



Review article

A review of the causes of poor fertility in high milk producing dairy cows

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ABSTRACT

Fertility in dairy cows has declined over the past five decades as milk production per cow has increased. Many hypotheses have been proposed to explain this including issues of genetics, physiology, nutrition and management, and these factors have been investigated at the animal, organ and cellular level at critical time points of the productive life of dairy cows. This paper reviews the physiological events and their causes and consequences affecting fertility in dairy cows and summarises these in a downloadable poster. We consider the following points to have the greatest negative impact on fertility and that they need to be prioritised in efforts to ameliorate the problem (others have been included in the review). Firstly, minimise negative energy balance and resolve any infection of the post partum uterus. Secondly, expression and detection of oestrus followed by insemination with high quality semen (day 0). Thirdly, ovulation and fertilisation of a high quality oocyte (day 1). Fourthly, an early increase in progesterone secretion from the corpus luteum (days 3–7). Fifthly, the uterine endometrium must produce an early and appropriate environment to stimulate embryo development (days 6–13). This leads to sixthly, a large embryo producing adequate quantities of interferon tau (days 14–18) that alters uterine prostaglandin secretion and signals maternal recognition of pregnancy (days 16–18). Future strategies to improve dairy cow fertility are needed for the benefit of the dairy industry and for cow welfare and should be based upon an integrative approach of these events.

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1. Introduction

Dairy production systems that use cows that have been highly selected for milk production in recent decades have suffered a decline in cow fertility. This has occurred in countries and regions that operate diverse production systems, from continuously calving herds found mostly in the UK and North America to seasonal calving herds found mostly in Ireland, New Zealand and Australia (Lucy, 2001; Dillon et al., 2006; Macdonald et al., 2008). Reproductive efficiency is high priority in all systems yet is considered higher in seasonal calving systems as the opportunity for a cow to calve and become pregnant is time limited to ensure a calf per cow per year in synchrony with grass growth (Dillon et al., 2006). Consequently, one of the greatest challenges of reproductive biologists, nutritionists and geneticists is to gain an understanding of the underlying biology of the dairy cow that contributes to low fertility and develop strategies to improve fertility. Fertility is a multi-factorial trait and its deterioration has been caused by a network of genetic, environmental and managerial factors and their complex interactions make it difficult to determine the exact reason for this decline. Despite this, researchers have identified key causes during the productive life of the dairy cow that negatively impact on her reproductive efficiency. This review focuses on factors in the early post

partum period (Fig. 1) that affect subsequent fertility during the breeding period and the successful establishment of a viable/sustainable pregnancy within 83 days of calving in 80% of dairy cows (Fig. 2).

2. Genetic and management effects on milk production and fertility

Over the last 30 years, genetic selection for increased milk production, particularly within the North American Holstein-Friesian genotype, has been very successful. Between 1985 and 2003, the rate of phenotypic gain in milk production per cow per year has been 193 kg for the United States, 131 kg for the Netherlands, 35 kg for New Zealand and 46 kg for Ireland (Dillon et al., 2006). Despite these countries having diverse production systems, genetic selection criteria and climatic conditions, they all report a substantial decline in reproductive performance during the same period. In seasonal pasture based systems of milk production, such as in Ireland and New Zealand, studies have reported conception rates to first service between 39 and 52% (Dillon et al., 2006; Macdonald et al., 2008). In US and UK feedlot systems of milk production, conception rates to first service as low as 30–40% have also been reported (Pryce et al., 2004; Norman et al., 2009). In recent years, the emphasis within selection indices for Holstein-Friesians

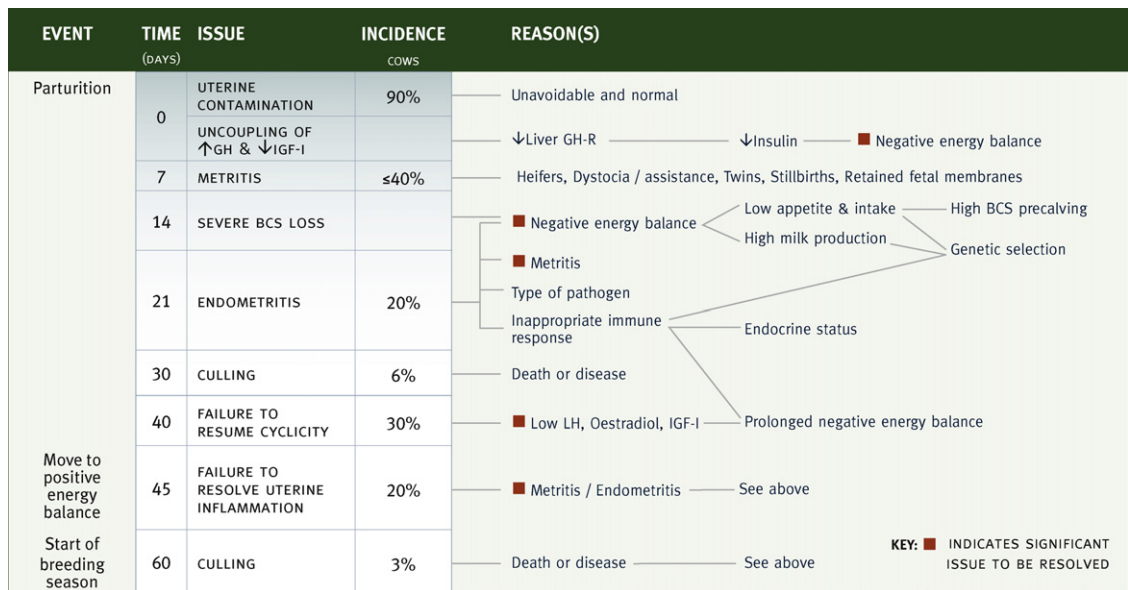


Fig. 1. Schematic presentation of the reasons for the major problems contributing to low fertility in dairy cows in the postpartum period. See text for explanation of incidence rates.

EVENT	TIME (DAYS)	ISSUE	INCIDENCE		REASON(S)
			COWS	HEIFERS	
Oestrus Ovulation	0	SHORT, LOW INTENSITY OESTRUS	5H	14H	<ul style="list-style-type: none"> Stress: Lameness, ↓BCS, Mastitis Low LH, Oestradiol Low oestradiol
		FAILURE TO OVULATE	10%	1%	
		FERTILIZATION FAILURE			<ul style="list-style-type: none"> AI Technician Poor oviduct environment Sire
		PREGNANCY RATE	85%	95%	<ul style="list-style-type: none"> Poor oocyte
		VERY EARLY EMBRYO MORTALITY			<ul style="list-style-type: none"> Poor uterine environment Severe negative energy balance Inappropriate lipid accumulation in oocyte Low P4 previous cycle Uterine pathology Immune modulation
	7	PREGNANCY RATE	55%	75%	<ul style="list-style-type: none"> Chromosomal abnormalities
		EARLY EMBRYO MORTALITY			<ul style="list-style-type: none"> Low progesterone Poor CL / Follicle Liver metabolism Poor embryo-uterus dialog
Maternal recognition of pregnancy	21	RETURN TO SERVICE	55%	30%	Failure of ovulation or fertilization, Embryo mortality
		CULLING	10%	5%	Failure to get pregnant
		PREGNANCY RATE	45%	70%	See above
		LATE EMBRYO MORTALITY			Embryo chromatin (epigenetics), Poor placental function, Disease
	75	PREGNANCY RATE	40%	65%	Epigenetics, Disease
Term /Birth	282/0	CALVING RATE	35%	60%	
		STILLBIRTH	7%	20%	Dystocia, Twinning, Inbreeding
	60	CALF MORTALITY	8%		Disease

KEY: ■ INDICATES SIGNIFICANT ISSUE TO BE RESOLVED

Fig. 2. Schematic presentation of the reasons for the major problems contributing to low fertility in dairy cows during pregnancy. Figures given are either incidence of the problem or pregnancy rates (days 0–282 of gestation) in cows and heifers.

has shifted from predominantly production to functional nonproduction traits associated with improved health and fertility (Miglior et al., 2005). There is now evidence that the phenotypic historical decline in fertility has reached a nadir and begun to improve (Crowe, 2007; Norman et al., 2009); however, future studies are needed to confirm this trend and to determine the alleviating factors. In a recent review (LeBlanc, 2010) readers are urged to critically evaluate studies that have made conclusions on the association between level of milk production and fertility based on incomplete or biased datasets. Other reasons for the decline in fertility such as poor nutrition, management and environmental factors are often not evaluated in these studies although they have a significant impact on reproductive performance. Hence, inappropriate management of high milk producing dairy cows may significantly contribute to the cause of poor fertility rather than direct genetic effects (LeBlanc, 2010).

Understanding genotype by environment interactions is crucial in determining the best health and management practices to achieve high levels of productive and reproductive efficiency. Recent studies have reported higher reproductive performance in high milk producing herds (herd average of >10,000 kg milk production per lactation) than low producing herds and concluded that this

was likely due to better nutritional and reproductive management (LeBlanc, 2010). In addition to increases in milk production, increases in herd size, changes in housing conditions and increases in do-it-yourself artificial insemination have all contributed to increased difficulty in managing the high producing dairy cow to achieve high fertility (Rodriguez-Martinez et al., 2008). However, unlike lactating dairy cows, nulliparous dairy heifers with similar genetic merit for milk production have higher conception rates (39% vs 64%, respectively) and this has not decreased during the period of genetic improvement in milk yield (Pryce et al., 2004). Hence, it is reasonable to suggest that demands of high milk production negatively impact a number of physiological pathways to reduce the likelihood of the concomitant establishment of pregnancy and that changes in management practices may go a long way to providing solutions to poor fertility in high producing cows.

Milk production per cow is expected to increase and it is projected that in the USA by 2050 it will be possible to maintain the same milk supply per head of population from eight million as opposed to the current nine million dairy cows (Santos et al., 2010). Therefore, it is important that the appropriate health and nutritional management strategies are optimised in parallel with a more balanced breeding program in order to produce a more robust dairy

cow capable of both high productive and reproductive performance.

3. Factors in the early post partum period affecting subsequent fertility

This section reviews events in the post partum period that impact the subsequent fertility of cows once the breeding season starts and are summarised in Fig. 1. In addition, events in the post partum period are also influenced by pre partum management, most notably nutritional management (Overton and Waldron, 2004; Roche, 2006). Poor nutrition during the prepartum period can lead to a cow at calving that is more susceptible to increased metabolic disorders, body condition score (BCS) loss and a more severe negative energy balance. At the other extreme, high dry matter intake increases the metabolic clearance rate of steroid hormones and this can lead to periods of suboestrus and decrease oestrus detection efficiency. These effects are discussed in more detail in the following sections.

3.1. Body condition score loss and negative energy balance

High milk producing dairy cows experience a substantial increase in energy requirements to facilitate the dramatic increases in daily milk yield, which peaks between 4 and 8 weeks postpartum. This requirement is only partially met by increased feed consumption (due to limitations in intake and appetite) with the remainder being met by mobilisation of body reserves resulting in animals entering negative energy balance (NEB) (Grummer, 2007). The consequences of severe NEB are an increased risk of metabolic diseases (see below), that largely occur within the first month of lactation, reduced immune function and a reduction in subsequent fertility (Roche et al., 2009).

Body condition score is an internationally accepted, subjective visual and tactile measure of body condition and temporal changes in BCS are used to monitor nutritional and health status of high producing cows during their productive cycle (Berry et al., 2007). It has been correlated with reproductive performance, both phenotypically (Buckley et al., 2003b) and genetically (Berry et al., 2003a) and supports the premise that nutritional status affects reproductive function. Cows in low BCS at calving, or that suffer excess BCS loss early postpartum, are less likely to ovulate, have a reduced submission rate to artificial insemination, conception rate to first service, 6-week in-calf rate and also have an increased likelihood for pregnancy loss and increased calving to conception interval (Berry et al., 2007; Roche et al., 2009). This can partly be attributed to impaired oocyte competence associated with a low BCS (1.5–2.5; 5-point scale) (Snijders et al., 2000). Fertility in cows that are over conditioned at calving (BCS \geq 3.5; 5-point scale) is also compromised as they have reduced dry matter intake (DMI) just prior to calving, take longer to increase DMI postpartum, tend to have greater fat mobilisation and therefore a more severe NEB early postpartum than cows with an optimum BCS at calving (Roche et al., 2009).

Heat stress can further exacerbate the effects of NEB. During periods of heat stress, lactating cows have a reduced appetite and higher BCS loss early postpartum compared to non heat stressed cows (Shehab-El-Deen et al., 2010). Furthermore, concentrations of glucose, IGF-I and cholesterol are lower, while concentrations of NEFA and urea are higher in blood and follicular fluid of heat stressed animals (Shehab-El-Deen et al., 2010). These changes, along with a decrease in dominant follicle diameter, and coupled with a more severe NEB in heat stressed cows make achieving high reproductive efficiency in subtropical and tropical climates a greater challenge. Thus, this highlights the importance of monitoring body condition score pre- and postpartum as an aid to nutritional and management decisions in order to ensure a mild, but not severe NEB occurs early postpartum and to minimise its carry-over effects into the remainder of the lactation (Roche, 2006; Chagas et al., 2007). It is also important to note that partitioning of nutrients is under genetic control; hence different nutritional and management strategies are required for individual animals. Recent reviews (Chagas et al., 2007; Thatcher et al., 2010) have expanded on different nutritional strategies to optimise BCS at critical stages of the productive life of the dairy cow and should be referred to for a more comprehensive analysis.

In conclusion, minimising BCS loss in the first few weeks post partum is an imperative. It is recommended that cows have a BCS of 2.75–3.0 (scale 0–5) at calving and that they are managed to suffer a BCS loss not more than 0.5 between calving and first service (Crowe, 2008).

3.2. Metabolic disorders

During the period which extends from 2 weeks pre-calving to about 4 weeks post-calving, dairy cows experience the stress of parturition, the commencement of lactation, the increased demand for energy and protein to meet milk production combined with reduced feed intake which is generally inadequate to meet her maintenance and production requirements. Thus cows enter a period of NEB characterised by marked changes in endocrine, metabolic and physiological status. This time period is also associated with increased oxidative stress in the dairy cow and this, coupled with the aforementioned stressors, may play a role in compromising the immune and inflammatory response of the cow to these changes (Sordillo and Aitken, 2009). Immunocompromised dairy cows are at risk of developing metabolic disorders, which include acidosis, fatty liver disease, retained placenta and displaced abomasums (Roche, 2006; Mulligan and Doherty, 2008). Metabolic disorders, caused by a mismatch between macromineral requirements and availability in the diet such as clinical hypocalcaemia (milk fever), hypomagnesaemia and ketosis can further exacerbate the degree of immunocompromise experienced in early lactation (Mulligan and Doherty, 2008). Cows that suffer from metabolic disorders in the peri parturient period are more likely to have increased incidence of mastitis, lameness and endometritis (Roche, 2006) all of which contribute to reduced reproductive efficiency (see below). Furthermore, these production diseases cause serious economic loss to

the dairy industry and also have animal welfare implications (Ouweltjes et al., 1996; Ahmadzadeh et al., 2009).

The onset of lactation is associated with an increase in growth hormone that drives nutrient partitioning (mainly in the liver and adipose) that supports milk production (Lucy, 2008). Due to NEB, insulin concentrations remain low which prevents an increase in liver growth hormone receptors and IGF-I secretion causing the somatotrophic axis to be uncoupled (Lucy, 2008). This negatively impacts reproduction as insulin and IGF-I are unable to synergise with the gonadotrophins on ovarian cells preventing the dominant follicle from ovulating (Beam and Butler, 1999) and delaying the resumption of cyclicity (Gutierrez et al., 1999). Conversely, cows that have greater plasma IGF-I concentrations during the first 2 weeks postpartum have an increased likelihood of a shorter calving to commencement of luteal activity (Patton et al., 2007). Similarly, the percent of cows ovulating within 50 days postpartum increased from 55 to 90% in cows fed a high starch diet that promoted greater insulin release in response to feeding (Gong et al., 2002). While an insulin promoting diet has the potential to hasten the onset of cyclicity after calving there is some evidence that maintaining cows on such a diet may have deleterious effects on embryo survival rates (Fouladi-Nashta et al., 2005). However, it has been suggested that this may be overcome by adopting a sequential feeding system whereby a glucogenic diet is offered early postpartum to enhance follicle development and resumption of ovarian cycles and a lipogenic diet is offered during the breeding season to increase availability of fatty acids which has beneficial effects on oocyte quality and embryo development (Garnsworthy et al., 2009). As lactation progresses, the somatotrophic axis becomes recoupled due to greater nutrient intake and improved energy balance resulting in increased insulin concentrations, expression of growth hormone receptors in the liver and finally liver production of IGF-I (Lucy, 2008).

In conclusion, based on the evidence above the implementation of nutritional strategies during the dry period and early postpartum is the principle route to minimising the effects of NEB, reducing BCS loss and thereby avoiding the development of metabolic disorders thus leading to a healthy cow capable of establishing a pregnancy (Roche, 2006; Chagas et al., 2007; Thatcher et al., 2010).

3.3. Uterine pathology, udder health and lameness

Uterine contamination at parturition or in the following days is unavoidable and normal with 80–100% of animals having bacteria in the uterine lumen in the first 2 weeks postpartum (Sheldon et al., 2006). The most prevalent uterine pathogenic bacteria in infected animals include *Escherichia coli*, *Arcanobacterium pyogenes*, *Fusobacterium necrophorum*, *Prevotella melaninogenica* and *Proteus* species and these are associated with increased endometrial inflammation and purulent vaginal mucus (Sheldon et al., 2009a). Many cows successfully deal with this bacterial contamination; however, at least 20% of cows are unable to resolve the contamination and develop metritis within 21 days postpartum. In approximately 15–20% of the herd, persistence of pathogenic bacteria for 3 weeks

or more results in clinical endometritis (Sheldon et al., 2009a). The risk of infection is increased in cows with twins, stillbirth, dystocia or retained fetal membranes (LeBlanc, 2008). A meta-analysis of 23 studies found that endometritis increased mean days open by 15, decreased the relative risk of pregnancy at 150 days in milk by 31%, and reduced the rate at which cows became pregnant by 16% (Fourichon et al., 2000). However, even cows that are treated successfully for clinical endometritis have conception rates that are approximately 20% lower than in unaffected animals and an extra 3% of animals remain infertile and are culled (Sheldon et al., 2009a).

Lactating dairy cows are predisposed to reduced immune competence and consequently are more susceptible to disease (see Section 3.2), especially invading pathogens causing mastitis (Ingvarsen et al., 2003; Sordillo and Aitken, 2009). The incidence of mastitis within the first 30 days postpartum is reported to be 23% (Zwald et al., 2004). A positive genetic correlation between mastitis and milk yield (range 0.15–0.68) has been reported (Ingvarsen et al., 2003) and consequently high yielding cows have an increased risk of developing mastitis. The effect of mastitis, particularly mastitis caused by gram-negative pathogens, on reproductive function has only recently been highlighted. Cows that experienced clinical mastitis (diagnosed when visible abnormalities in milk were observed) in the first 28 days after calving had delayed onset of oestrous behaviour (91 days) compared to their healthy herdmates (84 days) (Huszenicza et al., 2005). Cows with clinical mastitis required more services per conception compared to their healthy herdmates (2.1 vs. 1.6, respectively) and had longer days empty (140 vs. 80, respectively) (Ahmadzadeh et al., 2009). Moreover, the number of days to first AI was greater in cows where clinical mastitis occurred before first AI (93.6 days) than if it occurred between first AI and pregnancy or after 50–60 days after first AI (71 days) (Barker et al., 1998). Furthermore, cows that had a clinical mastitis case between AI and within 50 days of pregnancy had lower conception rates and were 2.80 times more likely to suffer late embryonic loss compared to cows with no symptoms of mastitis (Chebel et al., 2004; Santos et al., 2004). Additionally increased embryonic loss has been reported in cows that developed clinical mastitis after 50 days of pregnancy (Santos et al., 2004). These studies indicate that clinical mastitis in the early postpartum period had a profound effect on reproductive success.

Lameness is associated with increased number of services per conception and consequently lower conception rates to first service (Hernandez et al., 2001; Melendez et al., 2003). Cows that were lame within 30 days post calving were also 2.63 times more likely to develop ovarian cysts before breeding and were half as likely to become pregnant than cows without history of lameness within the first 150 days of lactation (Melendez et al., 2003). Melendez et al. (2003) proposed three hypotheses for the negative effect of lameness on fertility based on reviews of the literature and findings from his research group. Firstly, histamine and endotoxins released during the decline of ruminal pH in animals suffering rumen acidosis act indirectly to destroy the microvasculature of the corium causing laminitis. These substances can also potentiate their affects at the neuroen-

ocrine and ovarian level and compromise the LH surge system (Nocek, 1997). Secondly, stress induced hormones may alter the GnRH and/or LH surge system. Finally, the degree of NEB may be greater in lame cows and hence affect the somatotrophic axis (Melendez et al., 2003).

In conclusion, high producing dairy cows have reduced immune competence that can lead to increased incidence of lameness, mastitis and endometritis when compared to low producing dairy cows. We suggest that the main efforts to improve fertility and overall herd health during this time should be aimed at increasing dry matter intake during the transition period, minimising NEB, decreasing BCS loss early postpartum and resolution of uterine infection.

3.4. Resumption of cyclicity

A 'normal' post partum dairy cow can be defined as one which has resolved uterine involution, resumed ovarian follicular development, ovulated a healthy dominant follicle early postpartum and continues to have normal oestrous cycles at regular intervals of approximately 21 days, coupled with homeostatic concentrations of insulin, IGF-I and glucose (Roche, 2006). However, in seasonal grass based production systems, the incidence of anoestrous anoestrus can range between 13 and 48% prior to the start of the breeding season while in year-round non-grazing dairy production systems the incidence of anoestrus can range between 11 and 38% 60 days or more after calving (Rhodes et al., 2003). This wide variation can be attributed to differences in feed quality, composition, availability and also definitional differences. Up to 50% of modern dairy cows have abnormal oestrous cycles postpartum resulting in increased calving to first insemination intervals (Opsomer et al., 1998) and decreased conception rates (Garnsworthy et al., 2009).

A number of risk factors for delayed first ovulation have been identified. Primiparous cows had more days to first ovulation (31.8 ± 8.3 days) than multiparous cows (17.3 ± 6.3 days) (Tanaka et al., 2008). Additionally, primiparous cows have energetic demands for growth as well as lactation and may be in greater NEB than multiparous cows (Lucy, 2001). Other risk factors cited for delayed resumption of cyclicity include periparturient disorders, season of calving, management, mastitis, lameness and severe BCS loss (Crowe, 2008; Garnsworthy et al., 2008). In mastitic and lame cows, a delay in the resumption of cyclicity could add an extra 7 and 17 days, respectively to the calving to conception interval (Dobson et al., 2008). Compared to their healthy herd mates, cows with clinical endometritis were 4.5 times more likely to have delayed resumption of ovarian cyclicity and 4.4 times more likely to have prolonged postpartum luteal phases (Opsomer et al., 2000). Endometrial epithelial cells respond to uterine infection by altering the secretion and thereby function of prostaglandins from luteolytic (prostaglandin F₂ α) to luteotropic (prostaglandin E₂) action. This mechanism has been proposed to explain delayed resumption of cyclicity in infected cows (Peter et al., 2009; Sheldon et al., 2009b).

Pulsatile secretion of luteinizing hormone (LH) early postpartum is necessary for pre-ovulatory follicle growth, oestradiol secretion and ovulation of the dominant folli-

cle (Diskin et al., 2003; Crowe, 2008). However, low BCS coupled with severe NEB during this period suppresses pulsatile LH secretion, reduces ovarian responsiveness to LH stimulation and also reduces the functional competence of the follicle characterised by reduced oestradiol production (Diskin et al., 2003) and ultimately results in delayed ovulation (Butler, 2003). Heat stressed animals may also have low LH pulse amplitude and frequency, low oestradiol concentrations and smaller dominant follicles which can extend the interval from calving to first ovulation (De Renzis and Scaramuzzi, 2003).

In conclusion, management factors that stimulate the early resumption of ovulation, leading to a number of oestrous cycles before insemination, will result in more cows getting pregnant than poorly managed cows that have prolonged periods of post partum anoestrus.

4. Factors affecting fertility during the breeding season

In order to obtain a 365-day calving interval the breeding season needs to commence 60 days postpartum and the cow needs to conceive by 83 days postpartum assuming 282 days gestation length. Insights that occurred in the early lactation period need to be overcome so that the dairy cow is in optimum condition to be bred. These include resolution of uterine infection, recovery from NEB and the establishment of normal oestrous cycles. However, there are many reasons that can prevent successful establishment and maintenance of pregnancy and are reviewed in the following section and summarised in Fig. 2.

4.1. Oestrous behaviour

Normal oestrous cycles in cows coupled with overt signs of oestrus are essential so that insemination can occur at the appropriate time relative to ovulation. However, the percentage of oestrus animals that stand to be mounted has declined from 80% to 50% and the duration of detected oestrus has reduced from 15 h to 5 h over the past 50 years (Dobson et al., 2008). Coupled with poor expression, an inability to easily detect oestrus further hinders insemination at the correct time. Different methods of oestrus detection yield different detection efficiencies (Roelofs et al., 2010). Based on visual observation for standing heat and use of tail paint as an aid to detection an average oestrus detection rate of 70% has been reported with individual herd rates ranging from 25 to 96% (Mee et al., 2002). Studies that investigated oestrus detection rates using pedometers reported efficiencies between 80 and 100% (Roelofs et al., 2010). Risk factors for poor expression of oestrus are classified as either cow or environmental factors where cow factors include silent or anoestrous anoestrus, parity, milk production and health, and environmental factors include nutrition, housing, season and number of herd mates in oestrus simultaneously (Roelofs et al., 2010).

In modern dairy producing systems, the incidence of lameness can range from 2 to 20% (Bergsten, 2001) and most frequently occurs in the first 60–90 days of lactation (Rowlands et al., 1985). Following normal resumption of cyclicity after calving, lameness has no effect on the obser-

vation of oestrus but does lower the intensity of expression of oestrus, decreases locomotion and isolation from the sexually active group (Walker et al., 2008). In tie stall compared to free stall housing, overt signs of oestrus are reduced in cows. Furthermore, compared to free stall housing, cows on pasture exhibited less mounts per hour during oestrus (11.2 vs 5.4 mounts, respectively) and is partly explained because cows spend more time grazing than cows in confined housing. A reduced duration of oestrus behaviour was also observed in cows that were housed on concrete surface compared to those that had access to both concrete and exercise yard (approximately 5.5 vs 1.3 h, respectively). The reader is referred to a recent review for a more comprehensive look at the factors that disrupt an oestrus (Roelofs et al., 2010).

A number of physiological events also affect the expression of oestrus. Firstly, high producing dairy cows (≥ 39.5 kg/day) have shorter oestrus (6.2 h vs 10.9 h), less total standing time (21.7 s vs 28.2 s) and lower serum oestradiol concentrations (6.8 pg/ml vs 8.6 pg/ml) compared to lower producing dairy cows (< 39.5 kg/day) (Lopez et al., 2004). One hypothesis explaining the reduced oestradiol concentrations in high producing dairy cows is an increased metabolic clearance rate of oestradiol (Sangsrivong et al., 2002) due to the higher dry matter intakes in high producing dairy cows. In support of this, nulliparous heifers have higher circulating concentrations of oestradiol around the time of oestrus (Sartori et al., 2004; Wolfenson et al., 2004) and this may account for the longer duration of oestrus (11.3 ± 6.9 h) and longer standing oestruses (16.8 ± 12.8) observed in nulliparous heifers when compared to multiparous cows (Nebel et al., 1997). Secondly, NEB has been linked to decreased pulsatile LH secretion and IGF-I concentrations (Diskin et al., 2003). Both LH and IGF-I act synergistically to promote follicular development (Lucy, 2000) therefore follicular competence is compromised in these animals which leads to lower oestradiol concentrations resulting in poorer expression of oestrus. Finally, stressors such as lameness and mastitis reduce GnRH and hence LH pulse frequency, leading to short term decreases in follicular oestradiol production as well as delaying and reducing the magnitude of the LH surge (Dobson et al., 2007a). Heat stressed animals (tropical and subtropical regions) also experience an increased incidence of anoestrus and silent ovulation (De Rensis and Scaramuzzi, 2003). Ovulation failure after insemination to a given oestrus can range between 6 and 16% (López-Gatiús et al., 2005; Demetrio et al., 2007) and is 3.9 times more likely to occur during high ($> 25^\circ\text{C}$) ambient temperatures (López-Gatiús et al., 2005).

In conclusion, decreased duration and intensity of oestrus is a hallmark of high producing cows and is exacerbated during periods of heat stress. Therefore more attention and new tools to detect oestrus to ensure insemination occurs at the correct time are needed.

4.2. Fertilisation failure

Fertilisation rates in the 1980s in Holstein-Friesian dairy cows were greater than 95%; however, in a recent review of the literature, it was estimated that this figure has declined

to 83% (Sartori et al., 2010). In contrast, fertilisation rates in heifers have remained consistently high at and greater than 90% (Diskin and Morris, 2008; Sartori et al., 2010). What are the reasons for high fertilisation failure observed in high producing dairy cows? Factors such as heat stress, oocyte quality and sperm characteristics have received some attention and are expanded upon here. High ambient temperatures can have a deleterious effect on fertilisation success. Heat stress between 50 and 20 days prior to AI has been associated with a reduction in oocyte quality and early embryo development (Roth et al., 2001b). Similarly, cows exposed to heat stress prior to AI were 31–33% less likely to conceive than those not exposed to heat stress (Chebel et al., 2004). Similar fertilisation rates between lactating and non-lactating cows have been observed (87.8 and 89.5%, respectively) during the cool season; however, lactating dairy cows had lower fertilisation rates than heifers during high ambient temperatures (55.6 and 100%, respectively) (Sartori et al., 2010). These findings indicate that in addition to heat stress, physiological status (lactating and non-lactating) can significantly compromise fertilisation success. As previously mentioned in Section 3.1, the effects of heat stress on oocyte quality are likely a consequence of altered biochemical composition in follicular fluid (lower glucose, IGF-I and cholesterol and higher NEFA and urea) observed in lactating dairy cows during summer compared to winter months (Shehab-El-Deen et al., 2010). These findings support the hypothesis that exposure of ovarian oocytes to unfavourable physiological events during follicle development from primordial to pre-ovulatory stage may result in the ovulation of defective oocytes up to 3 months after the insult (Britt, 1992; Fair, 2010). Therefore, early postpartum disorders such as NEB, abnormal gonadotropin secretion, uterine infection and other disorders discussed earlier could have subsequent deleterious effects on oocyte development and competence.

Deficiencies in sperm characteristics such as viability, morphology and functional and molecular traits can impede fertilisation success. This can be through inability to reach the site of fertilisation (technician effect and bull effect), inability to penetrate the oocyte, inability to initiate fertilisation if contact is made with the oocyte, inability to prevent polyspermy and incompetence to maintain fertilisation process or subsequent embryogenesis (Saacke et al., 2000). Calving intervals and days postcalving to first AI were longer in herds that used do-it-yourself AI compared to herds that used professional technicians (Lof et al., 2007) however others reported no differences in reproductive performance (Buckley et al., 2003a).

In conclusion, oocyte quality is poorly defined and the effects of metabolic disorders and disease in the post partum period on oocyte quality are not well understood. However, management of cows to reduce diseases and disorders (as described above) will likely have the additional beneficial effects of increasing oocyte quality and fertilisation rates.

4.3. Embryo mortality

The ultimate test of the quality of an oocyte is its ability to be fertilised and develop to the blastocyst stage, to

establish a pregnancy and to produce a live calf. Embryonic mortality is one of the major causes of reproductive failure. Early embryo mortality occurs between fertilisation and day 24 of gestation, late embryo mortality occurs between days 25 and 45 at which stage embryonic differentiation is completed, while fetal mortality occurs after this and up to parturition ([Committee on Bovine Reproductive Nomenclature, 1972](#)). Based on fertilisation rates of 90%, embryonic and fetal mortality rates are approximately 40% and 56%, while calving rates are approximately 55% and 40% in moderate and high yielding dairy cows, respectively ([Diskin and Morris, 2008](#)). Based on six studies, estimates of fertilisation failure and early embryonic loss range between 20 and 45%, estimates for late embryonic/fetal loss ranged between 8 and 17.5% while estimates for late abortion ranged between 1 and 4% ([Humblot, 2001](#)). This indicates that most embryonic mortality occurs within the first 3 weeks of gestation and is consistent with other reports ([Inskip and Dailey, 2005](#); [Diskin and Morris, 2008](#)). However, timing of early embryo loss is not consistent across studies. Some studies report that the highest embryo loss occurs within the first week post conception ([Sartori et al., 2002](#)), while other studies suggest it occurs within the second week post conception ([Diskin and Sreenan, 1980](#)). For this reason, we have chosen to consider embryo mortality in three periods; very early mortality between days 0 and 7, early mortality between days 7 and 24, and late embryonic mortality from days 24 to 45 (with fetal mortality being after day 45).

4.3.1. Very early embryo mortality (days 0–7)

The causes of very early embryo mortality focus on the early embryos inability to develop as a consequence of poor oocyte quality or an inadequate uterine environment. As mentioned earlier, several studies have reported factors that act directly or indirectly on oocyte quality with consequential effects on embryo development after fertilisation. There is general agreement that in vitro embryo development (to day 7) of oocytes from cows with high-genetic merit for milk production is inferior compared to oocytes from cows of medium-genetic merit, irrespective of actual milk production ([Snijders et al., 2000](#)). Furthermore, physiological status (lactating or non-lactating) has a significant effect on embryo quality. Embryos recovered at day 7 from non-lactating Holstein-Friesian heifers and beef heifers were of higher quality compared to lactating Holstein-Friesian cows ([Leroy et al., 2005](#)). Higher quality embryos were also recovered at day 5 from non-lactating Holstein-Friesian heifers compared to lactating Holstein-Friesian cows ([Sartori et al., 2010](#)). The very early embryo remains in the oviduct for 4–5 days after ovulation before travelling into the uterus. The oviduct provides nutrients (e.g. ions, amino acids and glucose) and local growth factors (e.g. IGF-I and IGF-II) to the developing zygote ([Robinson et al., 2008](#)) that can be modified by maternal nutrition ([McGuire et al., 1992](#)) ([Pushpakumara et al., 2002](#)), energy balance ([Fenwick et al., 2008](#)) and lactation. These studies implicate the IGF signalling pathway within the oviduct as perturbing early embryo development in lactating cows but it should also be noted that disrupting the mechanism of oviductal muscular and ciliary movement for sperm and

oocyte transport may present the embryo at the wrong stage of development (too early or too late) to the uterus resulting in early embryo mortality ([Wiebold, 1988](#)).

The uterine environment before day 7 may also be suboptimal in lactating dairy cows for supporting early embryo development. In a recent study using a state-of-the-art endoscopic transfer technique, 1800 in vitro-produced embryos were transferred (on day 2 of the cycle) to the oviducts of nulliparous Holstein-Friesian heifers and postpartum lactating Holstein-Friesian cows at approximately 60 days postpartum and recovered five days after transfer ([Rizos et al., 2010](#)). The recovery rate was significantly higher in heifers (80%) than cows (57%) and, of the embryos recovered, 34% had developed to the blastocyst stage in heifers compared with 18% in lactating cows. This suggests that the reproductive tract of the lactating dairy cow provides a less favourable environment for very early embryo development than that of the heifer.

Progesterone is the hormone of pregnancy and its role in early pregnancy in cattle has received much attention in recent years. While interest has mostly been on luteal phase maternal progesterone concentrations after day 7 new information on concentrations before day 7 is now emerging. Animals that have an earlier increase in progesterone concentrations between days 4 and 7 after insemination (i.e. greater concentrations during this period) have a greater chance of maintaining a pregnancy than animals with a slower rise ([Diskin and Morris, 2008](#)). This hypothesis is supported by the observation that a five-fold increase in systemic progesterone concentrations early post conception was associated with an increase in embryo size on days 13 and 16 of pregnancy ([Carter et al., 2008](#)). Furthermore, a delay in the post-ovulatory rise of progesterone has been associated with decreased pregnancy rate both in cows and in heifers ([Diskin and Morris, 2008](#)). The present thinking is that progesterone has limited or no direct effect on the embryo ([Clemente et al., 2009](#)) but that an early rise in progesterone alters endometrial secretions (the histotroph) that stimulate embryo development after day 7 leading to a large conceptus that is better able to signal maternal recognition of pregnancy.

In conclusion, the need to ovulate good quality oocytes needs to be restated, and the development of very early embryos in a uterus that had experienced a minimum of metabolic disorders and disease is desirable. An adequate increase in circulating progesterone concentrations before day 7 also substantially benefits later embryo development.

4.3.2. Early embryo mortality (days 7–24)

The embryo descends into the uterus between days 5 and 7 after insemination ([Wiebold, 1988](#)). During this time up to day 15 the embryo forms a blastocyst which develops into an elongated filamentous conceptus and occupies the uterine horn. The microenvironment of the uterus plays a leading role in determining embryo quality ([Rizos et al., 2002](#)). Low concentrations of progesterone and IGFs can create a suboptimal uterine microenvironment that is unable to support early embryonic development ([Leroy et al., 2008a](#)). Uterine function is also compromised by the presence of pathogenic bacteria which can cause embryonic death and abortion ([Sheldon et al., 2006](#)).

As previously mentioned, an early rise in progesterone concentration is associated with enhanced conceptus development and size around the time of maternal recognition of pregnancy (Loneragan, 2010). The challenge of the elongating conceptus is to produce adequate concentrations of interferon tau to signal maternal recognition of pregnancy and inhibit the release of luteolytic prostaglandin F_{2α} from the uterus (Spencer et al., 2008). This is more easily achieved by a larger than a smaller embryo. Early embryo loss due to the failure of maternal recognition of pregnancy is thought to account for up to 25% of failures of conception in dairy cows (Sreenan and Diskin, 1983). It should also be noted that approximately 5% of embryos die because of gross chromosomal abnormalities preventing development (Peters, 1996).

In conclusion, prior uterine infection and the development of small embryos (because of inadequate uterine environment caused low progesterone concentrations) significantly increase the chances of embryo mortality and decrease the likelihood of maternal recognition and the establishment of pregnancy.

4.3.3. Late embryo and early fetal mortality (days 24–285)

Late embryo and early fetal loss has been defined as the death of the embryo between days 25 and 45 of gestation and days 46 until parturition, respectively (Committee on Bovine Reproductive Nomenclature, 1972). In cows managed on pasture based systems, the rate of loss between days 24 and 80 is approximately 7% in lactating cows (yielding on average 7247 kg of milk per lactation) and 6% in heifers, with 48% of these losses occurring between days 28 and 42 of gestation (Silke et al., 2002). However, in intensively managed dairy cows yielding between 11,000 and 12,000 kg of milk per lactation 20% of embryos were lost between days 28 and 98 of gestation (Vasconcelos et al., 1997).

Factors causing late embryo and early fetal loss are categorised as genetic, physiological, endocrinological and environmental (Diskin and Morris, 2008). In addition, infection with pathogenic agents can cause embryo and fetal loss in cattle. Many bacterial, viral, fungal and protozoal pathogens have been associated with infertility and abortion in cattle and the subject has been comprehensively reviewed (Givens and Marley, 2008).

Although the extent of late embryo and early fetal mortality is relatively low compared to losses observed within 24 days post insemination, it nonetheless presents financial losses and management difficulties to the dairy producer especially those operating a seasonal calving herd. Therefore, it is important to minimise exposure to environmental stressors and pathogens during mid to late gestation to avoid abortion and stillbirths.

4.3.4. Neonatal death, calf mortality, heifer rearing and fertility

The postnatal period is important in the context of generating sufficient dairy heifers to replace culled cows. Perinatal mortality, within the first 48 h of parturition following a normal gestation is correlated with dystocia (>50%) and the incidence is increasing in some countries (Meyer et al., 2001; Berglund, 2008). Stillbirth rates vary between 6 and 8% for cows and 11 and 30% for heifers (Meyer et al., 2001; Murray et al., 2008) with feto-pelvic incompatibility probably the main cause of perinatal mortality in heifers. Inbreeding also contributes to a higher incidence of dystocia and stillbirth while crossbreeding can be used as a tool to alleviate its effects (Berglund, 2008). Twin calving events also increase the risk of perinatal mortality; one or both calves are reported as dead in 28.2% of twin calving events compared with 7.2% in single births. Neonatal calf mortality is mostly attributed to infectious agents, such as rotavirus, coronavirus, enteropathogenic *E. coli*, salmonella species and cryptosporidium (Snodgrass et al., 1986).

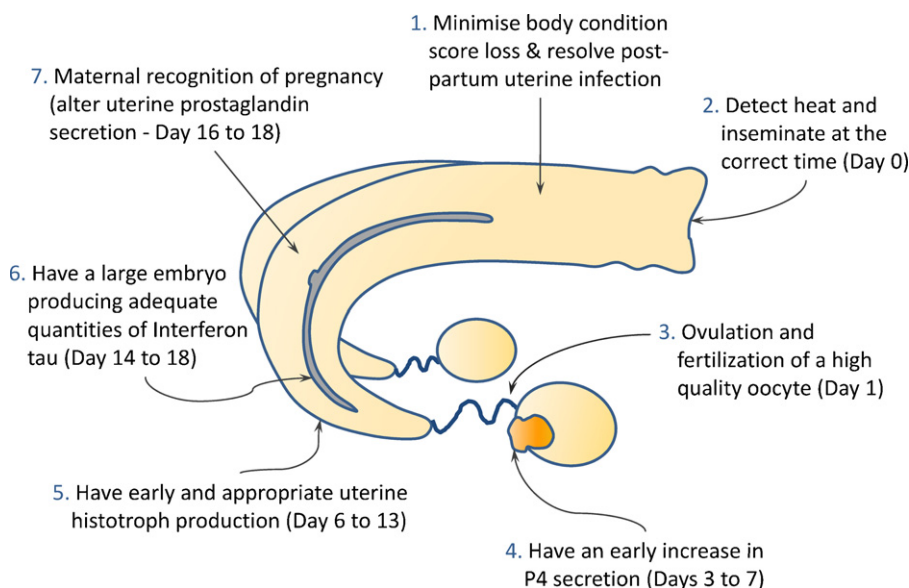


Fig. 3. Schematic presentation of the most important factors affecting the establishment of pregnancy in dairy cows.

5. Conclusions

It is clear that fertility in high milk producing dairy cows is impacted by many events (summarised above and in a [Supplementary Poster](#)). We now prioritise a number of these for improvement and summarise them in [Fig. 3](#). The first consideration is of NEB that leads to many negative outcomes and is a major factor contributing to the pathogenesis of infertility. In addition recovery from uterine inflammation and infection after parturition are critical for the uterus to provide a favourable environment for establishment and maintenance of pregnancy. Therefore, future strategies to improve fertility focusing on the early postpartum period should be based upon minimising the duration and degree of NEB and resolving uterine infection. On day 0 of the cycle (and pregnancy) detection of oestrus and insemination at the correct time relative to ovulation is paramount and needs to be followed by ovulation and fertilisation of a high quality oocyte (day 1). Once this has been achieved an early rise in progesterone concentrations (between days 3 and 7) is required to alter uterine endometrial secretions that stimulate embryo development (days 6–13) leading to a large embryo that produces adequate quantities of interferon tau (days 14–18) to alter uterine prostaglandin secretion and to signal maternal recognition of pregnancy (days 16–18) to the dam. The reductionist approach has investigated many of these issues in isolation; however, a holistic approach is now needed and future efforts to improve fertility in dairy cows needs to focus on genetic and management solutions to improve the physiological events associated with the establishment of pregnancy.

Conflict of interest

The authors declare that there is no conflict of interest in publishing this review.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anireprosci.2010.12.001.

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