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Review Article *Stress Management*

Bovine Embryonic Mortality with Special Reference to Mineral Deficiency, Heat Stress and Endocrine Factors: A Review

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Abstract

Embryonic Mortality is the major cause of reproductive and economic loss in cattle and Buffaloes. Embryonic Mortality is more common during the early than the late embryonic period, i.e., from day 8th to 16th at the hatching of blastocysts and initiation of elongation and commencement of implantation without affecting cycle lengths. Early embryonic mortality is a major source of embryonic and economic loss with mortality rate up to 40%. Embryonic mortality is also reported due to mineral deficiency and heat stress in cattle and buffaloes. Physical modifications of animal environment, nutritional management with Antioxidant, trace minerals and genetic development of breeds that are less sensitive to heat stress should be best solution. Embryonic death occurs at the time of maternal recognition of pregnancy, probably related to a failure of the Interferon tau (IFNι) secretory mechanism along with progesterone deficiency and luteal insufficiency. Recent research, both in terms of physiological mechanisms and pharmacological treatments has mostly focused on the period of maternal recognition of pregnancy or the anti-luteolytic effect. hCG/ GnRH /Progesterone supplementation have shown positive results. Supplementation of interferon as anti-luteolytic agent and supplementing Omega-3 has shown encouraging results. Ovarian examination, Animal history, blood/milk progesterone levels, PAG test and ultrasound appear to be the only practical tool presently available for diagnosis of embryonic mortality. This present review article is covering all the aspects of embryonic mortality with special reference totrace minerals, heat stress, hormonal impact and interferon tau.

Keywords: Embryonic mortality, trace minerals, heat stress, progesterone, interferon tau

1. Introduction

In India, agriculture is primarily Crop-Livestockmixed production system where the animal husbandry is avital and integral part. Animal husbandry plays a crucial rolein the Indian economy by supplementing the family income,strengthening household nutritional security and generatinggainful employment for 22.45 million people (Srivastava, 2016). India possess wealth of huge bovine population (299.6Million) which is the main source of milk production (Livestock Census, 2012), however, the average milkproductivity of the dairy animals in India is very low ascompare to other developed countries. There is large disparityin

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state wise as well as regional milk production in India (Kale et al., 2016). The milk production is mainly dependson the productive and reproductive performance of cattleand buffaloes reared by the farmers.

The success of dairy enterprise is dependent on the milk production of dairy cattle and buffaloes (Bajaj et al., 2006a). Production is directly related to the reproductive phenomenon. The reproductive efficiency is affected by very well-known factors like fertilization failure and embryonic mortality, the later being more significant (Bajaj et al., 2006b). Embryonic death/mortality denote the death of fertilized ova and embryos up to the end of implantation (Jainudeen and Hafez, 2000). Mortality is more common during the early than the late embryonic period, i.e., from day 8th to 16th at the hatching of blastocysts and initiation of elongation and commencement of implantation without affecting cycle lengths. Early embryonic mortality is a major source of embryonic and economic loss with mortality rate up to 40%. In animal production through repeat breeding and increased cost of artificial insemination (Sreenan and Diskin, 1986; Zavy, 1994; Bajaj, 2001), extended calving intervals and prolonged dry period resulting in reduced life time milk production (Roche et al., 1981) and reduced net calf crop (Maurer and Chenault, 1983).Earlier, it was believed that the bovine conceptus was resorbed, but transrectal ultrasound examination (Kastelic et al., 1991) had demonstrated that the conceptus and its breakdown products apparently eliminated by expulsion through the cervix, which either goes unnoticed or appears as a vulval discharge or clear mucus.

When, the interestrus or the interovulatory intervals are extended, it usually indicates embryonic loss that occurred around the period of Corpus Luteum (CL) maintenance (Van Cleef et al., 1991; Humblot, 2001). Measurement of progesterone in blood suggested that embryonic death at the time of CL maintenance delayed luteolysis and extended interestrus interval (Humblot, 2001). Therefore, when embryonic death precedes luteolysis, luteal regression is delayed by at least 3 days after the end of pregnancy (Kastelic et al., 1991). However, when luteolysis precedes and probably causes embryonic death, return to estrus are dependent upon the stage of follicle development. Humblot (2001) suggested that luteolysis and return to estrus prior to day 24 might be linked with early embryonic death (early embryonic loss) but if the CL is maintained and returns to estrus are delayed beyond day 24 and 24-49 (late embryonic loss). Pregnancy losses detected after day 50 known as fetal losses.

2. Embryo and Normal Embryonic Development

An embryo is a product of fertilization characterized by growth and differentiation leading to the establishment of different organ systems that make up the individual. Fertilization in the bovines occurs at ampullo-isthamus junction of the fallopian tube.The embryonic period can be divided into zygote, cleavage, morula, blastocyst, implantation and post-implantation. The zygote being the first structure formed as a result of successful fertilization cleaves mitotically into 2, 4, 8 and 16 cell stages. The cleaved embryo enters the uterine horn at the morula (mass of cells within the zona pellucida) stage about 4-5 days after fertilization. The morula then develops into blastocyst (having distinct blastocoele, trophoblast and embryonic disc) at days 6-7. The zona pellucida ruptures, resulting in hatching of the embryo after 9-10 days. The hatched blastocyst begins a process of elongation from about day 12-13, which is accompanied by the secretion of embryonic interferons. Early attachment (apposition) of the conceptus to the endometrium takes place from about day 19 and actual adhesion occurs by day 21-22.

3. Maternal Recognition of Pregnancy

Short (1969) first time used the term maternal recognition of pregnancy which means that in early pregnancy the luteal function is maintained and the normal luteolytic mechanism is inhibited. In bovines mononuclear cells of trophectoderm secretes specific proteins (bovine trophoblastic proteins, later recognized as Interferon tau) (Thatcher et al., 2001) having anti-luteolytic effect (Danet-Denosyers et al., 1994) and luteal protective agents like PGE_2 around day 8-9 (Bazer et al., 1994). Interferon-tau (IFN_t) mediates its antiluteolytic effect by inhibiting expression of endometrial oxytocin receptors and by transduction mechanism after oxytocin-receptor binding on the endometrial cells thus inhibiting the episodic release of $PGF_2\alpha$ (Demmers et al., 2001). Whenever, development of embryo is compromised or underdevelopment of trophectoderm, premature luteolysishappens.

The ovine and bovine IFN_t molecules have about 80% amino acid sequence homology whereas there is about 50% homology between IFN-α and IFN_t (Roberts et al., 1992). Both ovine and bovine IFN_t are secreted by the conceptus coincident with the blocking of luteolysis (Roberts, 1989). Hernandez-Ledezma et al. (1992) reported that bovine trophoblastic protein-1 (bTP-1/IFN_t) production begins at the expanded blastocyst stage on day 8-9 just prior to the rupture of zona pellucida and hatching. Embryonic mortality between day 14 and 19 is caused by luteal failure and occurs because certain embryos develop more slowly than normal and do not produce enough IFN_t to prevent luteolysis and maintain the pregnancy.

Martal et al. (1997) have stated many deleterious cytokines such as TNF-α, IFN-γ, IL-2 and beneficial cytokines such as TGF-β, LIF, CSF-1, GMCSF, IL-1, IL-3, IL-6, IL-10 and IFNι are involved in embryo survival in ruminants and other species. Kerbler et al. (1994) informed that an increased concentration of progesterone in cattle during early luteal phase is associated with enhanced embryonic production of the anti-luteolytic signal, IFN_t. The CL that is maintained during maternal recognition of pregnancy is capable to convert $PGF_2\alpha$ to its metabolite (PGFM) (Silva et al., 2000).

According to Spencer and Bazer (2004) establishment and maintenance of pregnancy results from signalling by the conceptus and requires progesterone produced by the Corpus Luteum (CL). Trophoblastic hormones in most of the mammals maintain progesterone production by acting directly or indirectly to maintain the CL. In domestic animals (ruminants and pigs), trophoblastic hormones maintain progesterone production by acting on the endometrium to prevent uterine release of luteolytic $PGF_2\alpha$.

4. Death of the Embryo and Time of Occurrence

Embryo death before day 13 of gestation results in return to estrus at the normal interestrus period. Death after day 13 extends the interestrus period beyond the generally accepted figure of 18-24 days.

Linares (1981) concluded that Early Embryonic Mortality (EEM) rather than fertilization failure was the major cause of repeat breeding in heifers as long as estrus detection and insemination had been properly performed. EEM is more important than fertilization failure in parous females in their relative contributions to reduced reproductive efficiency (Maurer and Chenault, 1983). According to Maurer and Chenault (1983), the critical period of embryo demise is day 7 of gestation when the morula develops into a blastocyst. Markette et al. (1985) studied the incidence of embryonic loss following embryo transfer during the first week of development and concluded that between 50 and 75% of the embryos of poor quality are eliminated during the first 3 weeks. Sreenan and Diskin (1986) reported that 20-25% of inseminations fail during the embryonic period, i.e., between day 1 and 42, most of the losses have occurred before day 25, the most substantial losses occurring between day 8 and 13 (8-9%) and days 14 and19 (13-15%). Dunne et al. (2000) carried out studies on embryo and fetal loss in beef heifers between day 14, 30 of gestation and full term by measuring embryo survival rates which were 68, 76 and 71.8%, respectively. This led to the conclusion that most embryo losses in heifers occurs before day 14 after insemination.

5. Causes of Early Embryonic Death

Survival of embryo is affected by nutrition which include Energy, protein and minerals, vitamins deficiency, temperature and heat stress, time of insemination, genital infections (Bajaj et al., 2006b), uterine environment and asynchrony (Bajaj, 2001), maternal age, genetic factors, immunological and endocrine factors.

5.1. Minerals

Dairy cattle require at least 17 minerals and three vitamins in their diet for optimal milk production, reproductive performance, and herd health. Although classical mineral or vitamin deficiency symptoms are rare, in many cases under and overfeeding of certain minerals and vitamins does occur. Even small imbalances or deficiencies can develop into reproductive, health, and milk production problems.

Generally, the two sources of minerals include natural feeds (forages and grains) and mineral supplements to balance the minerals present in the forages and grains. For the dairy cow, the major minerals (macrominerals) required are Calcium, Phosphorus, Magnesium, Potassium, Sodium, Chlorine, and Sulphur. Minerals required in much smaller, trace amounts (microminerals) include Iodine, Iron, Cobalt, Copper, Manganese, Zinc, and Selenium. Whether the requirement for a mineral is large (measured as a percent of dry matter) or small (measured in ppm), the proper level must be fed to achieve optimum performance and herd health.

5.1.1. Copper

Copper deficiency is responsible for early embryonic death and resorption of the embryo (Miller et al., 1988), increased chances of retained placenta and necrosis of placenta (O'Dell, 1990), low fertility associated with delayed or depressed estrus (Howell and Hall, 1970). Copper treatment is reported to improve conception rate as the copper treated cow require one service and the untreated cow require 1.15 services per conception (Hunter, 1977).

5.1.2. Cobalt (Co)

Cobalt is having important role in the synthesis of Vitamin B12 (Miller and Tillapaugh, 1967). Cobalt deficiency leads to reduce fertility and poor conditioning of the developing fetus. In dairy animal deficiency leads to prolonged uterine involution, irregular estrous cycle, lower conception rates and early calf mortality (Puls, 1994; Kumar, 2003).

5.1.3. Selenium (Se)

Among dairy animals, where subclinical selenium deficiency is there, reproductive performance may get retarded with delayed ovulation, increased services per conception and high incidence of mastitis (Goff, 2005). In pregnant animal marginaldeficiency of selenium leads to abortion, birth of weak calves that are unable to stand.Selenium supplementation reduces the incidence of retained placentas, cystic ovaries, mastitis and metritis (Patterson et al., 2003). Selenium helps in enhancing the reproductive efficiency by increasing the activity of glutathione peroxidase in blood and tissues.

5.1.4. Manganese (Mn)

Manganese is important in cholesterol synthesis (Keen and Zidenberg-Cheer, 1990) which in turn is necessary for the synthesis of steroids like progesterone, estrogen and testosterone. It is responsible for silent estrus and anoestrus (Corrah, 1996) or irregular estrus (Brown and Casillas, 1986) and decrease conception rate, birth of deformed claves and abortions in females and absences of libido and improper or failure of spermatogenesis in males (Kumar, 2003).

5.1.5. Zinc (Zn)

Zinc act as cofactor and coenzyme of many enzymes and various reproductive hormones. Zinc plays an essential role

in the maintenance and repair of uterine lining after calving, helps in early involution. Abnormal levels of zinc is associated with decreased conception rate, abnormal oestrous and abortion. Zinc as coenzyme, is involved in the formation of prostaglandins from arachidonic acid suggesting its profound effect on reproductive cycles and maintenance of pregnancy (Kumar et al., 2011).Zinc also increases the plasma beta carotene level that has been directly correlated to higher conception rate and embryonic development (Staats et al., 1988).

5.1.6. Iron (Fe)

Iron is essential for the synthesis of haemoglobin and myoglobin and various other enzymes that help in formation of ATP through electron transport chain. It helps in transport of oxygen to tissues, maintenance of various oxidative enzyme systems (Khillare et al., 2007).

5.1.7. Iodine (I)

Iodine due to its action on thyroid gland affects the reproduction. Iodine is regarded as essential for the developing foetus and maintaining the basal metabolic rate. Iodine through its effect on thyroid gland helps in secretion of gonadotropin by stimulating the anterior pituitary gland, thereby affects the oestrous cycle (Khillare et al., 2007). Deficiency of iodine affects the fertility and increases the abortion rate (Hetzel, 1990), the incidence of retained placenta and post-partum uterine infections, respectively (Hemken, 1960). Conception rate and ovarian activity is reduced with the impaired thyroid functions.

5.1.8. Chromium (Cr)

Chromium is essential for carbohydrate metabolism (Tuormaa, 2000). It is present in nuclear protein in higher amount thus has a role in gametogenesis and for healthy foetal growth.

It is also an integral part of the pregnancy specific protein that is secreted by uterine endometrium which helps in preventing the early embryonic mortality (Kumar et al., 2011).

It is having a crucial role in maturation of follicle thus maintaining the oestrous cycle and also in LH release which triggers the ovulation.

6. Heat Stress

The performance, health, and well-being of livestock are strongly affected by climate. High ambient temperatures, high direct and indirect solar radiation and humidity are environmental stressing factors that impose a strain on animals.

Thermal stress effects on livestock are of multifactorial nature. It directly alters and impairs the cellular functions in various tissues of the body and the redistribution of blood flow, as well as the reduction in food intake, which ultimately results in reduced production performance. Reproductive functions of livestock are particularly vulnerable to climate change; it has been established that large ruminants are more prone to heat stress compared with small ruminants (Singh et al., 2011). Heat stress is the major cause for infertility and reproductive inefficiency in livestock, resulting in profound economic losses. Heat stress reduces the libido, fertility and embryonic survival in livestock and favours the occurrence of diseases in neonates with reduced immunity. Heat stress affects the fertility and reproductive performance of livestock species through compromising the functions of the reproductive tract, disrupting the hormonal balance, decreasing the oocyte quality, and thereby decreasing embryo development and survival (Wolfenson et al., 2000, Gendelman et al., 2012b). In the tropical and subtropical regions, during the hot season, both the poor quality of oocytes and embryos results in decreased conception rate and subsequently with more days open resulting in huge economic losses to the dairy industry (Collier et al., 2006). The high ambient temperature and relative humidity directly affect reproduction by altering or impairing various tissues or organs of the reproductive system of animal (Dash et al., 2016). The threshold level of temperature humidity index (THI) for the high performance in terms of milk yield and reproduction is around THI 72 in tropical and subtropical climates. However, recent studies on THI in temperate climate emphasized that the THI lower than 68 is suitable for cattle performance and welfare (Gauly et al., 2013).

High environmental temperatures impair the female reproductive process at various stages of pubertal development, conception and embryonic mortality. Stress inhibits the reproductive hormones which subsequently excites the pituitary gland to release adrenocorticotropic hormone (ATCH). The ACTH stimulates the release of glucocorticoids and catecholamines, which act extensively to alleviate the effect of stress. However, ACTH-stimulated glucocorticoid release is responsible for an inhibitory effect on the reproductive axis. Heat stress reduces the length and intensity of estrus, alters follicular development and increases the rate of apoptosis in the antral and pre-antral follicles. Extreme environmental temperatures delay the onset of puberty in male and female animals. Furthermore, heat stress during follicular recruitment suppresses the subsequent growth and development to ovulation (Ozawa et al., 2005). Changes in the follicular growth disturb further progress and function of the oocytes (Roth et al., 2000, Hansen, 2009). The chronic release of ACTH, associated with heat stress, inhibits the ovulation and follicular development by altering the efficiency of follicular selection and dominance and glucocorticoids are critical to mediating this inhibitory effect on reproduction (Al-Katanani, 2002). Further, high level of glucocorticoids during heat stress directly inhibits the meiotic maturation of oocytes, and, in addition, corticotropic releasing hormone (CRH) inhibits the ovarian steroidogenesis, derived of the decrease in the secretion of luteinizing hormone (LH). The consequent decrease in estradiol results in reduced length and intensity of estrus expression (Masoumi et al., 2013).

In bovine, embryos are sensitive to maternal heat stress during the first 2 weeks after breeding (Wakayo et al., 2015, Nebel et al., 1997). A major source for a reduction in embryonic survival induced by heat stress may be due to the adverse effects of elevated body temperatures on developing zygotes and embryos. High ambient temperatures during oocyte maturation and ovulation or during the first 3–7 day of pregnancy reduced the embryonic viability and development. Although elevated temperatures affect the pre-attachment stage of embryos, the degree of the effect decreases as the embryo develops. Heat stress causes embryonic death by the interfering with protein synthesis, oxidative cell damage, reduction in successful pregnancy recognition and expression of stress-related genes associated with apoptosis. The exposure of lactating cows to heat stressafter the 1st day of estrus has reduced the development of embryos to blastocyst stage after 8th day of estrus (Ealy et al., 1993), the deleterious effects of heat stress on the embryos being most evident in early stages of its development (Demetrio et al., 2007). *In vitro* or *in vivo* exposure of embryos to high temperatures until day 7 (blastocyst stage) is accompanied by lower pregnancy rates up to day 30 and higher rates of embryonic loss occurred on day 42 of gestation (Demetrio et al., 2007). Embryos at day 1 are more susceptible to maternal heat stress than embryos at days 3–7. In addition, heat stressedembryo at the time of post-implantation period was found to be associated with foetal malnutrition and various other teratologic conditions in cows, which may ultimately culminatein embryonicdeath (Kadokawa et al., 2012).

7. Endocrine Factors

Endocrine factors/causes play an important role in embryonic death (Bajaj, 2001). To understand the influence of endocrine causes on embryo survival and mortality one should be familiar with the structural composition and functioning of corpus luteum and interaction between different reproductive hormones affecting luteal lifespan.

7.1. Cells of corpus luteum and their function

On the basis of morphology and biochemical properties corpus luteum is composed of two distinct steroidogenic cell types (Hoyer and Niswender, 1985):

7.1.1. Small luteal cells (follicular origin)

These cells derived from theca interna of preovulatory follicles (Priedkalns et al., 1968).

7.1.2. Large luteal cells (granulosa cell)

These cells derive from granulosa cells (O'shea, 1987). Small luteal cells are able to differentiate into large luteal cells as the cycle progresses (Hansel and Dowd, 1986). Farin et al. (1988) postulated that conversion of small luteal cells to large luteal cells occurs only during the early part of oestrus cycle.

7.1.3. Stem cells of corpus luteum

These different cell types contribute to circulating progesterone (P_4) in different manner. Luteinizing Hormone (LH) is the major luteotropin in domestic ruminants (Niswender et al., 1985) and cattle and there is marked difference in the response to LH by large and small luteal cells (O'shea, 1987).

Harrison et al. (1987) reported that small luteal cells possess higher number of LH receptors than large luteal cells. Niswender et al. (1985) found that 20% of the progesterone (P_4) in the ovarian vein in mid-cycle is secreted by small luteal cells whileearly 80% of P_4 is secreted by large luteal cells which have only few functional receptors for O'shea (1987) indicated that on per cell basis large luteal cells produce more progesterone than small cells.

7.2. Luteal function during early pregnancy

Plasma and milk progesterone concentration rise similarly in early luteal phase in pregnant and non-pregnant animals but the higher concentrations are maintained in pregnant cows for duration of pregnancy which are essential for maintenance of pregnancy. Anti-luteolytic substances secreted by embryo around day 13 are probably responsible for differences in progesterone patterns between pregnant and nonpregnant animals.

Lamming et al. (1989) found that milk progesterone concentrations in pregnant and nonpregnant cows rise indifferently until day 9, which later on diverged and the concentrations in pregnant cows remained higher. They also reported a significant dip in progesterone concentrations in pregnant animals on day 11, followed by a rise which reflects a rescue effect of the corpus luteum by the embryo.

Shelton et al. (1990) reported that the rate of rise in progesterone concentration was lower in the postovulatory period in cows identified for sub-fertility than in pregnant and nonpregnant heifers.

7.3. Role of oxytocin, oxytocin receptors (OTR) in luteal function

Wathes and Lamming (1995) have reported that during luteal regression, pulses of oxytocin stimulate synthesis and pulsatile release of $PGF_2\alpha$ following an increase in endometrial oxytocin receptors (OTR). Oxytocin receptor synthesis and $PGF_2\alpha$ release are inhibited by interferon production by the conceptus during early pregnancy. They also reported that OTRs are present during anoestrus, oestrus and late luteal phase and during most of pregnancy while the plasma oxytocin concentration causes parallel changes in plasma progesterone. These concentrations are basal at oestrus and rise from about day 2 of the cycle peaking around day 9 and falling from about day 12-13 before the onset of luteolysis (Wathes et al., 1993). The pattern is similar in the pregnant animal and plasma concentrations fall from 12-13 days after inseminations.

Plasma concentrations of $PGF_2\alpha$ are generally low for most of the cycle but pulsatile release starts at day 13 and the pulse frequency increases until luteolysis (day 17). In nonpregnant

ewes most oxytocin pulses occur in association with $PGF_2\alpha$ whereas, in pregnancy most pulses are not associated with $PGF_2\alpha$ (Hooper et al., 1986). This pattern might be similar in cattle.

Progesterone blocks the increase in OTR for about the first 10-12 days of the luteal phase, but the mechanism of its prolonged effect, followed by upregulation, is still unclear. McCracken et al. (1984) found that increasing progesterone concentration in the luteal phase down regulates the progesterone receptor for about 10 days. But there was no evidence whether the progesterone receptors increase prior to the OTR increase or the treatment with progesterone reduces its own receptor (Wathes and Lamming, 1995).

7.4. Interferon, oxytocin receptors interaction and luteal function

During early pregnancy the rise in OTR concentration is inhibited probably by the action of embryo derived IFN. The mechanism of action of IFN may involve suppression of both oestradiol and oxytocin receptors probably at the transcriptional level (Bazer et al., 1994). Bovine Interferon-alpha (bIFNα) has been shown to stimulate progesterone production by luteal cells *in vitro*, without affecting oxytocin output (Luck et al., 1992). Imakawa et al. (1993) reported that maternal granulocyte macrophage colony stimulating factor might be involved in stimulating embryo IFN production.

7.5. Types of abnormal luteal function

Abnormal luteal function is associated with reduced pregnancy rates (Hommeidaa et al., 2004). Two distinct type of abnormal luteal function have been reported (Troxel and Kesler, 1984):

7.5.1. Type-I (short luteal phase)

It is observed after a period of sexual rest and when breeding is initiated for the first time. In this condition short life span of corpus luteum (6-12 days) is observed.

7.5.2. Type-II (inadequate luteal phase)

It is observed at any stage during the reproductive life. Life span of corpus luteum is of more than 14 days but with depressed plasma progesterone.

7.5.3. Mechanisms contributing to reduced luteal function

Mechanism contributing to reduced luteal function can be classified into three main categories:

7.5.4. Deficiencies in the maturational process within the preovulatory follicle and/or inadequacies of ovulatory stimulus.

7.5.5. Short comings in the support of the CL once they have formed

7.5.6. Premature activation of the luteolytic process

Follicular deficiencies may reflect in the form of subnormal progesterone concentration and short lived CL may be the consequence of premature activation of the luteolytic process.

8. Diagnosis

Early embryonic deaths before regression of CL are indistinguishable from fertilization failure in that both cow and ewe return to estrus at the normal time. Death of one embryo in twin ovulating ewes may be undetected as pregnancy will continue. Several methods are used to determine embryonic mortality in cattle. The main being:

8.1. Reproductive history

It includes to take history of animal for accurate diagnosis. The history starts calving date , time, involution process, the date of first oestrus after calving, previous insemination carried out. It also include history of Oestrus cycle period, estrus duration period, intensity of estrus, nature of discharge. On the basis of the history veterinarian will get idea of pattern of repeat breeding in dairy animals whether it is fertilization failure or embryonic mortality.

8.2. Examining embryos

Examining embryos collected by *in vivo* flushing of reproductive tract at different days after breeding.

8.3. Determining progesterone in blood, milk and saliva

Determination of progesterone in blood and milk, 21 days after oestrus is the most common method used in the pregnancy diagnosis of ruminants until the early nineties (Zoli et al., 1992; Karen et al., 2003). Prvanovic et al. (2009) in his study on monitoring of early pregnancy and embryonic mortality using blood progesterone concluded that it is impossible to determine embryonic mortality alone on the basis of progesterone profile while pregnant and non-pregnant cows can be easily distinguished 21 day post AI. They also concluded that it is very easy and accurate to distinguish non-pregnant cows from cows that have suffered early embryonic mortality.

8.4. Pregnancy associated glycoprotein (PAG) test

The main advantage of Pregnancy Specific Proteins (PSP) for pregnancy diagnosis in cattle is their ability to prove the existence of placentation and the presence of live, vital embryos, while progesterone only proves the existence of corpus luteum. The most commonly used pregnancy specific protein for pregnancy diagnosis in cows is PAG (pregnancy-associated glycoprotein). Pregnancy-associated glycoprotein has been found in the serum of pregnant cattle and used as a pregnancy marker (Perenyi, 2002). As pregnancy failure occurs, PAG concentrations drop and disappear from maternal blood. The Pregnancy-Associated Glycoproteins (PAG) are synthesized by the monoand binucleate cells of the ruminant's trophectoderm. It's release into maternal blood circulation can be assayed by RIA and ELISA. RIA methods are very precise for measuring PAG concentrations in the maternal blood and milk of the ruminants. The sensitivity and specificity of this method are very high. The results are encouraging and use of milk and in blood for PAG test is helpful in detection of embryonic mortality in the ruminants (Sousa et

al., 2008). Prvanovic et al. (2009) in his study on monitoring of early pregnancy and embryonic mortality using PAG test concluded that embryonic mortality between 18-24 days after AI was evident from drastic decrease in PAG seven and half to nine days later and using PAG for pregnancy diagnosis enables us to prove the existence of live, vital embryos *in utero* 24 days after conception.

8.5. Ultrasound examination

Transrectal ultrasonography has been used to detect early pregnancy and to determine embryo/foetal death in recent years (Kahn, 1992; Romano and Magee, 2001). It is advantageous as it is a safe technique with no effects on embryo/foetus viability (Kahn, 1992; Ball and Logue, 1994; Baxter and Ward, 1997). It is advantageous over palpation per rectum pregnancy diagnosis in earlier diagnosis of pregnancy/non-pregnancy, determination of embryo/ foetus viability, determination of number of embryos, reduction of misdiagnosis (false negatives and false positives) and reduction of potential iatrogenic embryo/foetus attrition (Romano and Magee, 2001). In research studies maximum sensitivity and negative predictive values were obtained from day 29 on in cows and from day 26 on in heifers.

9. Treatment to Improve Pregnancy Rates

Various methods have been tried using different preparations for improving pregnancy rates by reducing embryonic mortality. They are as under:

9.1. Mineral supplementation

To overcome the mineral deficiency in cattle and buffaloes, farmers should start to feed minerals in the feed considering the milk production and reproduction of animals. To keep optimum animal reproduction role of trace minerals is important.

9.2. Heat stress management

There are three major key components to sustain the productivity of animals in hot environment: through physical modifications of environment, nutritional management and genetic development of breeds that are less sensitive to heat stress (Collier et al., 2006).Altering the environment may bebroadly divided into two categories comprising (i) provision of shade and (ii) evaporativecooling techniques (Dash et al., 2016). The environmental modifications such as shade and cooling systemsare critical in arid and semi-arid zones during heat stress to maintain milk production,milk component levels, reproductive performance and animal welfare (Brantly et al., 2013).

Dietarysupplements of vitamins, trace elements and minerals can ameliorate the adverse effects ofheat stress. Vitamin E and selenium injections reduce the rectal temperature and body weightloss in sheep during summer (Alamer*et al.*, 2011). Supplementation of inorganic chromium in the feed of buffalocalves reared under high ambient temperature improved heat tolerance and the animalimmune status without affecting nutrient intake and growth performance. It was also demonstratedthat the adverse effect of heat stress on the productive and reproductive efficiency ofMalpura ewes were reversed through mineral mixture and antioxidant supplementation (Alamer et al., 2011) .

9.3. Supplementing progesterone/progestogen

Research studies have reported that low concentration of progesterone can result in the development of a stronger luteolytic signal and hence it might be concluded that cows with lower plasma concentrations are apparently more prone to embryo loss. Macmillan and Peterson (1993) found that the conception rates to first insemination were increased when the CIDR device was inserted 6-8 days after insemination. Broadbent et al.. (1992) recorded a significant increase in conception rate among cattle when Crestar ear implants (Norgestomet) were given on day 7.

Peters and Ball (1995) stated that progesterone supplementation might also cause suppression of endogenous luteotropic support due to increased negative feedback. While, Mann and Lamming (1999) demonstrated that supplemental progesterone was beneficial to fertility increasing conception rates when administered prior to day 6 after AI in lactating dairy cows.

High milk producing dairy cows required to give exogenous progesterone supplementation as a series of experiments with dairy cows (Sangsritavong et al., 2002) has shown that peripheral concentrations of progesterone and oestradiol are lowered by increased plane of feed intake due to increased metabolic clearance rate of the steroids, which is related to liver blood flow. Liver blood flow remains high in high-producing, lactating dairy cows, which in turn results in a lowering of peripheral concentrations of progesterone thus increasing the risk of embryo death. Progesterone has also been shown to directly affect the growth and development of the bovine conceptus (Garrett et al., 1988) and to be positively correlated with interferon-t secretion (Kerbler et al., 1997).

9.4. Use of human chorionic gonadotropin (hCG)

An alternative approach to increase the progesterone levels is by use of Human Chorionic Gonadotropin (hCG) to enhance the production of progesterone by the animals own corpus luteum. Administration of human chorionic gonadotropin (hCG) induces ovulation with the subsequent formation of a functional accessory CL which in turn increases progesterone and may enhance embryo survival. Studies have supported that conception rate is better in cows with three follicular waves after insemination as compared to cows with two follicular waves and hCG induction of three-wave cycles may also contribute to higher pregnancy rates. Thatcher and Collier (1986) and associates have indicated that the injection of hCG (2000 IU) i.m.; (1000 IU) i.v. 5 days after oestrus induces ovulation of the first wave dominant follicle and formation of accessory corpus luteum and increases plasma

progesterone levels during the luteal phase. Santos et al. (2001) demonstrated that injecting 3300 IU of hCG in lactating cows 5 days after AI resulted in increased number of CL and higher plasma progesterone concentrations. Conception rates on days 28, 42 and 90 were improved by hCG treatment. The findings of Santos et al. (2001) were supported by findings of Nishigai et al. (2002), they administered hCG on day 6 and the pregnancy rates were increased (67.5%) with formation of accessory corpora lutea as compared to control cows (45.0%). or cows receiving hCG on day 1 (42.5%) after Lopez-Gatius et al. (2002) reported that cows having an additional spontaneous CL were eight times less prone to fetal loss than those with a single CL.

9.5. PMSG (pregnant mare serum gonadotropin) administration

Hirako et al. (1995) in their study on luteotropic effect of PMSG in cattle and reported significant increase in progesterone concentration on administration of 500 IU of PMSG on day 7 after estrus. They concluded that PMSG treatment increases progesterone secretion and luteal function without excessive follicular development.

9.6. Gonadotropin releasing hormone (GnRH) treatment

Administration of GnRH (250 µg or greater) at the time of insemination increases pregnancy rates by 12.5% and effect was more pronounced in repeat breeder cows (22.5%) (Morgan and Lean, 1993). Administration of GnRH at oestrus increases serum progesterone levels and the proportion of large luteal cells in the corpus luteum (Mee *et al.*, 1995).

MacMillan et al. (1986) reported an enhancement of the conception rate in dairy cows when GnRH (10 µgBuserelin) was injected on day 11 after breeding by AI. Injecting Buserelin at 3 days interval from day 12 (luteal phase) increases progesterone concentrations and maintains at luteal levels till the injections are continued, i.e., until day 48 after the preceding oestrus (Thatcher et al., 1989). This indicates that buserelin exerts a continued luteotropic or antiluteolytic effect under these circumstances.

Administration of hCG during luteal phase of the cycle induces ovulation of the dominant follicle (Price and Webb, 1989). Administration of GnRH on day 6 of the cycle resulted in ovulation in 75% animals with the formation of accessory corpora lutea (Webb et al., 1992). This not only induces additional progesterone secretion, but also downregulates oestradiol production.

Mann et al. (1995) reported that administration of buserelin on day 12 after insemination results in reduced plasma oestradiol concentrations and suppression of pulses of the $PGF_2\alpha$ metabolite (13, 14-dihydro-15-keto-$PGF_2\alpha$ (PGFM) from about day 13 onwards, confirming its antiluteolytic effect. Reduction in oestradiol concentrations at this time might inhibit the luteolytic mechanism and hence, pregnancy is maintained. They also concluded that GnRH treatment weakens rather than delays the luteolytic signal. The timing of buserelin/GnRH treatment appears critical since treatment at other times after insemination did not have any effect (MacMillan et al., 1986; Drew and Peters, 1994).

9.7. Interferons

Intrauterine infusion of recombinant ovine or bovine IFN_ι in non-pregnant cows extended oestrus cycle by abolishing oxytocin induced $PGF_2\alpha$ secretion on day 17 and hence proved to be more effective in preventing embryonic mortality than IFN_α (Meyer *et al,* 1995).IFNι is more effective than IFNα in preventing embryonic mortality as it has no side effects.

9.8. Omega-3 and reproductive performance

Research studies by workers (Mattos et al., 2000, 2002; Thatcher et al., 2001) have indicated that omega-3 fatty acids decreases secretion of $PGF_2\alpha$. Trials by research workers (Bonnette et al., 2001; Mattos et al., 2002; Petit and Twagiramungu, 2002; Ambrose and Kastelic, 2003) with natural sources of omega-3 fatty acids such as Eicosapentaenoic Acid (EPA), Dehydroascorbic Acid (DHA) and α-linolenic acids have indicated that these fatty acids are capable of decreasing the secretion of $PGF_2\alpha$ and compliment the antiluteolytic action of IFNι thereby improve pregnancy rates. EPA and DHA also have anti-inflammatory and immunosuppressive effects that compliment the normal immunosuppressive and anti-inflammatory effects of progesterone and IFNι in early pregnancy.

10. Conclusion

Dairy animals with Embryonic Mortality due to mineral deficiency should feed minerals as per the milk production and reproduction status. To overcome heat stress, physical modifications of animal environment, feeding of Antioxidant, trace minerals and genetic development of breeds will be best solution. To tackle Embryonic death during MRP supplementation of anti-luteolytic agent interferon, HCG/ GnRH /Progesterone and Omega-3 has shown encouraging results. Animal examination, history, progesterone levels, PAG test and ultrasound are the practical tools to handle embryonic mortality.

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