

Physiological Mechanisms Linking Reproduction to Nutrition in High-Producing Dairy Cows

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Introduction

Dairy cattle are inseminated and pregnancy is established during lactation. Therefore, lactation and the reestablishment of pregnancy must overlap. Unfortunately, recent changes in the genetics, productivity, and management of dairy cows have led to a decline in reproductive efficiency. Reproductive decline in dairy cows began in the mid-1980's and may be continuing on modern dairy farms (Lucy, 2001).

Most of the discussion about reproductive decline in dairy cattle has centered on the effects of milk production on reproduction (Hansen, 2000). The effects of nutrition and lactation on reproduction have been recognized for a long time. Ancient societies were well aware of the effects of nutrition as well as lactation on reproduction. Aristotle (384-322 BC) wrote that nutrition was the most important environmental factor controlling conception (Medvei, 1982). The effects of nutrition on reproduction in the modern era are similar to those reported by ancient societies. Cattle in poor condition or losing body weight generally have poor reproductive performance. The reason for this relationship is often explained by using the argument of nutrient prioritization. Postpartum cows prioritize their metabolizable energy toward production of milk and then toward regaining body condition (adipose tissue). It is only after these immediate needs are met that reproductive processes (perhaps viewed as non-essential for the individual but nonetheless essential for the species) are resumed. The mechanisms through which nutrition controls reproduction in postpartum cows are of great interest. Dairy cattle are maintained on approximately one-year calving intervals so that they are dried off at an optimal time in the lactation curve. The energy required to ovulate a follicle, form a corpus luteum, and maintain an early pregnancy is miniscule compared with the other energy demands of lactating cows. Therefore, the desire of bovine reproductive biologists is to establish pregnancy early in lactation when

seemingly little energy is required for the pregnancy. In late gestation, the energetic demands for pregnancy are greater but the energetic demands for lactation are less or nonexistent (dry cow). The problem is that this seemingly easy solution to maintaining a yearly calving interval is inconsistent with the evolution of reproduction in cattle. Cattle initiate cyclicity and are fertile after minimum nutrient requirements are met.

Physiology of Postpartum Dairy Cows

There is a need to think broadly about the relationship between nutrition and reproduction in postpartum cattle and to discuss the process in its basic components. The ruminant placenta produces copious amounts of steroids (progesterone, estrogens, and their derivatives) during late pregnancy and the steroids of late pregnancy have a suppressive effect on the reproductive hormones of the hypothalamus and pituitary. Thus, the first phase of postpartum reproduction is the recovery of the hypothalamus and pituitary from the effects of the previous pregnancy and the resumption of follicle stimulating hormone (**FSH**) and luteinizing hormone (**LH**) secretion. The LH surge mechanism for ovulation must also be reestablished. The first phase is relatively short and cows begin normal LH pulsatility one to two weeks after parturition and recover the LH surge mechanism shortly thereafter. There are a variety of factors that affect the resumption of LH pulsatility (most notably energy balance) and the relative impact of these depends on their intensity. Follicle stimulating hormone is needed for follicular growth in postpartum cows, but is not viewed as limiting for reproduction. In fact, most anestrus cows have relatively high concentrations of FSH.

The second phase in the process of postpartum reproduction is uterine involution. Uterine involution is rapid and is completed by 30 to 40 days postpartum. The timing of uterine involution

coincides with the recovery of complete fertility in

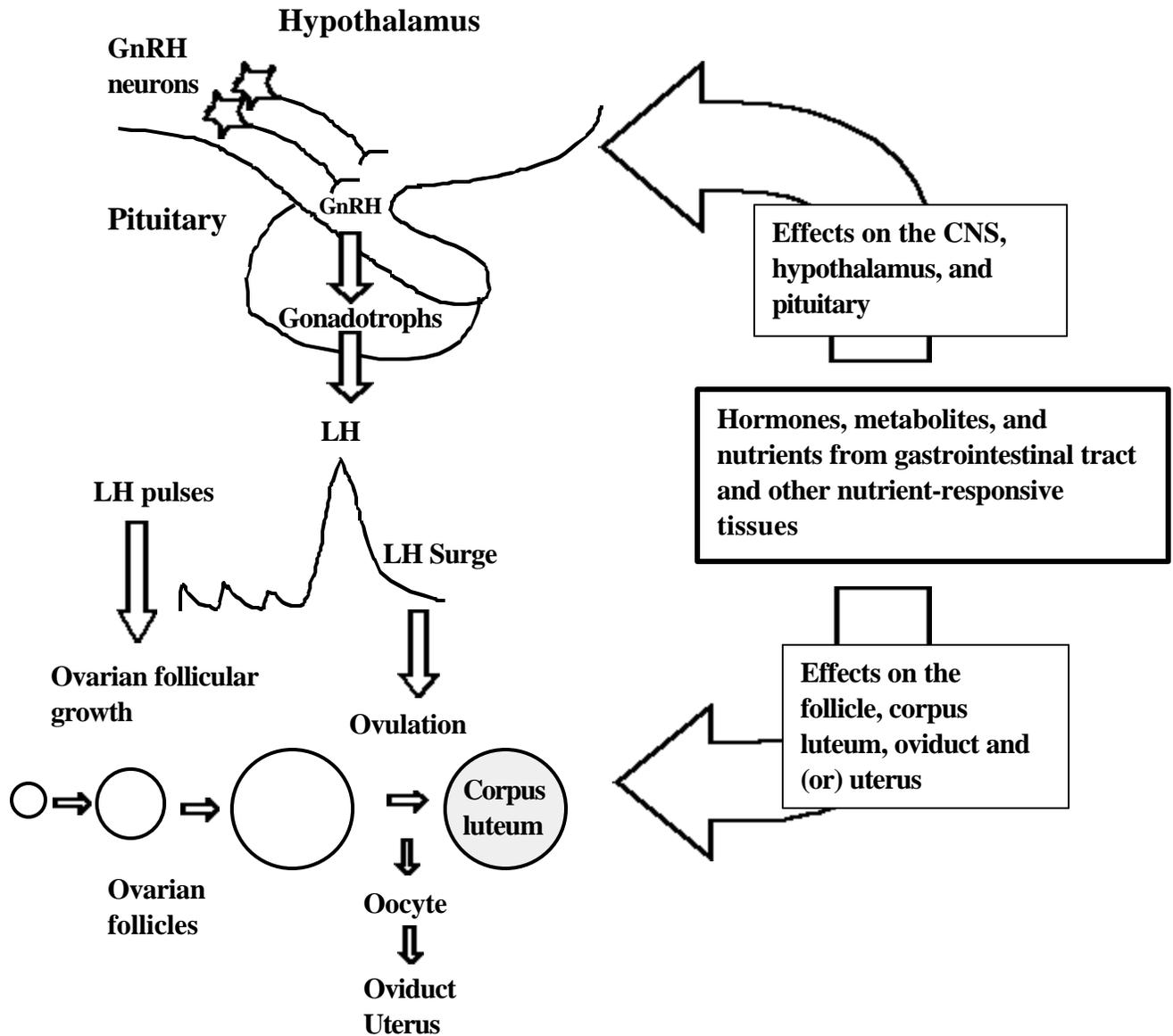


Figure 1. Conceptual model for the mechanisms through which nutrition affects reproduction in postpartum cows. Hormones, metabolites, and nutrients from the gastrointestinal tract and nutrient-responsive tissues affect GnRH and LH secretion through their actions on the central nervous system (CNS) and hypothalamus. These same hormones and metabolites may have direct effects on ovarian function (both follicles and corpora lutea) as well as the oocyte, oviduct, and uterus. The combined effects of each axis determine postpartum fertility.

postpartum cows. Thus, most investigators consider uterine involution as the initial block to the reestablishment of normal fertility. Uterine involution is not considered a major limitation to postpartum reproduction because most cows are inseminated from 40 to 80 days postpartum, when the process of uterine involution is complete.

The most intensely studied area of reproduction in postpartum cows is ovarian recovery after calving. Follicular growth continues during pregnancy but diameters of dominant follicles decrease, perhaps because of a decrease in LH pulsatility in late pregnant cattle (associated with high steroid concentrations during late pregnancy; see above). Follicular development begins shortly after calving with a transient increase in FSH, a follicular wave and the development of a dominant follicle. The first postpartum dominant follicle undergoes one of three fates (Beam and Butler, 1999): 1) ovulation; 2) atresia and turnover (followed by new wave emergence); or 3) cyst formation. The mechanisms that dictate these three events are of keen interest to reproductive biologists. A principal component of the process is the secretion of LH during the early postpartum period. Low LH pulsatility is associated with follicular turnover and anestrus; moderate LH pulsatility is associated with ovulation; and extreme LH pulsatility and lack of an LH surge is associated with the development of cystic ovaries (Silvia et al., 2002).

Changes in metabolic hormones are dynamic in postpartum cows and reflect the shifting metabolic status of the animal. Blood concentrations of insulin-like growth factor (IGF)-I, insulin, and leptin decrease shortly after calving (Butler, 2000; Lucy, 2000; Block et al., 2001). Insulin and IGF-I concentrations gradually increase postpartum, whereas leptin remains low in lactating cows. The blood concentrations of IGF-I, insulin, and leptin are greater in cows in positive energy balance. Cows in negative energy balance have lower blood concentrations of insulin and IGF-I. Secretion of LH and FSH is controlled primarily (LH) or in part (FSH) by gonadotropin releasing hormone (GnRH) from the hypothalamus. The aforementioned endocrine hormones, that are metabolically controlled, can influence GnRH secretion. Their actions may be on GnRH neurons, on the neuronal pathways that impinge upon GnRH neurons, or on the pituitary gonadotroph (Williams et al., 2002). The hormonal control (endocrine) arises from tissues that respond to the metabolic or

nutritional status of the animal (e.g., insulin from the pancreas; IGF-I from the liver; leptin from adipose tissue). It makes sense that these peripheral cues would act upon the hypothalamus to convey information from metabolically important tissues.

The same metabolites and hormones that influence GnRH secretion and ultimately LH and FSH secretion may act directly on the ovary to influence the sensitivity of the ovary to LH and FSH (Figure 1). Ovarian cells treated with either insulin or IGF-I have greater numbers of gonadotropin receptors and greater activation of second messenger pathways in response to gonadotropins (Lucy, 2000). There is also the potential for insulin and IGF-I effects that are completely independent of LH and FSH. Although the interaction of metabolic hormones with the ovary has been described for insulin and IGF-I (Butler, 2000; Lucy, 2000; Monget et al., 2002), it is likely that a variety of hormones, metabolites, and nutrients act on the ovary and change the ability of the ovarian cells to grow or respond to gonadotropins.

Postpartum cows will begin to cycle once LH pulsatility reaches a critical level. The increase in LH pulsatility stimulates the maturation of a dominant follicle (Mihm and Austin, 2002). The dominant follicle produces estradiol that reaches a threshold level to trigger an LH surge. The cow will have an LH surge and ovulate as long as the LH surge mechanism (positive feedback of estradiol) is established. Hypothetically, mechanisms that increase LH pulsatility through their actions on the hypothalamus and pituitary also coordinate an increase in the responsiveness of the ovary to LH. For example, LH pulsatility increases in cows during the postpartum period and blood insulin and IGF-I concentrations increase as well (Butler, 2000; Lucy, 2000). Thus there is a coordinated series of events that act to promote follicular development and eventually ovulation.

Physiological Factors Contributing to Infertility in Dairy Cattle

Selection indices for dairy cattle are heavily weighted for milk production. By selecting for milk production, we created dairy cattle that undergo a high level of nutrient partitioning and adipose tissue mobilization during early lactation. An essential question that must be addressed is whether or not dairy cows are inherently less fertile or if their

infertility is simply a function of their level of milk production and nutrient partitioning. The current perspective is that infertility in dairy cows in the United States is secondary to negative energy balance caused by high milk production during early lactation. In other words, the reproductive genotype of dairy cows is normal and their reproductive phenotype is a function of lactation. Although difficult to prove either way, most investigators would cite the fact that reproduction in virgin heifers has not changed during the period of declining fertility in lactating cows.

Interval to first ovulation and function of the corpus luteum

Interval to first ovulation is an important measure of reproductive efficiency because cows must be cyclic before breeding. Modern dairy cattle that have been selected intensively for milk production have longer postpartum intervals to first ovulation (Roche et al., 2000; Gong, 2002). Most investigators suggest that the reason for the delay in interval to first ovulation is greater negative energy balance in modern dairy cows. Negative energy balance delays the resumption of ovarian activity (Butler, 2000). In addition to negative energy balance, however, other factors are probably contributing to the increase in the interval to first ovulation in modern dairy cows. The longer interval to first ovulation reflects a compromised state of LH secretion and perhaps compromised local endocrine support within the ovary.

An additional observation arising from this work is that modern dairy cattle have an increased incidence of irregular or abnormal estrous cycles. Holstein cows were nearly seven-times more likely to have a prolonged luteal phase than traditional Friesian cows (Opsomer et al., 1998). Laming and Darwash (1998) found similar patterns of abnormal progesterone in UK cows. Our most recent work comparing dairy cattle selected for milk production with traditional 1964 dairy cattle (Waseca herd selection project, University of Minnesota, St. Paul) has also demonstrated a greater incidence of anestrus and a greater incidence of long luteal phases in cows selected for milk production (B.A. Crooker and M.C. Lucy, unpublished). Opsomer et al. (2000) concluded that negative energy balance, periparturient disorders,

and postpartum diseases were risk factors for delayed cyclicity and prolonged luteal phases. Therefore, common ailments of early postpartum cows caused luteal phase abnormalities. A change in luteal phase length in modern-day dairy cows is an important observation because it changes the approach used for reproductive management in dairy cattle. Cows that are not in controlled breeding programs will have delayed breeding because their estrous cycles are longer. Abnormalities in luteal phase length also make it more difficult to predict when cyclic cows will return to estrus.

Undernutrition or negative energy balance may compromise pregnancy through its effects on the corpus luteum. High-producing dairy cows have lower blood concentrations of progesterone and the lower blood progesterone concentration may lead to infertility (Lucy, 2001). There is a positive association between blood progesterone concentrations and pregnancy (Laming and Darwash, 1998). Cattle that are underfed have smaller corpora lutea and lower blood progesterone concentrations (Gombe and Hansel, 1973). Cyclic cattle that are underfed have progressively smaller and less estrogenic dominant follicles before they succumb to anestrus (Bossis et al., 1999). The smaller dominant follicles give rise to smaller corpora lutea. Steroidogenic capacity of luteal cells is also dependent on hormones such as somatotropin, insulin and IGF-I that are controlled by the nutrition of the cow (Lucy, 2000).

Ovarian follicular health

One hypothesis is that the increased incidence of anestrus and abnormal estrous cycles shares a common mechanism that involves LH secretion, metabolic growth factors, follicular development, and estradiol secretion (Figure 2). Presumably, the increase in anestrus is caused by a decrease in LH pulsatility that is secondary to negative energy balance in dairy cattle selected for high milk production. Lower metabolic hormone concentrations (e.g., insulin and IGF-I) may contribute to a decrease in ovarian LH responsiveness and create gonadotropin insensitivity at the ovary. It is possible that the compromised state of LH secretion and sensitivity continues in the cyclic animal and disrupts functional aspects of the dominant follicle. Lactating

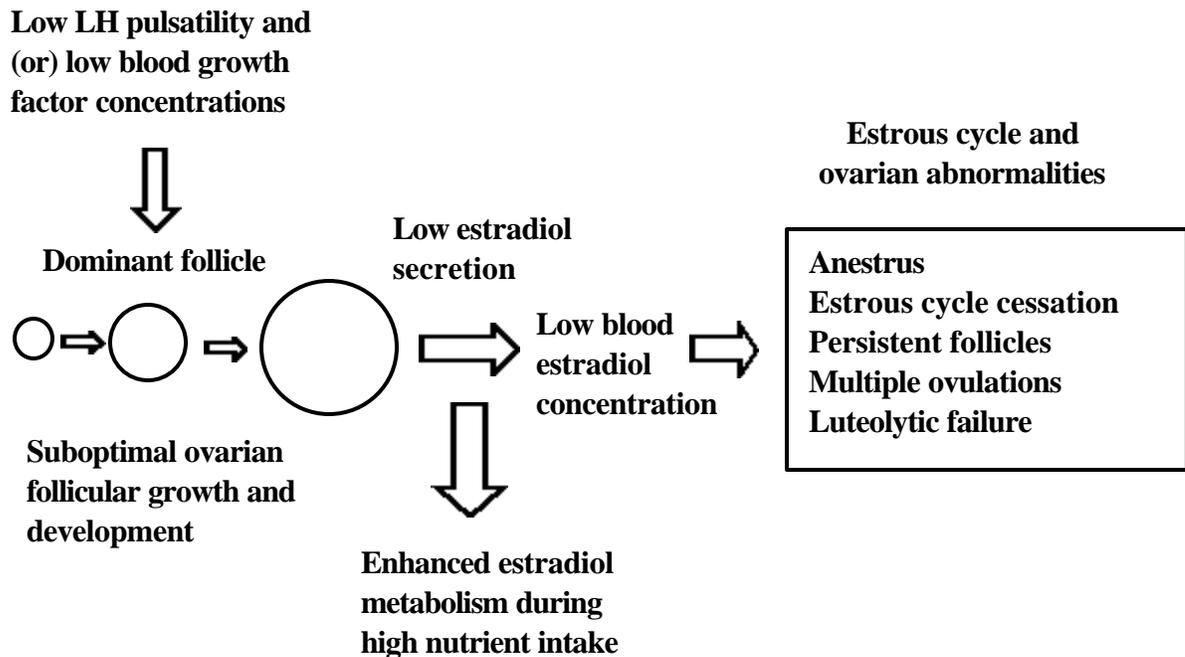


Figure 2. Mechanisms linking poor LH secretion and suboptimal follicular growth to estrous cycle and ovarian abnormalities. Low blood estradiol concentrations may be created by low follicular estradiol secretion (secondary to low LH pulsatility and [or] low blood growth factor concentrations) and enhanced estradiol metabolism during high nutrient intake. A variety of estrous cycle and ovarian abnormalities may be linked to low blood estradiol concentrations (see text for details).

cows had larger preovulatory follicles than heifers but lower preovulatory concentrations of estradiol in blood (Sartori et al., 2000). Thus, the dominant follicle must grow to a larger size to achieve equivalent blood estradiol concentrations. It is not known whether the lower blood estradiol is caused by poor steroidogenic capacity of the follicle or greater steroid metabolism in lactating cows with high nutrient intake (Sangsritavong et al., 2002). The additional developmental time needed by the follicle of lactating cows may create a *persistent follicle* scenario (and hence lower fertility) where the oocyte is exposed to an extended preovulatory period of relatively high LH pulsatility.

modern dairy cattle because there are positive genetic correlations between the incidence of twins and level of milk production (Kinsel et al., 1998). The greater ovulation rate in lactating cows may be caused by follicles that fail to produce enough estradiol to fully suppress FSH (Wiltbank et al., 2000). Long luteal phases in dairy cattle may be caused by insufficient estradiol as well because estradiol initiates the luteolytic cascade. Whether long luteal phases in high producing dairy cows are associated with a higher incidence of three follicular wave estrous cycles is not known. The lower fertility in two- relative to

The incidence of twinning has also increased in

three-follicular wave cows (Townson et al., 2002)

would be theoretically exacerbated by longer luteal phases in high producing dairy cows.

We found that 21% of luteal-phase postpartum dairy cows treated with a luteolytic dose of PGF_{2α} failed to ovulate the preovulatory follicle (J.M. Borman and M.C. Lucy, unpublished). The phenomenon was completely reversed by estradiol treatment after PGF_{2α} injection. Insufficient blood estradiol concentrations, therefore, may be a causative factor leading to ovulation failure following spontaneous luteolysis or luteolysis induced in estrous synchronization programs.

Early embryonic loss

Perhaps the most surprising component of reproductive loss in dairy cattle is the large number of seemingly normal embryos that undergo early embryonic death. There are high rates of embryonic loss between the period of conception and maternal recognition of pregnancy (about 17 to 19 days after insemination). Losses after this early period are considerably less, but nevertheless influence pregnancy rates. When reciprocal embryo transfer was done between repeat breeder and normal cattle, the repeat breeder cattle failed to achieve normal pregnancy rates even though an embryo from a *normal* cow was implanted. Conversely, normal cattle had normal rates of pregnancy when implanted with an embryo from a repeat breeder cow. Seemingly normal embryos may fail to develop within the uterus because the uterus may not synthesize adequate amounts of embryotrophic growth factors that are required by filamentous embryos. Mapletoft et al. (1986) examined pregnancy rates after embryo transfer and found that recipients with low body condition score had lower conception rates when compared to recipients with high body condition score. Embryonic loss after day 28 of pregnancy was highest in cows losing the greatest amount of body condition (Silke et al., 2002).

In addition to nutritional factors, reproductive management practices may influence the rate of early embryonic loss. Cows inseminated by timed AI have high rates of early embryonic loss (at least 20% between 28 and 60 days of pregnancy). Early embryonic loss in timed AI cows may occur when follicles are ovulated prematurely by GnRH (Perry et al., 2003). Rates of embryonic loss for cows inseminated at a spontaneous estrus may be lower

than those for cows inseminated by timed AI.

Management Factors Contributing to Reproductive Decline in Dairy Cattle

There is an antagonistic relationship between milk production and reproduction in dairy cattle; however, the effects of increased milk production on reproduction are relatively minor compared to the effects of other factors. For example, in their paper on the epidemiology of reproductive performance in dairy cows, Gröhn and Rajala-Schultz (2000) reported that the hazard ratio for conception was near 1.0 (neutral effect) for most levels of milk production (i.e., milk production was not a major factor for determining whether dairy cows will conceive). Studies of European cattle have also failed to create a definitive link between milk production and reproduction (Loeffler et al., 1999).

Practical experience also suggests a weak link between milk production and reproduction in dairy cows. Days open and interval to first service decrease for herds stratified from lowest to highest production (Nebel and McGilliard, 1993). Services per conception increase in high producing herds, but so does estrous detection efficiency. The improved reproduction in high-producing herds probably reflects a higher level of management that includes better nutrition as well as greater cow comfort and cleanliness. Thus, better management compensates for a slight decline in reproductive efficiency caused by level of production in dairy cows.

The previous studies suggest that the effects of milk production on reproduction are minor. Nevertheless, there is a slight antagonistic relationship between level of production and reproduction and the trend for poorer reproduction will continue as cows achieve greater production. Other changes within the dairy industry, however, probably have equivalent or greater effects on reproduction in dairy cows. Some of the decrease in reproductive efficiency in dairy farms may be attributed to *growing pains* as dairies expand and attempt to manage reproduction with methods developed for smaller herds.

Detection of estrus and the accuracy with which estrus is detected is an area of increasing concern. Traditional methods of visual estrous detection followed by artificial insemination do not work well

when cows are managed in large groups. Few studies have systematically evaluated the causes of poor estrous expression in dairy cows. The intensity and the duration of estrus depend on behavior of individual cows as well as social interactions among cows. Britt et al. (1986) concluded that milk yield did not influence the intensity of estrous expression. Their original study, however, demonstrated the importance of surface because duration of estrus, mounting activity, and standing activity were greater on dirt than on concrete. If a decrease in estrous expression is occurring in modern dairy cows then the most likely cause is the increased utilization of dairy confinement housing with concrete floors. Large herds require more time for estrous detection, identification, sorting, insemination, and record keeping simply because there are more cows. The responsibility for reproduction also falls on employees (instead of the owner) that may be overwhelmed by the number of cows that they manage. In some herds, non-electronic estrous detection aids (tail chalk, patches, etc.) have replaced visual detection of estrus and cows are inseminated based on rubbed tail heads, activated tail patches, or the appearance of vaginal mucous. Unfortunately, less definitive signs of estrus often lead to poorly timed or completely incorrect time of insemination.

Short and Long-term Solutions to Dairy Infertility

Genetic selection for improved reproduction

Selection of cows for improved reproductive efficiency is a possible solution to reproductive decline. Careful genetic selection may allow dairy producers to use the genetics of high milk production and still maintain acceptable reproductive rates. Reproductive traits have low heritabilities but the coefficient of variation of reproductive traits is very large. Therefore, genetic selection for improved daughter fertility is possible in dairy cattle. The problem is that there are negative genetic correlations between daughter fertility and milk yield. Scandinavian breeding programs include functional non-production traits (fertility, mastitis resistance, etc.) in addition to production traits in their selection indices for total merit (Philipsson et al., 1994). Although progress toward greater milk production may be less, their models suggest better economic efficiency when functional non-production traits are included in selection programs.

Pharmacological intervention

The dairy industry has very few tools for the pharmacological control of the estrous cycle and there is a desperate need for new methods and new tools for estrous cycle control. The best way to reverse current declines in reproduction is to intensively manage the reproductive biology of the dairy cow. Anestrus is difficult to manage in the United States because anestrous cows do not respond to PGF_{2α} and progestogens are not approved for use in lactating dairy cattle. This represents a severe limitation to reproductive management, especially considering the high incidence of anestrus in modern dairy cows. Most producers in the United States would welcome the approval of a progestogen for lactating dairy cows. The use of progestogens for treatment of anestrus is an obvious management strategy that should be employed once approved.

Most dairy cows are either untreated (inseminated at spontaneous estrus), treated with biweekly injections of PGF_{2α} followed by estrous detection, or enrolled in a timed AI program. Insemination at spontaneous estrus and the use of PGF_{2α} and estrous detection are good, but suffer from the age-old problem of detecting cows in estrus. Combining regular PGF_{2α} injections with some type of estrous detection aid (tail chalk, patches, electronic devices, etc.) improves the overall response, but requires additional management and attention to details. Timed AI for insemination of dairy cattle is an important change in reproductive management because cows are inseminated without estrous detection. Timed AI is a good approach but rates of embryonic loss after timed AI are high and calving rates for dairy cows after timed AI are 25 to 35%. Therefore, there is still a need to optimize methods for timed AI of dairy cattle.

Synchronization of reinsemination

Timed insemination and regular PGF_{2α} injections are good ways to control the time of first insemination. Only 25 to 35% of dairy cows, however, will be pregnant after first insemination. The fate of the 65 to 75% of dairy cows that are open after first insemination usually depends on detecting the return to estrus after pregnancy failure. The timing of second estrus after insemination is variable because many cows have an embryo that dies around the time

of maternal recognition of pregnancy and the normal luteolytic mechanisms are delayed. Other cows failed to respond to the initial synchronization and are completely *out-of-synch* with the group. The fact that inseminated cows represent a mixture of pregnant and nonpregnant cows and that nonpregnant cows have a variable return to estrus complicates methods that can be used to synchronize second service.

Unfortunately, very few reliable methods are available for synchronizing second service in United States dairy cattle. A hormonal approach involving a progesterone insert, estradiol benzoate injection, and PGF_{2α} injection was developed in Australia for the purpose of synchronizing three inseminations in a 56-day period (Cavalieri and Macmillan, unpublished). Similar methods need to be developed for United States dairy cows.

Conclusions

Cows selected for high milk production partition nutrients toward lactation. The partitioning of nutrients leads to cows with less adipose tissue mass (lower body condition) and greater infertility. For the immediate future, the best approach to improve reproductive rates will be to intensively manage the reproductive biology of the cow. This management should include treatment of anestrus with progestogens, synchronization of first service, and resynchronization of second and third services. In the longer term, a genetic approach that incorporates reproductive and health traits in selection indices will correct some of the reproductive decline. It is also likely, that continued research in the area of postpartum reproduction of dairy cattle will reveal critical control points that can be manipulated to improve reproductive efficiency in dairy cattle.

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