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The effect of embryonic death rates in cattle on the efficacy of estrus synchronization programs

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Abstract

Reproductive failure in inseminated cattle results from poor fertilization and embryo survival. Recent studies utilizing dairy and beef cattle indicate that fertilization rates are higher for nulliparous dairy and beef heifers and nonlactating beef cows than lactating beef and dairy cows and nonlactating dairy cows. Several factors affect fertilization rates, but the greatest impact was observed for high producing cows under heat stress, when fertilization was only 55%. Once fertilization has occurred, the fate of a successful pregnancy is then determined by the survival of the embryo and fetus. Losses of pregnancy are characterized by early embryonic death, which occurs prior to the period of corpus luteum (CL) maintenance in the cow at days 15–17 of the cycle, and late embryonic death, which occurs from CL maintenance to the end of the differentiation stage, at approximately 42 days of gestation. After 50 days of gestation, pregnancy losses are less frequent and characterize fetal death. Most pregnancy losses occur prior to the period of maintenance of the CL, but in high producing lactating dairy cattle, substantial losses continue to occur up to 42–56 days after insemination. Several factors affect pregnancy losses in cattle, such as compromised oocytes, which result in poorly developed embryos incapable of cross-talking with the endometrial epithelial cells, to inadequate uterine environment and infectious agents resulting in death of the embryo from undernourishment. Recently, studies have indicated that anovulation/anestrous, the metabolic status of the animal, some dietary ingredients, as well as occurrence of diseases, predispose the cow to experience embryonic and fetal death. Although some insemination protocols might impact embryo survival, when timed AI has been implemented properly, it has not influenced embryonic or fetal death in cattle. Improvements in reproductive programs in the future will have to focus on enhancing fertilization rates and minimizing embryonic losses to optimize conception rates in dairy and beef cattle.

Keywords: Embryo mortality; Estrus synchronization; Reproduction; Dairy cows

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1. Introduction

Revenue from dairy and beef farms is directly dependent upon reproductive efficiency because it affects milk production and the number of calves born. Pregnancy loss can have devastating effects on economical success in dairy and beef units. In dairy farms, it is estimated that each pregnancy lost results in an average loss of US$ 640.00 (Thurmond et al., 1990). In beef herds, pregnancy losses represent an even more important economic factor because most of the income is determined by the number of calves sold.

In spite of the increased knowledge of the reproductive biology of the cow, reproductive efficiency continues to decline in dairy herds. The continuous consolidation of production units with the trend for larger herds and continuous movement of cattle within and between countries are likely to render herds more susceptible to infectious agents that impact reproduction such as bovine viral diarrhea virus, *Neospora caninum*, *Leptospira* spp., among others. Zavy (1994) indicated that embryonic mortality in cattle is the main source of economic loss for livestock producers. Since the review article by Zavy (1994) a wealth of literature characterizing the timing and extent of pregnancy losses in cattle has been generated, although most of the causes remain unclear. With the advent of ultrasonography, accurate pregnancy diagnosis has been possible as early as 25 days after AI in cattle (Fricke, 2002), thereby facilitating the study of late embryonic mortality after the period of maternal recognition of pregnancy. Studies utilizing embryo transfer and early pregnancy diagnosis indicate that less than 50% of the viable embryos establish pregnancy by 27–30 days after ovulation in lactating dairy cows (Drost et al., 1999; Sartori et al., 2003), whereas in beef cattle 69 and 83% of the frozen and fresh embryos, respectively, establish pregnancy on day 37 of gestation (Spell et al., 2001).

2. Characterization of pregnancy losses

In order to properly standardize bovine reproductive terms, the Committee on Bovine Reproductive Nomenclature (1972) established that the embryonic period of gestation extends from conception to the end of the differentiation stage, at approximately 42 days of gestation, and that the fetal period extends from gestation day 42 to the delivery of the calf.

Two sources of pregnancy failure exist after breeding, fertilization failure and pregnancy loss. When the interestrus or the interovulatory intervals are extended in bred animals, it usually indicates embryonic loss that occurred around the period of corpus luteum (CL) maintenance (Van Cleeff et al., 1991; Humblot, 2001). Experiments with continuous measurements of concentrations of progesterone in blood suggest 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, returns 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; but, if the CL is maintained and returns to estrus are delayed beyond day 24, it could point to embryonic losses occurring after day 16 of gestation. Thus, losses of pregnancy prior to day 24 indicate early embryonic

losses, and those between days 24 and 42–50, indicate late embryonic losses. Pregnancy losses detected after day 50 characterize fetal losses.

2.1. Fertilization and early embryonic losses

Early experiments by Ayalon (1978) indicated that fertilization rates were usually high in bovine (∼95%), which suggests that embryonic death is responsible for most of the reproductive wastage following insemination in cattle (Zavy, 1994). Recently, studies in lactating beef cows suggest that fertilization rate averaged 75.0%, with a range from 60 to 100%. (Table 1). The low fertilization rate for lactating beef cows in the studies by Breuel et al. (1993) might be related to inseminations performed early postpartum, when anovulation and anestrous are prevalent in beef cows. In spite of the limited data to indicate that cows were in early postpartum, it is plausible that fertilization rates in lactating beef cows are not as high as previously thought and the 75.0% average for the studies by Breuel et al. (1993) represent the true fertilization rate in postpartum suckled cows subjected to AI. In nonlactating beef cows, fertilization rates averaged 98.6%, with a range from 94.0 to 100%, which is higher and, more importantly, less variable than in lactating beef cows. Data from two studies on growing beef heifers evaluated between days 2 and 16 after insemination (Maurer and Chenault, 1993; Dunne et al., 2000) showed high fertilization rate, averaging 88.0%, with a range between 75.0 and 100%. These data suggest that lactation might exert a negative effect on fertilization in beef cattle.

In dairy cattle, fertilization rates are similar between lactating and nonlactating cows and they averaged 76.2% (ranging from 55.3 to 87.8%) and 78.1% (ranging from 58.0 to 98.0%), respectively (Table 2). Several factors affect fertilization rate in cattle, but heat stress seems to have the greatest impact (Sartori et al., 2002). It is clear that thermal stress has greater impact on fertility of higher producing cows (Hansen, 2002), and this might be mediated by lower fertilization rates and higher pregnancy losses. In fact, Hansen (2002) indicated that embryos resulting from fertilization of compromised oocytes have a low probability of successful development.

It is no surprise that conception rates at days 27–31 after AI are usually 35–45% in dairy cattle. By days 5–6 post-insemination, only 65% of the fertilized eggs are considered viable, which represents only 50% of the total embryos/oocytes combined (Table 2), partially explaining the low conception in lactating dairy cows in the US (Lucy, 2001; Stevenson, 2001). It is known that cows experience reduced fertility when the nutrient requirements for maintenance and lactation exceed intake and lead to loss of body condition. In dairy cattle, the partition of nutrients towards milk synthesis affects reproduction partially because of reduced embryo quality and viability (Sartori et al., 2002). When embryo viability from studies with lactating and non-lactating dairy cows was summarized, approximately 50.0, 57.9, and 71.9% of the potential pregnancies in parous lactating, parous nonlactating and nulliparous heifers, respectively, were viable by days 5–6 post-insemination (Table 2). In beef cows, viability of embryos collected from parous lactating, parous nonlactating, and nulliparous heifers were 57.5, 79.5, and 77.6% (Table 1), respectively, and followed a similar pattern as in dairy cattle. However, when a lactating beef cow recovers body condition and reestablishes cyclicity, conception rate is similar to that in nulliparous heifers and it ranges from 50 to 65%.

Table 1
Fertilization rate and embryo quality in non-superovulated lactating and nonlactating beef cattle

Beef cattle	Method of collection	Number of structures	Days after AI	Fertilization (%)	Viable embryo,[a]		Reference
					Fertilized (%)	Total (%)	
Lactating							
Cows	Oviduct flush	14	3	85.7	91.6[b]	78.5	Breuel et al. (1993)
Cows	Oviduct flush	15	3	60.0	88.9[b]	53.4	Breuel et al. (1993)
Cows	Uterine flush	6	6	66.7	75.0	50.0	Breuel et al. (1993)
Cows	Uterine flush	5	6	100.0	20.0	20.0	Breuel et al. (1993)
Overall	Oviduct and uterine flush	40	3–6	75.0 (60.0–100)	76.7 (20.0–91.6)	57.5 (20.0–78.5)	
Nonlactating							
Cows	Slaughter	19	2–5	100.0	89.5	89.5	Maurer and Chenault (1993)
Cows	Slaughter	17	6–8	100.0	76.5	76.5	Maurer and Chenault (1993)
Cows	Slaughter	17	14–16	100.0	82.4	82.4	Maurer and Chenault (1993)
Cows	Uterine flush	20	6	94.0	73.0[c]	68.6	Ahmad et al. (1995)
Cows	Uterine flush	14	6	100.0	14.0[c]	14.0	Ahmad et al. (1995)
Overall[d]	Uterine flush and slaughter	73	2–16	98.6 (94.0–100)	80.6 (73.0–89.5)	79.5 (68.6–89.5)	
Heifers	Slaughter	34	2–5	91.2	83.9	76.5	Maurer and Chenault (1993)
Heifers	Slaughter	32	6–8	75.0	75.0	56.3	Maurer and Chenault (1993)
Heifers	Slaughter	22	14–16	100.0	95.5	95.5	Maurer and Chenault (1993)
Heifer	Surgical	37	14	89.2	97.0	86.5	Dunne et al. (2000)
Overall	Slaughter and surgical	125	2–16	88.0 (75.0–100)	88.2 (75.0–97.0)	77.6 (56.3–95.5)	

[a] Embryos graded as 1–3 (Robertson and Nelson, 1998).
[b] Embryos described as having abnormal blastomeres were considered as non-viable (Breuel et al., 1993).
[c] Proportion of embryos that were classified as excellent or good morulas (≥16 cells) (Ahmad et al., 1995).
[d] Proportion of viable embryos did not include the results from Ahmad et al. (1995) with persistent follicles.

Table 2
Fertilization rate and embryo quality in non-superovulated lactating and nonlactating dairy cattle

Dairy cattle	Method of collection	Number of structures	Days after AI	Fertilization (%)	Viable embryo,[a]		Reference
					Fertilized (%)	Total (%)	
Lactating							
Cows	Uterine flush	38	6	55.3	33.3	18.4	Sartori et al. (2002)
Cows	Uterine flush	41	6	87.8	52.8	46.4	Sartori et al. (2002)
Cows	Uterine flush	45	5	73.3	78.8	57.8	Cerri et al. (in press)
Cows	Uterine flush	41	5	87.2	85.3	74.4	Cerri et al. (in press)
Overall	Uterine flush	165	5–6	76.2 (55.3–87.8)	65.6 (33.3–85.3)	50.0 (18.4–74.4)	
Nonlactating							
Cows	Uterine flush	38	6	89.5	82.3	73.7	Sartori et al. (2002)
Cows	Uterine flush	39	6–7	67.0	93.0	62.3	Dalton et al. (2001)
Cows	Uterine flush	39	6–7	79.0	90.0	71.1	Dalton et al. (2001)
Cows	Uterine flush	37	6–7	98.0	89.0	87.2	Dalton et al. (2001)
Cows	Uterine flush	39	6–7	66.0	92.0	60.7	Dalton et al. (2001)
Cows	Uterine flush	39	6–7	74.0	90.0	66.6	Dalton et al. (2001)
Cows	Uterine flush	39	6–7	82.0	66.0	54.1	Dalton et al. (2001)
Cows	Uterine flush	26	6	81.0	N/A[b]	N/A	DeJarnette et al. (1992)
Cows	Uterine flush	24	6	83.0	N/A	N/A	DeJarnette et al. (1992)
Cows	Uterine flush	19	6	68.0	57.1	36.3	DeJarnette et al. (1992)
Cows	Uterine flush	19	6	58.0			DeJarnette et al. (1992)
Cows	Uterine flush	20	6	70.0	90.3	65.1	DeJarnette et al. (1992)
Cows	Uterine flush	23	6	74.0			DeJarnette et al. (1992)
Cows	Uterine flush	21	6	90.0	94.7	85.2	DeJarnette et al. (1992)
Cows	Uterine flush	22	6	77.0	76.5	58.9	DeJarnette et al. (1992)
Overall	Uterine flush	444	6–7	78.1 (58.0–98.0)	74.1 (57.1–94.7)	57.9 (36.3–87.2)	
Heifers	Uterine flush	32	6	100.0	71.9	71.9	Sartori et al. (2002)

[a] Embryos graded as 1–3 (Robertson and Nelson, 1998).
[b] N/A: not available.

Table 3
Late embryonic mortality in lactating dairy cows

No. of pregnancies	Days of gestation at diagnosis					
	First	Second	Interval (days)	Pregnancy loss (%)	Pregnancy loss (% per day)	Reference
256	28	38–58	∼20	28.0	1.40	Cartmill et al. (2001a)
110	27–30	40–50	∼16	42.7	2.67	Cartmill et al. (2001b)
261	30	44	14	12.5	0.89	Cerri et al. (2003)
195	28	42	14	17.9	1.28	Chebel et al. (2003a)
74	31	45	14	10.8	0.77	Chebel et al. (2003b)
1465	31	45	14	12.5	0.89	Chebel et al. (in press)
251	27	41	14	17.5	1.25	Galvão et al. (in press)
167	28	39	11	11.4	1.04	Juchem et al. (2002)
139	27	45	18	20.7	1.15	Moreira et al. (2001)
172	28	45	17	9.3	0.55	Santos et al. (2001)
372	31	45	14	11.4	0.82	Santos et al. (2004a)
215	27	41	14	9.9	0.71	Santos et al. (2004c)
705	28	42	14	3.2	0.23	Silke et al. (2002)
488	28	42	14	10.5	0.75	Vasconcelos et al. (1997)
Overall: 4870	27–31	38–50	∼15	12.8 (3.2–42.7)	0.85 (0.23–2.67)	

2.2. Late embryonic losses

The advent of ultrasonography and other methods for early pregnancy diagnosis has allowed researchers to characterize the timing and extent of late embryonic losses in cattle (Tables 3–5). Humblot (2001) evaluated embryonic losses in Holstein cows in 44 herds in France and observed that early and late embryonic death after first AI were 31.6, and 14.7%, respectively. Late embryonic death after day 27 of gestation ranged from 3.2% in dairy cows producing 6000–8000 kg of milk per year in Ireland (Silke et al., 2002) to up to 42.7% in high producing cows under heat stress (Cartmill et al., 2001b). Extensive late embryonic death is observed in dairy cattle (Table 3), and data from these data indicate a rate of pregnancy loss between ∼30 and ∼45 days of gestation of 0.85% per day, or approximately 12.8%, which is higher than that observed for beef cows (Beal et al., 1992).

2.3. Fetal losses

In cattle, fetal losses are usually less prevalent than early and late embryonic losses, and causes of fetal death are usually undetermined. The veterinary diagnostic laboratory of the University of California Davis summarizes the number and causes of abortion in submitted cattle fetuses. For the years of 1998–2001, of the 1486 aborted fetuses from dairy cattle submitted to the diagnostic laboratory 55.9% had lesions and an infectious agent associated with the abortus, whereas 44.1% were of undetermined causes, indicating that almost half of the fetal losses in dairy cattle are not caused by known infectious agents.

Studies with dairy and beef cattle indicate that fetal losses are variable and confounded by the day when pregnancy is first diagnosed. When pregnancy was diagnosed prior to 35 days

Table 4
Late embryonic and fetal losses in lactating dairy cows and primigravid dairy heifers

Number of pregnancies	Days of gestation at diagnosis				
	First	Second	Interval (days)	Pregnancy loss (%)	Reference
Lactating cows					
1547	35–48	180	∼139	9.9	Ettema and Santos (in press)
89	28	56	28	13.5	Fricke et al. (1998)
86	28	64	36	12.8	Gümen et al. (2003)
601	38–44	90–96	∼52	10.7	López-Gatius et al. (2002)
3162	41	120–150	∼84	9.6	Labèrnia et al. (1996)
285	25–35	Term	∼250	22.0	Pursley et al. (1998)
156	45	90	45	8.3	Santos et al. (2001)
57	25–32	60–66	∼34	18.6	Sartori et al. (2003)
64	26–58	Term	∼238	8.6	Szenci et al. (1998)
148	28	98	70	18.9	Vasconcelos et al. (1999)
Overall: 6195	25–70	56–term	28–250	10.7 (8.3–24.0)	
Primigravid					
72	30	Term	∼250	4.2	Dunne et al. (2000)
1933	35–48	Term	∼238	1.5	Ettema and Santos (in press)
1050	41	120–150	84	2.8	Labèrnia et al. (1996)
147	30	75	45	10.2	Rivera et al. (in press)
131	28	84	56	6.05	Silke et al. (2002)
Overall: 3333	28–58	75–term	45–250	2.52 (1.5–10.2)	

of gestation, fetal losses in dairy cattle were high (Table 4). It is likely that these high values are the result of late embryonic mortality occurring prior to day 42 of gestation. However, in studies in which the first pregnancy diagnosis was performed after day 35 of gestation, fetal losses were usually limited to less than 10.7%. In primigravid cows, embryonic and fetal losses in dairy and beef cattle are usually low, and they averaged 2.5 and 4.2%, respectively

Table 5
Late embryonic and fetal losses in lactating beef cows and primigravid beef heifers

Number of pregnancies	Days of gestation at diagnosis		Interval (days)	Pregnancy loss (%)	Pregnancy loss (% per day)	Reference
	First	Second				
Lactating cows						
138	25	45	20	6.5	0.33	Beal et al. (1992)
223	29–33	54–61	∼26	10.8	0.42	Stevenson et al. (2003)
Primigravid						
149	30	60	30	4.0	0.13	Lamb (2002)
271	35	75	40	4.1	0.10	Lamb (2002)
105	30	90	60	4.8	0.07	Lamb (2002)
Overall: 525	30–35	60–90	30–60	4.2 (4.0–4.8)	0.09 (0.07–0.13)	

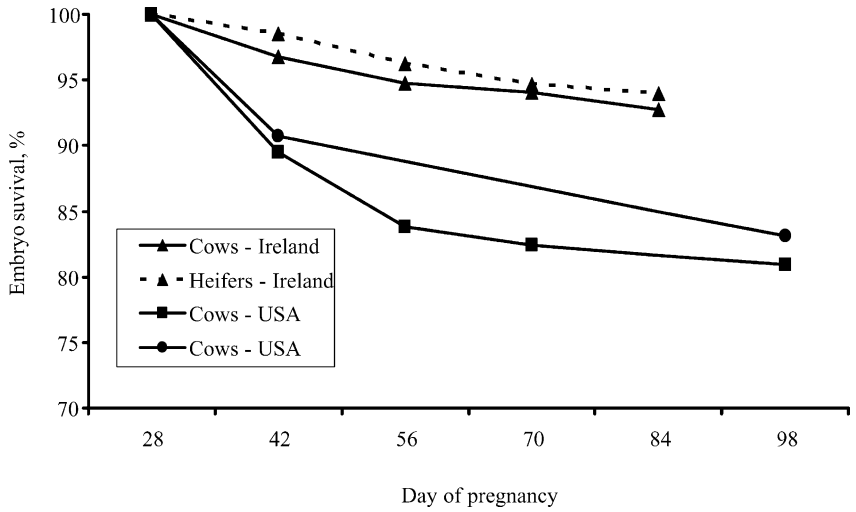

Fig. 1. Curves for embryo survival after day 28 of gestation in lactating dairy cows and primigravid dairy heifers in Ireland and the USA. Adapted from Santos et al. (1991; ●), Silke et al. (2002; ▲), and Vasconcelos et al. (1997; ■).

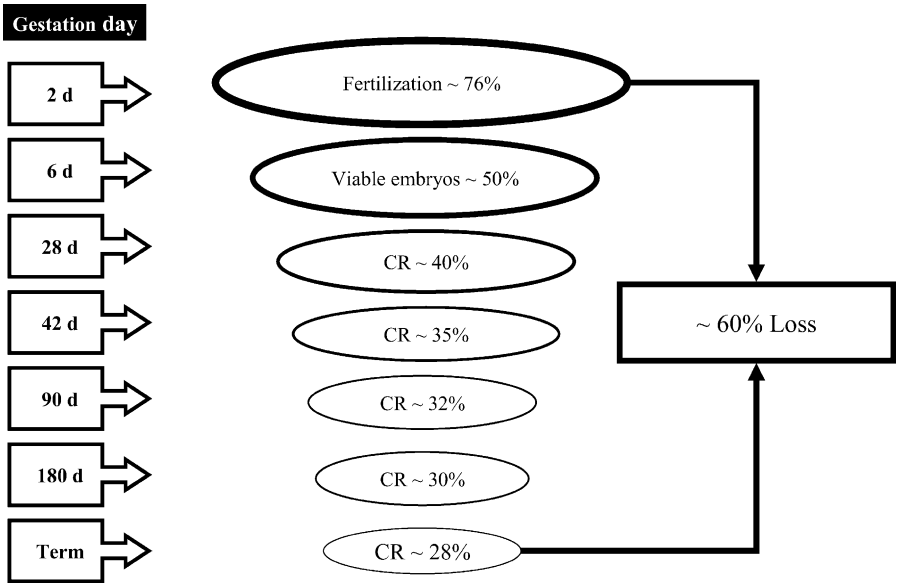

Fig. 2. Timing and extent of pregnancy losses in the high producing lactating dairy cow. CR: conception rate.

(Tables 4 and 5). Survival curves for pregnancy maintenance in three studies with lactating dairy cattle clearly indicates that the rate of pregnancy loss is more pronounced in the first 42 days of gestation in the US; however, results from Ireland indicate a similar rate of pregnancy loss throughout the first 80–90 days of gestation (Fig. 1). Based on the results summarized in Tables 2–4, we suggest that pregnancy losses in dairy cattle from fertilization to term might represent up to 60% (Fig. 2).

3. Factors associated with pregnancy losses

3.1. Oocyte quality and persistent follicles

In cattle, subluteal concentrations of progesterone during the estrous cycle preceding insemination induce increased frequency of LH pulses resulting in a persistent dominant follicle (Inskeep, 2002; Bridges and Fortune, 2003). In beef cows, larger pre-ovulatory follicles, that maintained dominance for an extended period before the LH surge, reduced conception rate compared to smaller pre-ovulatory follicles (36% versus 91%; Breuel et al., 1993). Exposure of the oocyte to high peak frequency of LH induces the premature resumption of meiosis (Revah and Butler, 1996; Mihm et al., 1999), and the biochemical and morphological changes in the oocyte in persistent follicles reduce fertility in cattle (Mihm et al., 1994; Inskeep, 2002) due to embryo mortality before the 16-cell stage (Ahmad et al., 1995). Therefore, extending the period of follicle dominance either by exogenous progestins (Mihn et al., 1994) or when cows have cycles with two waves of follicle growth (instead of three follicle growth waves; Townson et al., 2002), compromises fertility. Fortunately, the presence of a persistent follicle does not alter the developmental potential of oocytes from smaller follicles; that is, if the persistent follicle regresses, normal fertility is resumed (Smith and Stevenson, 1995).

3.2. Duration of proestrus and subsequent luteal phase

Peters and Pursley (2003) evaluate the effect of timing of the final GnRH of the Ovsynch protocol (day 0 GnRH, day 7 $PGF_{2\alpha}$, day 9 GnRH, 12–16 h timed AI) on ovulatory follicle size, subsequent luteal function, and pregnancy rates in lactating dairy cows. Administration of GnRH at the moment of $PGF_{2\alpha}$ injection or 2 days later did not affect synchronization rate and regression of the CL. However, cows receiving the GnRH simultaneously with $PGF_{2\alpha}$ treatment ovulated a smaller follicle and had lower pregnancy rate (14.7% versus 31.3%). When GnRH was given at 0, 12, 24 and 36 h after the $PGF_{2\alpha}$ treatment, synchronization rate was similar for all four treatments, but more cows receiving GnRH at 0 h experienced short luteal phase than those receiving GnRH at 36 h after $PGF_{2\alpha}$, with a linear increase in pregnancy rate as the interval from of $PGF_{2\alpha}$ to GnRH increased.

Altering ovulatory follicle size by manipulating the interval from follicle deviation to induced ovulation increased the incidence of short luteal phase and reduced pregnancy rates in dairy cows (Vasconcelos et al., 2001). The increased occurrence of short cycles and the reduced pregnancy rates in cows with small ovulatory follicles or those with short proestrus might be related to exposure to estradiol prior to ovulation. Recent studies by Mussard et al.

(2003) suggest that reducing the proestrus length induces subsequent short luteal cycles and reduces pregnancy rates regardless of size of the ovulatory follicle (follicles ≥10 mm), even when cows received a viable embryo on day 7 of the cycle. When beef cows were subjected to Co-Synch timed AI protocol (day 0 GnRH, day 7 $PGF_{2\alpha}$, day 9 GnRH and timed AI) or inseminated upon detection of spontaneous estrus (Perry et al., 2003), embryonic/fetal survival was reduced when follicles <11 mm were induced to ovulate with GnRH, but not when ovulating spontaneously. It is possible that small follicles ovulating spontaneously were competent and secreted adequate amounts of estradiol during proestrus, whereas small follicles induced to ovulate with GnRH were not sufficiently mature. Inadequate proestrus might reduce exposure to estradiol prior to ovulation, which has been shown to result in increased responsiveness of the endometrium to oxytocin and greater release of prostaglandin (Mann and Lamming, 2000). Ahmadzadeh et al. (2003) observed that 0.25 mg of estradiol cypionate given with the final GnRH of the Ovsynch tended to increase conception rates in beef cows (68% versus 57.5%; $P = 0.14$). Furthermore, inducing ovulation with 1 mg of estradiol cypionate in the Heatsynch protocol increased conception rate compared to cows inseminated at estrus (Cerri et al., 2003).

3.3. Progesterone and the uterine environment

Sub-optimal cross-talk between the conceptus and the endometrial epithelial cells leads to secretion of $PGF_{2\alpha}$ and resumption of ovulatory cycles with cessation of pregnancy (Thatcher et al., 1986; Mann and Lamming, 2001; Thatcher et al., 2001). Progesterone secretion by the CL is essential for orchestrating the histotrophic environment for nourishment of the conceptus. Indeed progesterone and estradiol act as systemic regulators leading to local oviductal and endometrial timed events and they program the uterus to regress the CL if there is sub-optimal communication between conceptus and uterus via secretion of $PGF_{2\alpha}$ (Robinson et al., 2001). An important component of the luteolytic mechanism is the peri-estrus induction of endometrial estradiol and oxytocin receptors. Exposure to progesterone reestablishes the lipid pool of endometrial phospholipids necessary for subsequent $PGF_{2\alpha}$ synthesis. With prolonged progesterone exposure there is a down regulation of progesterone receptors such that there is an up-regulation of endometrial estradiol receptors that are important for induction of oxytocin receptors (Robinson et al., 2001). However, progesterone also inhibits luteolysis by decreasing sensitivity to oxytocin by binding to oxytocin receptors and blocking the second messenger system (Grazzini et al., 1998). Nevertheless, the most important effect of progesterone in blocking luteolysis is by enhancing conceptus development which, in turn, stimulates secretion of interferon-τ (Mann and Lamming, 2001).

Mann and Lamming (2001) indicate that not only are progesterone concentrations important for pregnancy, but a delay in post-ovulatory rise in progesterone compromises conceptus development and its ability to secrete interferon-τ, which results in reduced conception rates (Darwash and Lamming, 1998). Although no pre-established progesterone concentration determines a successful pregnancy (Mann and Lamming, 1999), progesterone concentrations on days 4 and 5 after mating (but not later) were correlated with uterine luminal concentrations of interferon-τ on day 16 (Wathes et al., 2003). Because progesterone plays a major role in stimulating the production of several endometrial proteins and growth factors (Geisert et al., 1992), supplemental progesterone during the first 4 days after AI increased

morphological development and biosynthetic activity of day 14 conceptuses (Garret et al., 1998). 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. Collectively, these data indicate that progesterone availability in the early diestrus phase may benefit conception rates and embryonic survival.

3.4. Pregnancy recognition (CL maintenance)

The mononuclear cells of the trophectoderm in early stages of development are responsible for the production and secretion of interferon-τ (Thatcher et al., 2001). It is first produced by the conceptus on day 12 of pregnancy because of expression of trophoblastic interferon genes (Farin et al., 1990), but its concentrations in the uterine lumen only peak on days 15–17 of gestation. The antiluteolytic effect of interferon-τ results from the inhibition of endometrial expression of oxytocin receptors and possibly through the transduction mechanism after oxytocin-receptor binding on the endometrial cells and inhibits the episodic release of $PGF_{2\alpha}$ (Demmers et al., 2001). Compromised development of the embryo and underdevelopment of the trophectoderm are, therefore, responsible for premature luteolysis. Therefore, some of the embryonic losses in cattle are thought to be mediated by the inability of the embryo to suppress the luteolytic cascade during the period of CL maintenance (Thatcher et al., 1986). It is still unclear what maintains the CL and, therefore, the pregnancy after interferon-τ has declined. Recently, Silva et al. (2000) demonstrated that the CL that is maintained during maternal recognition of pregnancy is capable of processing $PGF_{2\alpha}$ to its metabolite (PGFM). The authors demonstrated that day 13 CL from ewes with viable embryos had greater concentrations and activity of prostaglandin dehydrogenase (PGDH) than day 13 CL from cyclic ewes.

There is compelling evidence that failure of the conceptus to produce luteotropic signals, or perhaps failure of the CL to respond to luteotropins contribute to early embryonic death in cattle (Thatcher et al., 1986, 2001). Treatment of cows with oxytocin on days 5 through 8 after AI reduced pregnancy from 80 to 33%, but this effect was reverted when an anti-prostaglandin agent was administered concurrently with oxytocin (Leemaster et al., 1999). Elli et al. (2001) demonstrated that administration of an anti-prostaglandin agent at embryo transfer increased pregnancy rates (82% versus 56%). These data indicate that suppressing $PGF_{2\alpha}$ secretion favors establishment and maintenance of pregnancy in cattle by reducing embryonic mortality.

3.5. Heat stress

Exposure to high environmental temperatures compromised steroidogenesis and viability of oocytes (Zeron et al., 2001), reduces oocyte quality (Hansen et al., 2002), and reduces fertilization rate (Sartori et al., 2002; Table 2). Al-Katanani et al. (2002) observed a decline in oocyte competence during heat stress. Chebel et al. (in press) observed that cows exposed to heat stress prior to AI were 31–33% less likely to conceive than those not exposed to thermal stress. Drost et al. (1999) demonstrated that transfer of in vivo produced embryos from cows exposed to thermoneutral temperatures increased pregnancy rate in heat-stressed recipient cows compared to that in heat-stressed cows subjected to AI. Cartmill et al. (2001b)

observed an extremely high pregnancy loss (42.7%), which was substantially higher than that observed for cows at similar stage of gestation not exposed to heat stress (Table 3). These results demonstrate the negative effects of heat stress on oocyte quality, which compromises fertilization and early embryo development, thus further exacerbating pregnancy losses.

3.6. Insemination protocol

A wide range of hormonal programs are available to synchronize estrus or ovulation, thereby optimizing service rate. Lucy (2001) indicated that most studies evaluating late embryonic losses in cattle involved animals subjected to timed AI protocols. Based on results from Smith and Stevenson (1995), it was suggested that cows inseminated following spontaneous estrus may have lower rates of embryonic death than those bred following timed AI (Lucy, 2001).

Long-term treatments with progestins for estrus synchronization lower fertility because of reduced conception and increased pregnancy loss, which has been attributed to the prolonged persistence of the ovulatory follicle (Ahamad et al., 1995; Inskeep, 2002). However, short-term treatments with progestins (<8 days) have also resulted in reduced conception rates in cattle when compared to cows inseminated following spontaneous estrus (Xu et al., 1996; Chenault et al., 2003). Extensive studies with lactating dairy cows in New Zealand indicate that a single treatment with $PGF_{2\alpha}$ during diestrus improved conception rates (69% versus 60%) compared to untreated controls (Macmillan et al., 2003). However, 2 injections of $PGF_{2\alpha}$ 13 days apart reduced conception rates compared to untreated cows (61.1% versus 70.5%), with marked reduction in conception observed when the second $PGF_{2\alpha}$ was given during the early (days 5–9) diestrus (Xu et al., 1997). In those cows, supplemental progesterone reestablished normal conception rates. Therefore, synchronization protocols that induce estrus with the dominant follicle growing under a low progesterone environment might reduce conception rates, perhaps as a result of increased early and late embryonic losses.

Macmillan et al. (2003) indicated that timed AI protocols in dairy cattle utilizing standard GnRH doses (i.e. 100 μg of gonadorelin) to induce ovulation might decrease conception rates because of incompetent CL when small follicles are induced to ovulate, and suggested that cows inseminated following the Ovsynch protocol have greater occurrence of short cycles. However, the short inter-insemination interval for cows timed inseminated might have been caused by lack of synchronization of ovulation at AI, which is 84–87% in cows in the Ovysnch (Fricke et al., 1998; Vasconcelos et al., 1999) and 86% for Heatsynch (Galvão et al., in press). Therefore, the 13–16% of the cows that do not synchronize because of lack of CL regression or ovulation would alter the inter-insemination interval.

Pregnancy loss in 6 published studies with cows inseminated following timed AI was 11.2%, which was similar to that of cows inseminated upon estrus detection (12.7%; Table 6). In five of the six studies, pregnancy loss was not altered by insemination protocol. In only one study (Cartmill et al., 2001b), a tendency for increased pregnancy loss was observed with timed AI and, in spite of insemination protocol, pregnancy loss was extremely high (42.7%), perhaps associated with heat stress during the study. In spite of lack of evidence that timed AI results in increased embryonic losses in cattle, it is possible that synchronization protocols that limit the length of the proestrus or result in incompetent follicles might compromise fertility by increasing pregnancy losses.

Table 6
Effect of insemination protocol on pregnancy losses in cattle, % (number of pregnancies)

Reference	Insemination protocol[a]		*P*
	Estrus detection	Timed AI	
Cartmill et al. (2001a)	28.1 (82)	27.4 (172)	NS
Cartmill et al. (2001b)	29.3 (41)	50.7 (69)	<0.07
Cerri et al. (2003)	12.4 (92)	11.0 (169)	NS
Chebel et al. (in press)	13.2 (1089)	10.4 (376)	NS
Gümen et al. (2003)	12.5 (40)	13.0 (46)	NS
Santos et al. (2004a)	9.7 (145)	12.7 (165)	NS
Overall	12.7 (1366)	11.2 (756)	–

NS: not significant.

[a] Estrus detection: cows were inseminated following detection of spontaneous estrus, or estrus induced with $PGF_{2\alpha}$ or combination of GnRH and $PGF_{2\alpha}$. Timed AI: cows were subjected to a synchronization of ovulation protocol (Ovsynch or Heatsynch) with fixed time AI.

3.7. Resynchronization of nonpregnant cows

When a CIDR was inserted on day 14 ± 1 after AI and removed 7 days later, pregnancy rate to the pre-enrollment AI were reduced in high producing dairy cows (Chenault et al., 2003). However, in lower producing cows, resynchronization with a CIDR insert from days 16 to 21 after AI had no negative impact on fertlity (Xu et al., 1997). It was observed that presence of severe vaginal irritation in cows administered CIDR inserts was associated with reduced conception rates in the pre- and post-treatment AI (Chenault et al., 2003). Treatment with GnRH on day 21 after AI, when pregnancy status was undetermined, had no effect on pregnancy rate and pregnancy loss to the pre-treatment AI and resulted in similar resynchronized pregnancy rate in dairy cows (Chebel et al., 2003a). Fricke et al. (2003) observed that treatment with GnRH on day 19 after AI resulted in similar pregnancy rates and pregnancy loss to the pre-enrollment AI, but resynchronized pregnancy rates were lower than in cows treated on days 26 and 33. In cows with two waves of follicle development, injection of GnRH on day 19 is expected to result in ovulation and recruitment of a new follicular wave. However, pregnancy alters follicle development and attenuates dominant follicle growth in the ovary bearing the CL (Thatcher et al., 1991). Therefore, it is possible that in pregnant cows experiencing early and late embryonic death, follicle development is altered and ovulatory response to GnRH on day 19 of gestation might be compromised, which, in turn, might affect subsequent fertility to the Ovsynch protocol. These data suggest that GnRH should be used after day 20 following the previous AI for resynchronization of nonpregnant cows to achieve an acceptable resynchronized pregnancy rates.

3.8. Body condition score

López-Gatius et al. (2002) indicated that a 1 unit drop in body condition score (BCS; 1–5 scale) from calving to 30 days postpartum increased the odds ratio (OR) for pregnancy loss by 2.41-fold. Similarly, Silke et al. (2002) observed that cows losing 1 unit in BCS from days 28 to 56 of gestation had a 3.2-fold increase in OR for pregnancy loss in the same

period. Therefore, the metabolic status of the cow, as evidenced by changes in BCS, affects embryonic and fetal survival.

3.9. Cycling status

Rhodes et al. (2003) indicated that between 11 and 38% of the cows in year-round calving production systems are anovulatory by 50–60 days postpartum, whereas 13–43% of the cows in pasture-based systems are anovulatory prior to the beginning of the breeding season. Even when cows ovulate following a period of anovulation or anestrous, fertility is low. The first postpartum luteal phase can be of short duration (<12 days), which is usually associated with lack of previous exposure to progesterone (Inskeep, 2002) or adequate estradiol during proestrus (Mann and Lamming, 2000). Lower plasma concentrations of progesterone in the preceding estrous cycle resulted in premature release of $PGF_{2\alpha}$ in the subsequent cycle (Shaham-Albalancy et al., 2001). Therefore, anovulation poses a risk to establishment and maintenance of pregnancy in cattle.

Studies in the literature indicated that, generally, late embryonic losses were numerically higher for anovulatory cows (Table 7), although only one study indicated statistically significant differences (Cartmill et al., 2001b). In only one study, anovulatory cows experienced numerically less pregnancy loss than cyclic cows (Santos et al., 2004b). Overall, pregnancy loss was 15.7 and 26.3% for cyclic and anovular cows, respectively. When logistic regression analyses were performed with the data from all studies controlling for cyclicity status and study, anovular cows were 2.01 times more likely to experience pregnancy loss than cyclic cows (OR = 2.01; 95% confidence interval 1.41, 2.88; $P < 0.001$). Therefore, reducing the prevalence of anovulatory cows prior to first postpartum AI is expected to minimize pregnancy losses in cattle.

3.10. Milk yield

Reproductive performance of dairy cattle has decreased in North America, Europe, and Israel (Royal et al., 2000; Lucy, 2001; Stevenson, 2001; Zeron et al., 2001; López-Gatius,

Table 7
Effect of cyclicity status prior to insemination on pregnancy losses in dairy cattle, % (number of pregnancies)

Reference	Cyclicity status[a]		*P*
	Cyclic	Anovular	
Cartmill et al. (2001a)	24.0 (223)	33.0 (33)	NS
Cartmill et al. (2001b)	36.8 (95)	80.0 (15)	<0.05
Cerri et al. (2003)	10.8 (204)	14.6 (48)	NS
Gümen et al. (2003)	12.3 (81)	20.0 (5)	NS
Pursley et al. (2001)	15.1 (186)	35.0 (46)	–
Santos et al. (2004a)	10.4 (270)	17.5 (40)	NS
Santos et al. (2004c)	10.2 (186)	7.7 (26)	NS
Overall	15.7 (1245)	26.3 (213)	–

NS: not significant.
[a] Cyclicity status was determined based upon two sequential blood samples collected 10–14 days apart for measurements of progesterone.

2003), which has partially been attributed to the emphasis on high milk yield per cow (Royal et al., 2000).

Increased milk yield is accompanied by an increase in feed intake and overall metabolic rate in dairy cows, which might influence peripheral concentrations of ovarian steroids (Sangsritavong et al., 2002). If higher producing cows have a slower rise in progesterone during early diestrus, it could compromise early embryonic development (Mann and Lamming, 1999), and consequently reduce conception (Darwash and Lamming, 1998; Wathes et al., 2003). Also, Snijders et al. (2000) observed that cleavage rate and the number of oocytes developing into blastocysts were lower when they were derived from high versus medium genetic merit cows. However, the same study indicated that 120-day milk production was not associated with cleavage rate and blastocyst development in in vitro cultured oocytes. Nevertheless, studies by our group have not observed associations between milk yield and late embryonic and fetal losses in dairy cows (Cerri et al., 2003; Chebel et al., in press; Santos et al., 2004c), which agrees with findings by others (López-Gatius et al., 2002; Silke et al., 2002). Furthermore, in none of the studies (Cerri et al., 2003; Chebel et al., in press; Santos et al., 2004c) was milk production associated with conception rates on days 30–31 after AI. Therefore, there is little or no indication that milk production is a risk factor for increased pregnancy losses in dairy cattle.

3.11. Diseases

Periparturient diseases have been associated with reduced reproduction in cattle (Gröhn and Rajala-Schultz, 2000). Cows suffering from clinical mastitis are at increased risk for reduced conception and increased fetal loss (Santos et al., 2004a). Chebel et al. (in press) observed that lactating cows experiencing clinical mastitis in the first 45 days after AI were 2.8 times more likely to experience late embryonic death between 31 and 45 days of gestation. Schrick et al. (2001) indicated that not only clinical, but also subclinical mastitis is associated with increased risk for pregnancy loss in cattle. Other diseases have been associated with reduced conception rates such as retained placenta and milk fever (Chebel et al., in press). López-Gatius et al. (1996) demonstrated that cows with retained placenta and pyometra were 1.8 and 2.6 times more likely to experience fetal loss, respectively, than cows not experiencing these diseases. In fact, cows diagnosed with even more moderate uterine problems such as subclinical endometritis at 40–60 days postpartum had marked decrease in conception rates (Gilbert et al., 1998). These data indicate that periparturient problems that affect the health of the cow and compromise the uterine environment are detrimental to embryonic and fetal survival.

3.12. Dietary ingredients

Cottonseed contains gossypol that can be toxic to mammalian cells. Recent studies by our group (Santos et al., 2003; Villasenor et al., 2003) indicated that 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).

3.13. Sire

Although sire has a major effect on conception rates in cattle, little is know about the effects of sire on pregnancy losses. When evaluated, sire has been shown to have an effect on fetal loss in cattle. López-Gatius et al. (2002) indicated that pregnant cows sired by one of the bulls utilized in their study were 3.43 times more likely to experience pregnancy loss than pregnant cows sired by other bulls.

4. Strategies to improve embryo survival in cattle

4.1. Bovine somatotropin (bST)

Treatment with bST improves fertilization rate, accelerates embryo development, and improves embryo quality (Moreira et al., 2002a,b). In fact, treatment with bST increased pregnancy rates in cows inseminated following the Ovsynch protocol or upon estrus detection (Moreira et al., 2001; Santos et al., 2004c). Improvements in conception rates observed by Santos et al. (2004c) were the result of reduced embryonic death between days 31 and 45. Because bST accelerates embryo development, it is expected that it also improves embryo survival in cyclic cows.

4.2. Induction of accessory CL with hCG

Santos et al. (2001) injected 3300 IU of hCG in lactating cows 5 days after AI, and cows receiving hCG had increased number of CL and higher plasma progesterone concentrations. Conception rates on days 28, 42, and 90 were improved by hCG treatment, but late embryonic and fetal losses remained unaltered. Therefore, the positive effect of hCG stimulating conception rates was mediated by reducing early embryonic losses. Recent findings by Nishigai et al. (2002) support the increased pregnancy rate in cows receiving hCG on day 6 (67.5%) when an accessory CL is formed compared to control cows (45.0%) or cows receiving hCG on day 1 (42.5%) after AI. In fact, cows with an additional spontaneous CL were eight times less likely to experience fetal loss than those with a single CL (López-Gatius et al., 2002), an effect that was not related to twin pregnancy because cows carrying twins were 3.1 times more likely to experience pregnancy loss (López-Gatius et al., 2002).

4.3. Attenuating follicle development

Presence of an estrogenic follicle at the time of CL maintenance is thought to up-regulate oxytocin receptors and potentially enhance $PGF_{2\alpha}$ release (Robinson et al., 2001). Santos et al. (2004a) replaced the second GnRH (100 μg gonadorelin) injection in the Ovsynch with the GnRH agonist Deslorelin in an implant form containing 450 and 750 μg to suppress follicle activity and improve pregnancy maintenance. Deslorelin 450 tended to reduce pregnancy loss compared to GnRH ($P < 0.13$), an effect that was not observed for Deslorelin 750. Therefore, strategies that minimize follicle growth during the period of CL maintenance might reduce pregnancy loss in lactating dairy cows.

4.4. Supplemental progesterone

Mann and Lamming (1999) observed that supplemental progesterone significantly increased conception rates when administered prior to day 6 after AI in lactating dairy cows. Furthermore, the benefits of supplemental progesterone were more clearly evident when utilized in lactating cows of lower fertility, i.e. cows with conception rates of less than 50%. Therefore, timing of administration of supplemental progesterone is critical (days 4–5 of gestation) probably because it alters the secretory activity of the endometrium, thus influencing embryonic growth (Garret et al., 1998; Geisert et al., 1992). However, progesterone supplementation immediately after AI should be avoided because it advances the uterus and increases the occurrence of short cycles (Van Cleeff et al., 1996; Garret et al., 1998; Lynch et al., 1999). Progesterone supplementation can also be utilized in beef and dairy cattle to reduce the rate of anovulation prior to the first postpartum AI, which is known to reduce reproductive performance partly because of greater pregnancy losses (Inskeep, 2002). Therefore, incorporation of progesterone releasing devices in programs such as pre-synchronization protocols might increase the proportion of cyclic cows at first postpartum AI and improve embryo survival.

4.5. Pre-synchronization to optimize reproductive protocols

Timed AI protocols such as the Ovsynch are widely utilized in dairy herds because of the poor estrus detection commonly observed in high producing cows (Stevenson, 2001). However, fertility response to the Ovsynch is dependent on the stage of the cycle when the initial GnRH is administered (Vasconcelos et al., 1999). Initiation of the program during mid diestrus (days 5–12 of the cycle) improves conception rates in lactating dairy cows (Moreira et al., 2001; Thatcher et al., 2002) because it increases ovulation to the first GnRH (initiation on days 5–9) and the number of cows with high progesterone (>1 ng/ml) at the moment of the $PGF_{2\alpha}$. Response to pre-synchronization protocols such as the Presynch (Moreira et al., 2001) is only effective in cyclic cows. Because up to 43% of the lactating cows may be anovulatory or anestrous (Rhodes et al., 2003) prior to first postpartum AI, response to the Presynch will vary from herd to herd. Future research to optimize response to timed AI protocols for first postpartum AI should focus on pre-synchronization methods that not only optimize ovulation to the first GnRH, but also reduce the proportion of anovular cows early postpartum.

4.6. Nutrition

Many metabolic and endocrine signals involved in reproductive processes are regulated by nutritional status. Fat supplementation at 2–4% of diet for lactating dairy and beef cows positively influences energy and reproductive status of cows (Staples et al., 1998), in spite the provision of calories. The ability of the fatty acids of the ω-3 family, α-linolenic ($C_{18:3n-3}$), eicosapentaenoic (EPA; $C_{20:5n-3}$), and docosahexaenoic (DHA; $C_{22:5n-3}$) and ω-6 family, linoleic ($C_{18:2n-6}$) to modulate $PGF_{2\alpha}$ secretion by bovine endometrial cells (Mattos et al., 2003) has been suggested as a possible contributor to embryo survival in cattle (Mattos

et al., 2000). In some studies, feeding fat sources rich in ϖ-3 fatty acids, with the premise that inhibiting prostanoid synthesis might enhance maternal recognition of pregnancy and ultimately improve embryo survival, enhanced reproduction (Burke et al., 1997; Petit and Twagiramungu, 2002). Fat supplementation prepartum also had a delayed positive effect on fertility in dairy cows and improved pregnancy rates (Frajblat and Butler, 2003). Feeding a Ca salt of linoleic and monoenoic C18 *trans* fatty acids increased conception rates in lactating cows compared to Ca salts of palm oil (Juchem et al., in press), which was attributed the increased conception rates to higher fertilization rate (87.2% versus 73.3%), and the greater proportion of embryos graded as 1 and 2 (73.5% versus 51.5%), respectively (Cerri et al., in press).

5. Conclusion

Fertilization failure and embryonic death are the most important factors affecting the success of reproductive programs in dairy and beef cattle, with fetal death being of minor importance. Failure of fertilization is an important problem in dairy cows and lactating beef cows, but of less importance in heifers and nonlactating beef cows. The lactating dairy cows seem to be most susceptible to reproductive failure in part due to the low fertilization rate ($\sim$76%) and embryo viability in the first few days of gestation, but also because of the extensive embryonic and fetal death ($\sim$60%). Ovulation of persistent follicles, lack of adequate proestrus period, luteal insufficiency, underdeveloped embryos, poor uterine environment, sire, some dietary components, environmental stresses, diseases, and the metabolic status of the cow have all been associated with embryonic mortality in cattle. However, data suggest that genetic merit, milk yield, insemination protocol, and re-synchronization method are not clearly implicated with increased risk for pregnancy loss. When estrus is induced by sequential injections of $PGF_{2\alpha}$, conception and embryonic survival may decrease when the ovulatory follicle develops under a low progesterone environment. Implementation of timed AI protocols such as the Ovsynch and Heatsynch results in similar rates of embryonic and fetal mortality when compared to insemination upon estrus detection. However, induction of ovulation of small, incompetent follicles, results in reduced embryo survival because of luteal inadequacy and short cycles. Future research to optimize establishment and maintenance of pregnancy in cattle should focus on hormonal, nutritional and environmental management strategies that improve oocyte quality and the uterine environment, enhance embryo development and the cross-talk between the endometrial cells and conceptus for CL maintenance, and improve placentation to ultimately result in a successful pregnancy past the embryonic period, when pregnancy loss is less likely to occur.

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