatal losses (embryonic mortality and foetal death) are the most important causes of reproductive losses in animals and have a substantial impact on the profitability of animal production.

As defined by the Committee on Reproduction Nomenclature (1972), the embryonic period extends from fertilization to the completion of the differentiation stage, which occurs at approximately 45 days. The greater part of embryonic losses occurs during the first days after fertilization and during implantation (Wathes, 1992). Conception rate is defined as the proportion of inseminated cows that are

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Table 1: Pathways of early embryo development

Event	day
Estrus	0
Ovulation	1
Fertilization	1
First cell division	2
8-cell stage	3
Migration to uterus	5-6
blastocyst	7-8
Hatching	9-11
Maternal recognition pregnancy	15-17
Attachment to the uterus	19
Adhesion to uterus	21-22
Placentation	25
Definitive attachment to the uterus	42
calving	285

detected pregnant at diagnosis by molecular measurement (PSPB, PAG), by ultrasound or by palpation per rectum, and pregnancy rate is defined as the proportion of cows with successful pregnancies among animals treated or eligible to be bred.

In general, fertilization rates in cattle are accepted to be close to 90 %, whereas conception rates are usually believed to be between 50 and 60 % (Sreenan and Diskin, 1986). Estimations of fertilization rates for both dairy and beef bulls have ranged from 85 % to 95 % (Hawk, 1979; Diskin et al., 1980). Thatcher and co-authors (1993) and Peters (1996) generalized that fertilization failure is 10 %. In 2001, Sreenan and collaborators calculated that fertilization rates of 90 % and calving rates of 55 % are normal for heifer and moderate yielding dairy cows, indicating an overall embryonic and foetal mortality rate of about 40 %.

Embryonic losses can be classified as early embryonic mortality when cows come back into heat within 25 days after fertilization, and late embryonic mortality (LEM) when losses occur between Days 25 and 45 of gestation (Humblot, 2001). Foetal loss or abortions are used to describe pregnancy losses between days 45 and term of gestation (Forar et al., 1996).

The timing of embryonic losses has been investigated in a number of studies, and the results are variable. Embryos were most susceptible to mortality during development from the morula to blastocyst stage on days 5 to 8 (Maurer and Chenault, 1983). In multiparous cows, 67 % of embryonic losses occurred by day 8, whereas 92 % of the estimated losses were seen by day 8 in nulliparous females. Similarly, in repeat-breeding cows, the majority of losses occurred 6 to 7 days after breeding (Ayalon, 1978). In the same context, Thatcher and his group (1994) concluded that approximately 30 % of repeat breeder cows experienced embryonic loss by day 7 of pregnancy. Following artificial insemination (AI), embryonic mortality varied from 8 % (Boyd et al., 1969), with most embryonic losses occurring prior to day 15, to 23 % (Roche et al., 1981) with most embryonic losses occurring between days 8 and 16. In other studies, embryonic mortality occurring before day 42 was estimated to be either 20 % with most of the losses occurring between days 16 and 18 (Ayalon, 1978), or 42 % with the majority of embryonic loss occurring between days 8 and 16 (Diskin et al., 1980). The adhesion stage of the implantation process starts at day 21–22 in cows (Gandolfi et al., 1992; Guillomot, 1995). Losses around implantation have been estimated around 10 % to 15 % (Sreenan and Diskin, 1986) Estimations of late embryonic death rate (days 27 to 42) averaged 10 % to 12 % (Thatcher et al., 1994; Smith and Stevenson, 1995; Vasconcelos et al., 1997; Inskeep, 2002; Inskeep, 2004). In other study, Humblot (2001) showed that fertilization failure and early embryonic losses, late embryonic/foetal losses and late abortions represent 20-45 %, 8-17.5 % and 1-4 % of pregnancy failures, respectively. In 1997, 20.2 % of the embryos were lost between days 28 and 98 after insemination in intensively managed dairy cows reported by Vasconcelos and collaborators. In the other study, Grimard and co-authors (2006) reported that the frequency of late embryonic/foetal (between day 21 and day 80) death was 15.4 % and first service conception rate at 80-100 days after AI was 45.8 %.

Equally, some embryonic losses have been estimated to be around 20 %-40 % in cows (López-Gatius et al., 1996; Hanzen et al., 1999). In 2000, a review on embryonic mortality in cattle written by Vanroose and collaborators estimated that embryonic losses in cows were approximately 20-40 %. In contrast, foetal death has been estimated to be around 5 % (Lambert et al., 1991) but may exceed 10 % (López-Gatius et al., 1996).

The variations in these results points to the importance of factors such as breed, aspect of nutrition, hormonal background, time of insemination, and animal health as being influential on the timing and on the magnitude of embryonic loss in cattle. According to Santos et al. (2004), there are some others factors that can be associated with pregnancy losses (the oocyte and semen quality, heat, stress ...). This article aims to give a review of the principal causes affecting embryonic mortality, and to emphasize more recent information bearing upon fertility losses in cattle.

Specific infection

The pathogens enter the uterus by the haematogenous route (*T. gandii*) or via the vagina around natural service (campylobacter foetus) or during insemination (BVDV by contamination of semen). Non specific pathogens are mainly bacteria that enter the uterus by ascending infections or during insemination acute endometritis, mating or artificial insemination has a direct effect on the embryonic environment and is, in severe cases, accompanied by the production of luteolytic substances such as prostaglandin (De Winter et al., 1995). Bacterial infections cause mostly a diffuse and severe purulent inflammation. Viral infections are characterized by a necroting endometritis, causing diffuse and total lymphocytic and plasmacytic changes in the endometrium.

In the 1970s, researchers at the University of Minnesota reported that cows receiving an intrauterine infusion of bovine pestivirus (bovine viral diarrhoea virus, BVDV) at the time of artificial insemination had a lower conception rate than uninfected cattle (Archbald et Zemjanis, 1977). Prior to the publication of these findings, pestivirus infection in cattle was mainly recognized as the cause of mucosal disease (Pritchard, 1963), but also had been reported to be associated with abortions, stillbirths and congenital malformations (Kahrs et al., 1970; Kendrick, 1971). There are reports of low conception rates related to pestivirus-infected (PI) bulls (McClurkin et al., 1979; Paton et al., 1990; Kirkland et al., 1994). When the semen of a PI bull was frozen and subsequently used for AI, the first service conception rate was found to be 38 %, even though the semen was assessed to be of satisfactory quality (Kirkland et al., 1994). As the poor conception rate was observed in the immune and susceptible cows, it is believed that the virus probably had a direct effect on fertilization.

In a general way, bovine pestivirus is an important cause of embryonic losses in cattle. Infection of susceptible cattle around the time of insemination, during the embryonic and early to mid fetal period, can result in conception failure and increased embryonic mortality (McGowan and Kirkland., 1995).

Genital bovine tritrichomonosis is a sexually transmitted disease induced by *Tritrichomonosis foetus* (*T. foetus*), a non-invasive flagellate protozoan that colonizes the reproductive tract mucosa (Cobo et al., 2004). The disease is characterized by the repetition of oestrus and infertility due to embryonic or foetal death (Skirrow and Bondurant, 1988; Felleisen, 1999; Rae and Creews, 2006; BonDurant, 2007). Recently, Barteito and associates (2008) have constituted a first approach to study the described pregnancy alterations in bovine genital tritrichomonosis using an experimental model of pregnant rodent females. The results of latter research has shown that embryonic losses, in the infected group, was significantly higher and occurred in the early and middle phases, in accordance with the time of embryo death in infected bovines. In infected animals at the early phase of pregnancy, there was evidence of embryonic death without inflammatory changes in the uterus, suggesting a pathogenic mechanism that does not involve direct tissue damage. In the later days, *conceptus* losses were associated with endometritis and changes in the decidua.

Before hatching (zona pellucida intact embryos) a virus, *e.g.* bovine herpes virus 1 (BHV-1) and BVDV, might be present in the follicular fluid or in the granulosa cell of bovine oocytes (Bielanski et al., 1993) and can also contaminate the embryos by adhering to the glycoprotein layer which surrounds the oocytes, so called “zona pellucida”. Virus adhering to the zona pellucida or to fertilizing spermatozoa might be inserted into the oocyte (Bowen, 1979). After hatching or removal of the zona pellucida, the embryonic cells are susceptible to some infectious agents (Wrathall and Sutmöller, 1998).

It is known that BHV-1 causes infection in hatched embryos that result in embryonic mortality (Miller, 1991). In BHV-1 seronegative cattle, artificial insemination with BHV-1 contaminated semen can result in markedly reduced conception rates and endometritis. Infections of BVDV seronegative heifers resulted in a lower pregnancy rate due to fertilization failure or embryonic death. The presence of BHV-1 and BVDV in an *in vitro* embryo production system has obvious adverse effects on fertilization and embryonic development (Guérin et al., 1992). It was also demonstrated that the zona pellucida of *in vitro* produced embryos was an effective barrier against viral infections, but enough to allow entry of BHV-1 and BVDV in the outer layers of the zona pellucida (Vanroose et al., 1999).

Consequently, the embryo can become infected when it hatches out of a virus contaminated zona pellucida. The importance of the zona pellucida was also demonstrated for *in vivo* derived embryos (Singh et al., 1982). Some bacterial and protozoal infections, such as trichomoniasis and campybacteriosis, which are venereal diseases, are characterized by endometritis resulting in infertility and embryonic mortality. Other infections such as brucellosis, arcanobacter pyogenes infections, candidiasis, leptospirosis, neosporosis, and fungal infections are more commonly associated with late embryonic mortality, fœtal death and abortions (Larson et al., 1994).

Inbreeding or Genetic factors

No significant differences in the incidence of embryonic mortality were found between Holstein-Friesian and Guernsey cattle (Casida, 1950). In contrast, Mares and co-workers (1961) and Canneally and his team (1963) noted that inbred dams had a lower incidence of embryo survival. In one review, inbreeding has been reported as a cause of embryonic mortality (Hanzen et al., 1999). It has also been proven that the embryonic mortality differs from breed to breed. In an old paper, Erb and Holtz (1958) reported that heifers had a higher rate of embryonic death than cows of fourth or fifth parity. On the other hand, older animals have lower follicular activity and lower oocyte quality resulting in a decrease of the developmental competence of embryos. Furthermore, the quality of the endometrius deteriorates with increasing age (Vanroose et al., 2000).

Chromosome abnormalities detected by the presence of tetraploid cells in 1 of 8 blastocysts, 12-16 days old, by McFeely and Rajakoski (1968) contribute to early embryonic mortality in cattle. The analysis of the literature in bovine, ovine, porcine and equine species permitted to estimate otherwise that the chromosomal anomalies could be the origin, globally, of about 20 % of cases of embryonic or foetal mortality (King, 1990), and the abnormalities could spontaneously occur during gametogenesis, fertilization, or embryogenesis and as such would not be related to the maternal or paternal chromosomal constitution.

Chromosomal aberrations are a major cause of early pregnancy failure in animals (King, 1990); it is likely that most of the embryonic death due to chromosome abnormalities occurs early in gestation since the abnormalities are less frequently observed in older embryos. In other report (Iwasaki and Nakahara, 1990a), the results found chromosomal abnormalities in 37.5 % of bovine embryos cultured *in vitro* and 28 % in bovine embryos cultured *in vivo* in rabbit oviducts. In a subsequent study (Iwasaki and Nakahara, 1990b), bovine embryos cultured *in vitro* showed an incidence of chromosomal anomalies of 18.2 %, whereas embryos cultured *in vivo* had an abnormally rate of 22.2 %. King (1990) reported that chromosomal abnormalities may account for approximately 20 % of the total embryonic and foetal loss. Results from different laboratories have reported that superovulation of cattle can result in chromosomal abnormalities which are likely linked to fertilization (King et al., 1979; Greve et al., 1984), it has been suggested that superovulated oocytes may be more susceptible to polyspermic fertilization and retained mitotic activity of the polar body (Iwasaki and Nakahara, 1990a), so chromosomal aberration may also originate by penetration of more than one sperm cell (polyspermia).

Inskeep and associate (2005) thorough review of the subject of folliculogenesis and embryo loss include a discussion of the possibility premature ovulation follicles. They cite others who showed that undersized follicles that are forced to ovulate during a timed AI produce less estradiol, yield lower conception rates and exhibit reduced luteal function after ovulating (Perry et al., 2005; Mussard et al., 2007; Perry et al., 2007). The results showed a decrease conception rate and an increase in late embryonic early foetal mortalities.

Kidder and coworkers (1954) reported fertilization rates of 100 % from bulls of high fertility and of 71.4 % from bulls of low fertility. Similar results were obtained by Bearden and colleagues (1956) 96.6 % from bulls of high fertility and 76.9 % from bulls of low fertility. Like the oocyte, the male gamete influences fertility not simply by affecting fertilization rate but also, to some extent, by imparting characteristics to the embryo that influence its ability to proceed through development. Thus, one can observe differences in embryonic mortality between bulls *in vivo* (Wijerante, 1973) and *in vitro* (Hillery et al., 1990; Shi et al., 1990). In the rabbit, embryos formed from fertilization of oocytes with spermatozoa that had been exposed to elevated temperature had reduced survival (Howarth et al., 1965; Burfening and Ulberg, 1968). One cause of male derived embryonic loss is induction of chromosomal abnormalities. The incidence of non disjunction in bovine spermatogenesis has been estimated at 2.8 % (Logue and Harvey, 1978). Defective chromatin structure can also presumably lead to failure of pronuclear decondensation or early embryonic death; bulls with stable chromatin as determined by acid denaturation are more likely to give rise to offspring in heterospermic fertilization tests than bulls with less-stable DNA (Ballachey et al., 1988).

High environmental temperatures

A cow's ability to express its genetic potential for milk production, reproduction, and health depends upon her environment. If environmental conditions are not optimal, performance will be lower than could otherwise be expected. Heat stress is one environmental factor that can cause large decreases in milk yield and reproduction. Dairy cow reproduction declines during heat stress in two ways. The intensity of estrus is less during heat stress so estrus detection becomes difficult. Secondly, fertility following insemination is reduced. In a recent study in Alberta, Canada, Ambrose and co-workers (2006) revealed that the pregnancy rate per AI is lower for cows during the summer (23 %) than for other seasons (32 %). Likewise in the same year, Grimard et al. (2006) had observed a specific effect of season on late embryonic/foetal death. These data show that LEM was lower during summer (9.7 %) than the other seasons such autumn, winter and spring (23.3 %, 29.7 % and 26.8 %, respectively). This observation is in agreement with the low frequency of late embryonic losses (7.2 %) recorded by Silke and collaborators (2002) in high yielding Irish dairy cows managed according to a pasture-based production system and mated in spring and summer.

Effects of heat stress on reproduction are closely tied to the increase in body temperature that heat-stressed cows experience. Body temperature increases during heat stress when the cow cannot lose all of the metabolic heat to the surrounding environment. Moreover, Gwazdauskas and collaborators (1973) reported that an increase in uterine temperature of 0.5° C above average is associated with a decline in conception rate of 12.8 %. Another paper also reveals that heifers exposed to high air temperatures have much lower rectal temperatures than lactating cows (Sartori et al., 2002). This difference exists because heifers, which are not lactating, produce less metabolic heat than cows. Not surprisingly, heifers are much more resistant to the adverse effects of heat on reproduction than lactating cows. Accordingly, high-producing cows can be more susceptible to heat stress than cows producing less milk. In the study, led by Al Katanani and associates (1999) conducted in Florida and Georgia in the southern United States, fertility was measured indirectly by the 90 day non return rate. The non return rate at 90 day declined in the summer and the magnitude of the decline was greatest for cows producing milk more than 9072 kg/lactation, intermediate for cows producing between 4527-9072kg and lowest for cows producing less than 4536 kg (Figure 1). Similarly, this seems to have been the case in north-eastern Spain between 1991 and 2000 (López Gatius et al., 2003a). During this time, milk yield increased over 30 %. There was no decrease in first service pregnancy rate per AI during the cool season but pregnancy rate in the warm season declined from 36.4 % in 1991 to 22.1 % in 2000 (López Gatius, 2003b).

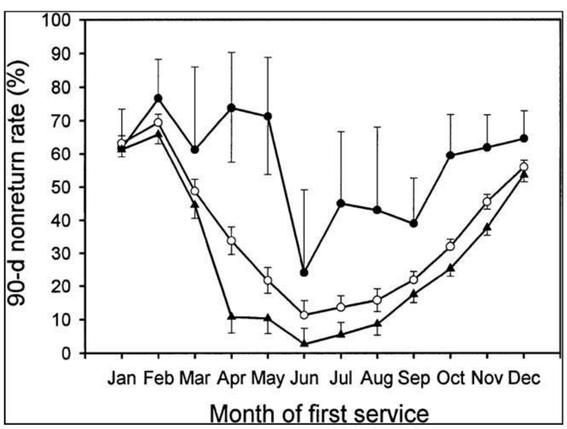

Figure 1: Seasonal variation in 90-day non-return rate to first service as affected by mature equivalent milk yield. Lines represent cows producing less than 4536 kg milk (closed circles), 4536 to 9072 kg (open circles) and 9072 kg (triangles). Data are from Al-Katanani et al. (1999) and the figure is reproduced with permission from Journal of Dairy Science

High environmental temperatures during the first months of gestation can also have detrimental effects on the embryo (Dela-Sota et al., 1998). The mechanism for this effect has been explained by a direct damaging effect of a high uterine temperature on the embryo and by the shunting of blood away from the uterus to the periphery in an attempt to maintain body temperature, resulting in a reduced nutriment load (Dziuk, 1992). Although hyperthermia and hypothermia can probably both adversely affect the embryo, hyperthermia seems to have more deleterious effects on the development process. It is well established that short term exposure to heat stress at the time of breeding results in a lowered conception rate in cattle (Gu et al., 1991).

Heat stress around the time of ovulation can also compromise fertility in different species. Sartori and collaborators (2002) reported that lactating cows had a greater increase in body temperature in response to an increase in environmental temperature than heifers and that the reproductive performance of heifers did not change during the summer. In a study with superovulated cows, it was shown that heat stress at day 1 after insemination reduced embryonic survival but heat stress at day 3, day 5 or day 7 after insemination had no effect on embryo survival (Ealy et al., 1993). In the same context, whereas high body temperature measured on day 7 had a negative effect on conception rates and embryonic losses following artificial insemination or an embryo transfer (ET) in lactating Holstein cows (Demetrio et al., 2007).

In 2003, Sugiyama and other researchers demonstrated that *in vitro* heat stress during the critical stage of early embryo development (1cell, 2 cell, 4 cell and ≥8 cell) significantly increases the incidence of early embryonic mortality. The results of these experiments indicated that increased maternal body temperature adversely affects embryonic development and survival in cattle. The findings of this study suggest that cooling the cow environment during periods of hot weather is desirable not only at time of insemination but also a few days after insemination to improve pregnancy rates.

Laboratories in Louisiana (Rocha et al., 1998), Wisconsin (Rutledge et al., 1999), Israel (Zeron et al., 2001), and Florida (Al-Katanani et al., 2002a; b) have reported a reduction in oocyte competence during the summer. The summer decline in oocyte competence is presumably due to heat stress. In sheep, heat stress 12 days before oestrus reduced fertilization and lambing rates (Dutt, 1964). In addition, retrospective analysis of a large reproduction data set in lactating dairy cattle revealed a negative association between heat stress 10 days before breeding and subsequent pregnancy rate (Al Katanani et al., 1999). Near oestrus, the oocyte also appears sensitive to damage.

The exposure of cows to elevated temperatures is known to have a variety of effects, including decreased sexual activity, decreased fertility, depressed appetite, and decreased milk production, all of which contribute to the goal of decreasing the production of metabolic heat in order to maintain thermo-neutrality. It has been known for over 45 years that the seasonal effect of heat stress has the most negative impact on the female (Stott, 1961). In an older paper, Stott and Williams (1962) speculated that a low fertilization rate and a high rate of embryonic mortality were the major factors responsible for the low seasonal breeding efficiencies occurring during periods of high ambient temperature and humidity. Whereas, in another study (Ryan et al., 1993) which reported on the seasonal heat stress of cows in Saudi Arabia, a decrease in embryo viability was seen in cows from day 7 (59 %) to day 14 (27 %) during the hot season, but was not decreased during the cool season for the same period of pregnancy. Pregnancy rates for this study from days 25 to 35 were 21 % in the hot season compared to 36 % during the cool season. Based on the number of unfertilized ova which were collected from cows during the hot and the cool seasons, the authors felt that fertilization failure was not affected by season of breeding.

Thermal stress after mating had disastrous effects on beef heifers exposed to 32° C for 72h immediately after insemination; none of the animals became pregnant compared with a 48 % conception rate in heifers exposed to 21° C (Dunlap and Vincent, 1971). In dairy cows, the first 4-6 days after service were determined to be the most critical (Wiersma and Scott, 1966; 1969). High humidity increased the effect of high temperature (Ingrahan et al., 1974) and the average temperature-humidity index of the 2^{nd} day before insemination was most related to conception.

Specific nutrient deficiencies or malnutrition

To our knowledge, there is few experimental data on the correlation between nutrition and proven embryonic mortality. However, there are other reports which indicate an adverse effect of a high plane of nutrition on fertility in heifers (Joubert, 1954). Larsen and Larsen (1964) found that the level of feeding imposed after the first calving had very little effect upon the number of services needed per pregnancy. A severe negative energy balance of high yielding dairy cows after calving may affect oocycte quality and may enhance embryonic mortality once the cow has been inseminated (Butler and Smith, 1989).

According to Heuer et al. (1992) both the fat/protein ratio and the percentage of fat are good predicators of fertility. Recently, Gabor et al. (2008) found a significant positive correlation between the early and late pregnancy rates and the milk protein/milk fat ratio (P = 0.013). This positive correlation might be caused by lower milk production because it is usually associated with higher milk-protein content.

It has been known for a long time that cows bred when they are gaining weight have higher pregnancy rates compared to cows bred while losing weight (Wiltbank et al., 1962). Cows that have severely depressed blood glucose levels have been reported (McClure, 1970) to have a reduced first-service pregnancy rate. It has been suggested that the lower pregnancy rate in undernourished cows may be the result of an abnormal hormonal environment, particularly in regard to the level of progesterone. In addition, it has been shown that cows with a negative energy balance tend to have lower progesterone levels (Villa-Gody et al., 1988). A severe deficiency in vitamins (vitamin A) or other nutrients (Cu, Zn, I) that serve as regulators of metabolism can cause embryonic mortality (Grahan et al., 1995). Moreover, malnutrition or a severe negative energy balance may affect the follicular development, the quality of the oocyte, and secretory and motile activity of the oviduct which is where the fertilization process takes place. These findings demonstrate that nutrition affects the very early stages of conceptus conceptus (Foxcroft, 1997; Butler et al., 1989).

Some authors have reported a negative effect of low body condition score (BCS) at AI on first service conception rate (Loeffler et al., 1999; Pryce et al., 2001; Buckley et al., 2003), but a non-significant effect of high BCS (≥3.5) on fertility. In other studies, the results obtained showed low reproductive efficiency of the experimental females, this might partly explain that cows were thin at mating with BCS 1-2 rather than the recommended BCS of 2.5 (Grimard et al., 2006). López-Gatius et al. (2003a), however, in their meta-analysis of the effect of BCS at mating on first service conception rate indicate that this relationship is very heterogeneous. Silke et al. (2002) observed that BCS loss between 28 and 56 days of pregnancy to be significantly associated with an increased frequency of LEM. In the study of Grimard and co-authors (2006), there was a low number of cows with high BCS, but the difference in the incidence of LEM between the two extremes of BCS (<2 and >2.5) was high (22.7 and 38.5, respectively).

Hormonal unbalance

Before implantation, embryonic signalling is necessary for maternal recognition of pregnancy. This initiates the hormonal changes, which are needed to elicit the uterine transformation necessary for implantation (Gandolfi et al., 1992; Geisert et al., 1992; Hansen, 1997). Some authors attribute an important role of low levels of progesterone to failures of the reproductive process in cow. By evidence, progesterone can be lower because secretion by the corpus luteum is reduced, or because metabolism of P_4 is increased. Therefore, understanding bases for the occurrence of low progesterone is necessary. The post ovulatory rise of P4 is of particular interest as it maintains the synchrony between the embryo and the uterus. An overall analysis of studies concerning progesterone supplementation revealed a significant improvement in the pregnancy rate of 5 % following progesterone supplementation (Mann et al., 1998). Reduced secretion of progesterone below a threshold required to establish pregnancy has been demonstrated as a cause of embryonic mortality in cattle (Mann et al., 1998; Mann and Lamming, 1999; 2001). In a recent study, Campanile and co-authors (2005) have concluded that a reduced capacity P4 secretion can explain around 50 % of embryonic mortalities in buffalos synchronised and mated by AI during a period of low reproductive activity and that other as yet unidentified factors also have a significant effect on embryonic survival.

A deficiency of P4 caused by primary luteal insufficiency has been reported as a cause of embryonic mortality, but is probably not of frequent occurrence (Wathes, 1992; Mann et al., 1998). In 2005, Stronge and co-workers demonstrated that low P4 between day 5 and day 7after AI was associated with low fertility in dairy cows. In another study, Mann et al. (2006) observed that P4 supplementation on day 5 after AI resulted in better embryonic development. These data indicate that the concentration of P4 is important during the first days after insemination and it may be one of the factors that determine the success or failure of pregnancy in lactating dairy cows. Recently, Gabor and co-authors (2008) reported that the significant negative correlation between the serum progesterone concentration and late embryonic loss is well known because P4 is responsible for maintaining the pregnancy and any decrease of it can induce embryonic loss.

Thatcher and associates (1995) reported that the signal in the cow to maintain the corpus lateum is interferon τ, which is derived from the embryonic trophoblast around day 14 through 17, and is referred to as maternal recognition of pregnancy. When recipients show a regular return to oestrus (between 19 and 22 days after their first oestrus), it can be assumed that early embryonic mortality occurred, i.e. before maternal recognition of pregnancy took place. Both after AI and ET of *in vivo* or *in vitro* produced embryos, high rates of such early embryonic losses have been reported (Markette et al., 1985; Farin and Farin, 1995; Hasler et al., 1995; Ravelli et al., 1998), especially when quality grade 2 embryos had been used for transfer. Heyman and his group (2002) concluded on the basis of plasma progesterone levels, that on day 21, no significant differences in the percentage of presumed pregnancies between groups of recipients to which either cloned or IVF embryos had been transplanted.

In cattle where 45 % of artificial insemination fails (Diskin and Sreenan, 1980; Sreenan and Diskin, 1986) a reliable and specific marker is necessary to study the course of pregnancy in a large number of cows. In this specie, the diagnosis of early pregnancy is still frequently based on the use of progesterone assays in milk or plasma which reflects luteal activity but is not a specific signal of pregnancy. Additional monitoring of the course of pregnancy and placental function and foetal well-being has to rely on the measurements of proteins (different PAGs, PSPBs) and hormone (progesterone, placental lactogen ...). Recently, a study was designed by Chagas e Silva and associates (2008) in order to evaluate the relationship between plasma P4 concentrations and survival of whole and half embryos in recipient dairy heifers. The results show that early embryonic mortality of half embryos was significantly higher than that of whole embryos. This may be the result of a lower production of interferon τ, due to the small number of trophoectoderm cells. Nevertheless, the late embryonic loss of half embryos was also significantly higher than of whole embryos. This shows that upon bypassing the maternal recognition of the pregnancy period, half embryos still present a lower viability, compared to whole embryos.

Divers types of stress

Embryonic loss is increased when the dam is exposed to one or more of the many stresses that cows can experience (Hansen, 2002). Stress has a deleterious effect on reproductive efficiency in animals (Dobson and Smith, 1995) Stressors (*e.g.* transport) affect the reproductive function via actions at the hypothalamic level (GnRH) or at the ovarian level (P4) (Vanroose et al., 2000). The sensitivity of embryos to other stresses appears to change little during the period of preimplantation development. This has been shown for bovine embryos exposed to hydrogen peroxide (Morales et al., 1999). For other toxic stresses, such as chlorambucil in the rat (Giavini et al., 1984), embryonic activity increases during development. For cadmium, this pattern reflects increased uptake of the heavy metal (De et al., 1993).

The adrenal hormones are commonly used as signs of stress (Lefcourt and Elsasser, 1995) as well as prostaglandins (Senger, 1999). In 2003, Merrill and his team established a study to determine if flunixin meglumine reduces early embryonic mortality in cows subjected to stress, and to determine the effects of a single administration of flunixin meglumine on $PGF_{2\alpha}$ and cortisol release. Flunixin meglumine is a potent nonsteriodal, anti-inflammatoire agent that inhibits cyclooxygenase preventing conversion of arachadonic acid to prostaglandin $F_{2\alpha}$ (Anderson et al., 1990; Odensvik, 1995). The results of this study showed that injection of flunixin meglumine (1.1 mg/kg) would reduce early embryonic mortality under stress conditions.

Environmental toxicants, tetragenic compounds and mycotoxins can have drastic adverse effects on the survival of embryos when ingested at crucial early stages of gestation (Christianson et al., 1992; Brendemuehl et al., 1994).

Other origin of stress, such as trauma after pregnancy diagnosis by rectal palpation or by ultrasound scanner can result in pregnancy loss. There is a risk that the embryo or the foetus becomes damaged. However, Vaillancourt and collaborators (1979) found no indication that embryonic loss at the time or shortly after early pregnancy examination was increased. In 1997, Baxter and reported that ultrasound examination had no detrimental effect on the foetus. Rectal palpation is also a safe procedure when performed correctly. In bovine practice, rectal examination is one of the most frequent procedures performed by veterinarians and is the most frequent method used for pregnancy diagnosis. The rectal examination between days 34 and 41 of pregnancy using the foetal membrane slip technique did not affect embryo/foetal viability (Romano et al., 2007).

Conclusion

The embryonic period extends from fertilization to the completion of the differentiation stage in the cow which occurs at approximately 45 days, and is more sensitive than any other period of development. Embryonic losses in cattle should refer to fertility losses during the embryonic period; and as well as in the other domesticated farm animals, is the major source of economic loss for livestock producers. This review has attempted to classify the various components which contribute to embryonic mortality in bovines. We have tried to present information on a historical basis followed by more contemporary research findings. Different factors influence survival and productivity of dairy animals. From these data, it is apparent that there are numerous factors which can have a significant impact upon the incidence of embryonic mortality including: specific infection, inbreeding or genetic factors, high environmental temperature, nutrient deficiencies or malnutrition, hormonal imbalance and other types of stress.

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