

Fertility in high-producing dairy cows: Reasons for decline and corrective strategies for sustainable improvement

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The fertility of dairy cows has declined worldwide and this change is surprising given the importance of good fertility to the dairy industry. The decline in fertility can be explained by management changes within the dairy industry and also negative genetic correlations between milk production and reproduction. Four primary mechanisms that depress fertility in lactating cows are anovulatory and behavioral anestrus (failure to cycle and display estrus), suboptimal and irregular estrous cyclicity (this category includes ovarian disease and subnormal luteal function after breeding), abnormal preimplantation embryo development (may be secondary to poor oocyte quality), and uterine/placental incompetence. The solution for improving fertility in high-producing dairy cows will include both short-term and long-term components. For the immediate short-term, using high fertility sires and implementing controlled breeding programs will help. Controlled breeding programs improve reproductive efficiency in confinement-style dairy herds and can be combined with post-insemination treatments to enhance fertility. An additional immediate short-term solution involves changing the diet so that dietary ingredients invoke hormonal responses that benefit the reproduction of the cow. The short-term solutions described above do not address the fundamental need for correcting the underlying genetics for reproduction in high-producing dairy cows. Crossbreeding will improve reproductive performance perhaps because it alleviates inbreeding and also lowers production in cows with an extreme high milk production phenotype. The current crisis in dairy reproduction will be permanently solved, however, when the genetics for dairy reproduction are improved through a balanced genetic selection strategy.

Introduction

Reproduction is important for sustainable dairying worldwide but reproductive efficiency has declined for dairy cows. Reproductive traits have low heritability so a major component of reproductive decline can be attributed to changes in the dairy industry (larger farms, less-skilled labor, etc.) that make reproductive management more difficult (Lucy 2001). Nonetheless, fertility breeding values for dairy cows have shown evidence of decline since 1957 (Lucy

2005; data from United States dairy cows). The genetic decline in dairy fertility can be explained in part by negative genetic correlations between milk production and reproduction (Hansen 2000). One widely held theory is that the strategic use of adipose tissue for energy and milk substrates in early lactation leads to low postpartum body condition that in turn leads to poor reproductive performance (Lucy 2003; Pryce & Harris 2006). The dissemination of high-milk producing genetics (predominately Holstein) from relatively few sire families led to a global problem in dairy reproduction (Lucy 2001). Reproductive decline is perhaps most acutely felt in seasonal pasture-based systems where non-pregnant cows are not carried over until the next calving season (Harris and Kolver 2001). Confinement-style dairy farmers that practice continuous calving also view reproduction as an area of concern (Lucy *et al.* 2004; Moore & Thatcher 2006).

Reproductive rates are declining in lactating dairy cows but reproductive rates in dairy heifers (non-lactating) remain relatively high. A conception rate of 64% was found when over 330,000 inseminations to over 220,000 United States Holstein heifers were examined (January 2003 to October 2004; Kuhn & Hutchinson 2005). The conception rate is considerably higher than the 20 to 40% conception rate typically reported for lactating cows in the United States. One conclusion from the Holstein heifer data is that the reproductive system of modern dairy cattle is essentially normal when lactation demands are not imposed. Perhaps unexpectedly, however, the same study found a positive association between heifer fertility and daughter pregnancy rate (DPR; the cow fertility trait used in the United States). Subsequent analyses have reported negative genetic correlations between heifer fertility and breeding values for lactation traits (milk, fat, and protein; VanRaden 2006). Failing to address the antagonistic genetic relationship between milk production traits and reproductive traits, therefore, will erode the fertility of both lactating cows and heifers.

Four primary components of infertility in dairy cows

Infertility in dairy cattle is multi-faceted and will require a holistic approach that addresses the problem. The scientific literature on dairy cow infertility is extensive. Indeed, the key words "dairy cow infertility" returned at least twice as many citations when compared to equivalent citations in other farm animals (Fig. 1). Dairy cattle, like any species, have a theoretical optimum for conception rate that is probably above 70% (a conception rate that can be achieved in dairy heifers selected for fertility; Andersen-Ranberg *et al.* 2005). Factors that impinge upon the lactating cow act collectively to decrease conception rate from the optimum (Fig. 2). Four primary mechanisms that depress fertility in lactating cows will be discussed herein. They are anovulatory and behavioral anestrus (failure to cycle and display estrus), suboptimal and irregular estrous cyclicity (this category includes ovarian disease and subnormal luteal function after breeding), abnormal preimplantation embryo development (may be secondary to poor oocyte quality), and uterine/placental incompetence. It is not surprising that reproduction is in decline when one considers that each of these primary components acting alone can cause infertility.

Anovulatory and behavioral anestrus

A period of anovulatory anestrus (ovarian follicular development without ovulation; also termed the anovulatory period) is normal for postpartum cows. In beef cows (considered highly fertile relative to dairy), suckling inhibits LH pulsatility and the lack of LH pulsatility leads to anovulatory anestrus (Williams & Griffith 1995). As long as nutrition is adequate, the anestrus beef

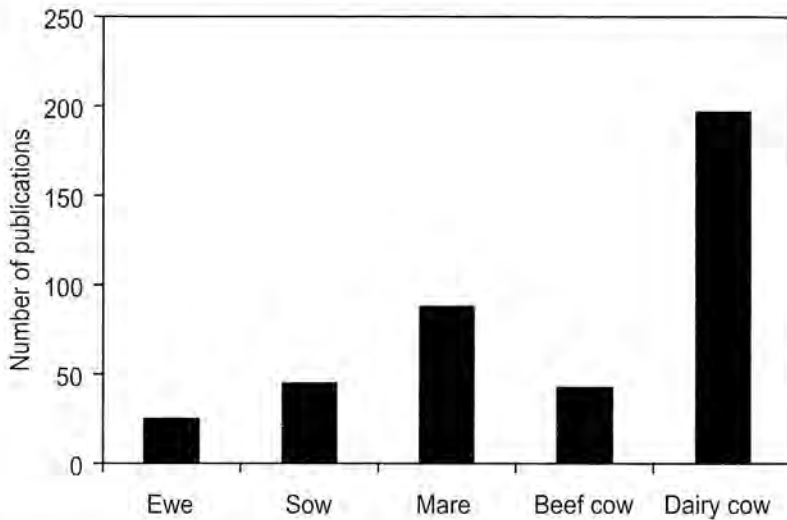


Fig. 1. Number of scientific publications for "infertility" for different farm animal species returned in a June 2006 search of the PubMed scientific citation database (National Center for Biotechnology Information; National Library of Medicine, Bethesda, Maryland, USA).

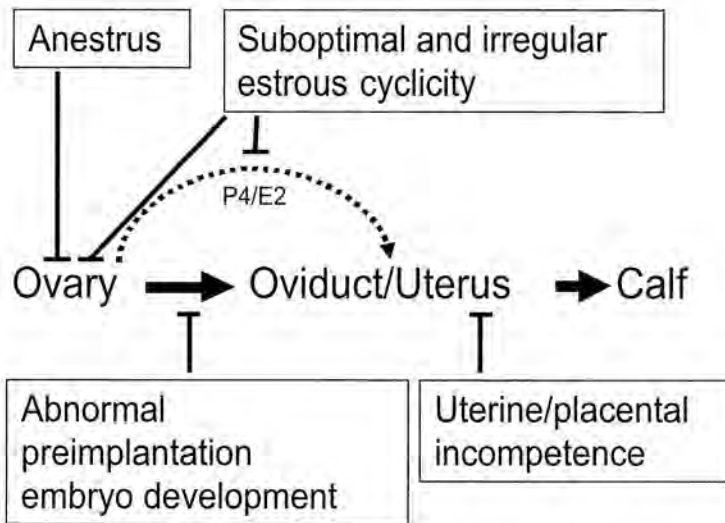


Fig. 2. Four primary components of infertility in dairy cows (light gray boxes) that act at different levels of the reproductive process. The primary components act collectively to inhibit (blunt end lines) ovarian and oviductal/uterine function (see text for details). P4/E2 = progesterone/estradiol.

cow is fertile once she starts cycling (Lucy *et al.* 2001). Likewise, New Zealand dairy cattle (grazing management system) are anestrus for longer than North American dairy cattle (confinement management system) but have better fertility (Meyer *et al.* 2004). Thus, the length of postpartum anovulatory anestrus *per se* may not be a major factor contributing to infertility of cattle unless the anestrus period extends into the breeding period.

High-producing dairy cows have extended periods of anovulatory anestrus (Roche *et al.* 2000; Gong 2002; Lucy 2003). The anestrus is caused by negative energy balance that contributes to a hormonal milieu (low blood LH, insulin, and IGF-I) that is inadequate for preovulatory follicular development, the LH surge and ovulation (Lucy 2003). In dairy cows, anovulatory anestrus is symptomatic of a catabolic state (Beam & Butler 1999). A benign state of anovulatory anestrus in beef cows and low-producing dairy cows is not the same biologically for high-producing dairy cows because the underlying causes of anestrus are different. Although a beef cow can be treated and recover from anestrus with normal fertility (Lucy *et al.* 2001), an anestrus dairy cow that is treated has lower fertility (Gumen *et al.* 2003) perhaps because her anestrus is a consequence of negative energy balance. Anovulatory anestrus can be treated with progestogen supplementation (Wiltbank *et al.* 2002; Rhodes *et al.* 2003). Routine progesterone treatment of anestrus dairy cows has been questioned, however, particularly in New Zealand. McDougall & Compton (2006) found that cows treated for anestrus calved early in the next calving season but failed to retain any advantage during the subsequent breeding period. Treating an anestrus cow and keeping her may only perpetuate the anestrus problem within a herd.

Until recently, behavioral anestrus (lack of estrus behavior for a cyclic cow) was viewed as only occurring at first postpartum ovulation (Inskeep 1995). Otherwise, cows classified as behaviorally anestrus were thought to have had estrus activity but this activity was not observed by humans (failed detection of estrus). Examination of data from electronic mount detectors demonstrated that high milk-producing cows had shorter estrous periods, fewer standing events, and less standing time when compared to low-milk producing cows (Lopez *et al.* 2004). The differences in estrous expression were linked to low blood estradiol concentrations in high-producing dairy cows. Low rates of estrous expression caused by low blood estradiol may explain the popularity of injectable formulations of estradiol for increasing blood estradiol, enhancing estrous expression and promoting ovulation in dairy cows (Moore & Thatcher 2006). The use of estradiol for this purpose is only approved in some dairying countries (Lucy *et al.* 2004).

Suboptimal and irregular estrous cyclicity

Cows with estrous cycle abnormalities have poorer reproductive performance than their normal-cycling herdmates (Hommeida *et al.* 2005; Mann *et al.* 2005; Petersson *et al.* 2006). The prevalence of estrous cycle abnormalities can approach 50% in some herds. Estrous cycle abnormalities are classified into three primary types: 1) extended period of anovulatory anestrus, 2) temporary cessation of luteal phases, and 3) long luteal phases (greater than 20 days). Factors known to affect postpartum cows such as negative energy balance, periparturient disorders, and postpartum diseases are risk factors for abnormal estrous cycles (Opsomer *et al.* 2000). The incidence of twinning and cystic ovarian disease has also increased in modern dairy cattle because there are positive genetic correlations between these abnormalities and level of milk production (Vanholder *et al.* 2006; Wiltbank *et al.* 2006). Lucy (2003) proposed that a common physiological mechanism (low LH pulsatility, low blood growth factor concentrations, and enhanced steroid metabolism) may underlie the increased incidence of anovulatory anestrus, abnormal estrous cycles, and twinning. This common mechanism appears to be a consequence of the hormonal and metabolic state that supports a high level of milk production. Cystic ovarian disease apparently arises through a completely different physiological mechanism because cystic cows have high blood LH activity (Vanholder *et al.* 2006).

There is accumulating evidence that one component of infertility in dairy cows is caused by low blood progesterone concentrations after insemination (Stronge *et al.* 2005; McNeill *et al.* 2006a; Starbuck *et al.* 2006). A slow rise in progesterone delays embryonic development because early

embryonic growth is partially dependent on progesterone perhaps acting at the level of the oviduct or endometrium (Green *et al.* 2005; Mann *et al.* 2006; McNeill *et al.* 2006b). Cows with low progesterone had equivalent blood LH concentrations and *in vitro* steroidogenic capacity when compared to normal cows (Robinson *et al.* 2006). Thus, the corpus luteum (CL) may be normal but its capacity to elevate blood progesterone may be less in lactating cows. The relatively large body size of dairy cows may create a large tissue pool size and steroid metabolism may be greater (Wiltbank *et al.* 2006). The combined effects of pool size and turnover rate may lead to low blood progesterone. The same mechanism may lead to low blood estradiol in high-producing dairy cows (see above).

Abnormal preimplantation embryo development

The metabolic state of high-producing dairy cows may have a direct effect on the oocyte. Snijders *et al.* (2000) found that *in vitro* fertilized oocytes from dairy cows in low body condition had a lower cleavage rate and a lower developmental rate when compared with oocytes from dairy cows in better body condition. Oocyte quality could be improved, however, when low body condition heifers were fed at a high level (Adamiak *et al.* 2005). Sartori *et al.* (2002) flushed the reproductive tract of lactating cows and found fewer cleavage stage embryos when compared to similar flushes in nonlactating cows. Nonesterified fatty acids (NEFA) are released from adipose tissue in early lactation and their concentrations are increased in follicular fluid (approximately 40% of serum concentrations; Leroy *et al.* 2005). The increase in NEFA within follicular fluid may decrease the proliferation of granulosa cells (Vanholder *et al.* 2005) and may also affect the oocyte directly. Both Burkhart *et al.* (2005) (confinement system dairy cows) and McDougall *et al.* (2005a) (pasture system dairy cows) found that high NEFA concentrations were predictive of low fertility postpartum. The addition of NEFA to *in vitro* maturation medium decreased maturation rate, fertilization rate, cleavage rate, and blastocyst yield for *in vitro* cultured embryos (Leroy *et al.* 2005). Collectively the data suggest that early embryonic development is compromised by lactation perhaps through elevated NEFA that enters the follicular fluid and damages the oocyte. Fewer embryos reach the cleavage stage because oocyte quality is low.

If the primary mechanism leading to infertility involves the oocyte or early embryo then embryo transfer should improve conception rates in postpartum dairy cows. Heat stress is known to negatively affect the early embryo, for example, and heat-stressed dairy cows subjected to embryo transfer have a higher conception rate than those inseminated by conventional AI (Hansen *et al.* 2001). Embryo transfer pregnancy rates for dairy cows were increased by greater than 10% over control dairy cows inseminated at estrus in two studies (Demetrio *et al.* 2006; Vasconcelos *et al.* 2006) but a third study failed to demonstrate an effect (Sartori *et al.* 2006). Thus, there is some evidence to support the concept that fertility can be recovered in dairy cows by circumventing the period of oocyte and early embryonic development. The condition of the recipient cow, however, is one factor that can potentially affect the outcome because Mapletoft *et al.* (1986) reported that body condition has a large effect on embryo transfer success (higher body condition score cows have higher pregnancy rates after transfer). Thus uterine environment as affected by body condition plays some role in the fertility of dairy cows.

Uterine/placental incompetence

The uterus of postpartum cows may appear grossly normal but nonetheless fail to support preg-

nancy (Gilbert *et al.* 2005). Failure to support the pregnancy typically manifests itself during the early embryonic period (Santos *et al.* 2004). Embryonic loss was traditionally viewed as occurring during the period of maternal recognition of pregnancy (days 17 to 21 of pregnancy; Thatcher *et al.* 2001). Losses during this early period extended the estrous cycle in inseminated cows but were manageable because cows returned to estrus during the fourth week after AI. Ultrasonography revolutionized pregnancy detection in beef and dairy cattle because pregnancy could be detected as early as day 25 after insemination (about 1 to 2 weeks earlier than manual palpation; Miyamoto *et al.* 2006). Examination of ultrasound data revealed that appreciable numbers of embryos died after the initial pregnancy examination (done between days 25 and 28 after AI; Santos *et al.* 2004). This later period of embryonic loss leads to the "phantom cow syndrome" where inseminated cows fail to return to estrus and are difficult to resynchronize using conventional methods (Cavaliere *et al.* 2005). A likely period for embryonic death may be during placentation (fourth to sixth week of pregnancy) because placentation involves intricate communication between maternal and fetal tissues (King *et al.* 1982). Whether or not the incidence of embryonic loss is greater now than in the past is debated because the capacity to routinely detect early pregnancy in cattle evolved with the use of ultrasound in cattle (after 1984; Pierson & Ginther 1984).

Embryonic loss in modern dairy cattle probably arises from predisposing factors that are common in dairy systems. Dairymen may inseminate cows early postpartum because they are fearful that they will not observe a subsequent estrus. Cows inseminated early postpartum are more likely to have embryonic loss whether they are in confinement or pasture-based systems (McDougall *et al.* 2005b; Meyer *et al.* 2006). Disease is a predisposing factor as well. Gilbert *et al.* (2005) found that 53% of cows had evidence of uterine inflammation (endometritis) at 40 to 60 days postpartum. Cows with endometritis had lower first service conception rates, required more services per conception, and had pregnancy rates at 300 days postpartum that were 26 percentage points lower than cows with a healthy endometrium. Similar effects were observed in pasture-based dairy cows (McDougall *et al.* 2006). A link between mastitis and early embryonic loss has also been established (Chebel *et al.* 2004). The mastitic mammary gland activates immune cells whose inflammatory cytokines adversely affect the ovary and uterus (Hansen *et al.* 2004).

The final predisposing factor for embryonic loss arises from the relatively low body condition of postpartum dairy cows. Several studies have tied high postpartum milk production or low postpartum body condition to early embryonic loss (Grimard *et al.* 2006; Vasconcelos *et al.* 2006). Silke *et al.* (2002) found that embryonic loss after day 28 of pregnancy was highest in cows losing the greatest amount of body condition.

Short-term strategies for increasing fertility in dairy cows

There are both short and long-term solutions for solving dairy infertility. Some short-term solutions have no conceivable drawbacks and should be enacted immediately. Other short-term solutions can be implemented immediately but they are not necessarily sustainable solutions for dairy cow infertility because they may be too expensive, too difficult to enact, or unacceptable in the eye of the public or the dairy farmer. Individual solutions have more or less merit depending on the laws governing dairy production and the economics of the dairy production system.

Using high fertility sires

The importance of semen handling and AI technique to successful reproduction cannot be understated. Assuming that semen is handled properly and placed appropriately within the

female reproductive tract then the next obvious step is to use highly fertile dairy sires. Dairy sire fertility is calculated and published in the United States by the Animal Improvement Programs Laboratory (AIPL; Beltsville, Maryland, USA) as Estimated Relative Conception Rate (ERCR). Dairy sires have inherent differences in fertility that are related to capacitation time and sperm survival in the female reproductive tract (Saacke *et al.* 2000). The ERCR is the estimated deviation from herd conception rate that can be expected with the use of a specific sire (i.e., +4 is four percentage points above herd average, etc.). Given inherent variation in reproductive data, ERCR should only be used for sires with a large number of services. Cornwell *et al.* (2006) used high versus low fertility sires in a timed AI program and demonstrated a tendency for an increase in conception rate when high fertility sires were used (6 percentage point increase; $P = 0.12$). There is little difference in Net Merit (NM\$) for sires that are stratified across a wide range of ERCR (Fig. 3). Thus, it is possible to achieve genetic gain while using sires with superior fertility in an AI system.

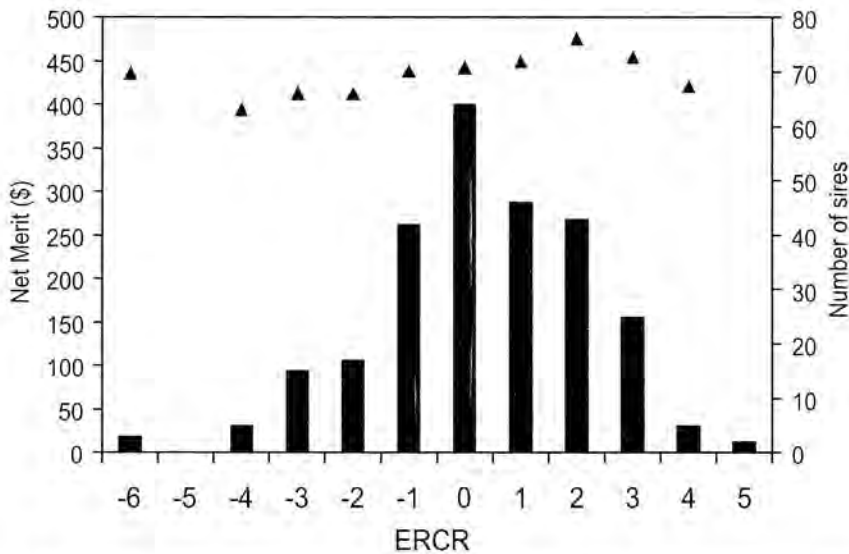


Fig. 3. Average Net Merit (triangle) and number of active artificial insemination sires (bar) for different estimated relative conception rates (ERCR; statistics are for the May 2006 evaluation; Animal Improvement Programs Laboratory; Beltsville, Maryland, USA).

Intensive reproductive management programs (synchronization and resynchronization)

An immediate solution to combat infertility in dairy herds involves intensive management of the estrous cycle and ovulation (estrous synchronization and timed AI). Numerous review articles have been published on the methods that can be used to do this (Diskin *et al.* 2002; Rhodes *et al.* 2003; Lucy *et al.* 2004; Moore & Thatcher 2006). Most approaches employ a method for controlling follicular wave development, promoting ovulation in anestrus cows, regressing the corpus luteum in cyclic cows, and synchronizing estrus and (or) ovulation at the end of treatment. In many dairy herds, cows are inseminated after spontaneous estrus for a predetermined period and then cows that have not been inseminated are managed intensively (timed AI). More intensive approaches to reproductive management involve programmed breeding for all inseminations without any type of estrous detection.

There is variation between countries in availability and regulatory requirements for hormonal treatments used in estrous synchronization. For example, estradiol benzoate is actively used in New Zealand and Australia but is not registered in the European Union or the United States. The only approved estradiol for United States dairy cows (estradiol cypionate) was voluntarily removed from the market by its manufacturer (Pfizer Animal Health). New Zealand and Australia have had intravaginal progesterone releasing devices for use in lactating cows for over 15 years but the devices were only recently approved for United States dairy cattle. In the United Kingdom, PGF_{2α} must be administered by a veterinary surgeon and this requirement makes its routine use too expensive. There is global public concern about the blanket application of hormones to food-producing animals.

Timed AI is popular in large confinement dairies because the benefits of a timed AI system increase under conditions of poor estrous detection rate (Lucy *et al.* 2004). A popular method for timed AI practiced in North American herds is "Ovsynch" (GnRH; wait seven days; PGF_{2α}; wait two days; GnRH; Lucy *et al.* 2004). Cows are either inseminated at the same time as the last GnRH (Cosynch) or 16 to 24 hours after the final GnRH treatment (Ovsynch). In a meta analysis of 53 research papers, Rabiee *et al.* (2005) concluded that conception and pregnancy rates after synchronization programs with estrous detection and after Ovsynch were similar. The Ovsynch program has distinct advantages over estrous synchronization procedures because estrous detection is not required and every cow is inseminated at the end of treatment (100% submission rate). A progesterone-containing device (CIDR) can be added into the Ovsynch program (inserted after the first GnRH and removed after the first PGF_{2α}) and this will improve conception rate in some herds (Stevenson *et al.* 2006). Follicular wave synchronization followed by timed AI is more efficacious when cows are between days 5 and 12 of the estrous cycle. Thus, a pre-synchronization strategy can be employed in which cows are treated with a series of PGF_{2α} injections before the Ovsynch protocol (Thatcher *et al.* 2002). Pre-synchronization improves conception rate after Ovsynch by 5 to 10%.

Cows that are not pregnant after first insemination can be resynchronized for second AI. Progesterone-alone can be used for the purpose of grouping estruses in cows that are not pregnant after first insemination (McDougall 2003). For resynchronization timed AI, the first GnRH injection of Ovsynch can be given to all cows approximately one week before pregnancy diagnosis (Chebel *et al.* 2003). Cows that are subsequently diagnosed non-pregnant can be injected with PGF_{2α} and 48 hours later injected with GnRH before timed AI. An alternative method is to simply start cows back on Ovsynch once they are diagnosed non-pregnant (Sterry *et al.* 2006).

An obvious detraction for pre-synchronization timed AI methods (for example, Presynch-Ovsynch) is that a series of five injections is required and the injections occur over a 45-day period. If a post-insemination treatment is applied (see below) and cows are placed back on a re-synchronization program then a cow that is not pregnant to first insemination (the most-probable outcome) will receive nine injections before her second insemination and a total of ten injections if she is again treated post-insemination (Fig. 4). Assuming a 35% timed AI conception rate, a group of 100 cows would receive 860 injections and achieve 58 pregnancies after two inseminations (about 15 injections per pregnancy). Many managers of large herds feel that scheduling reproductive treatments and inseminations is simpler and more effective than multiple daily sessions of estrous detection. Their approach has merit, given the difficult nature of estrous detection in large herds (Lucy 2001). The example stated above assumes no estrous detection. In reality, North American herds that use Presynch-Ovsynch and re-synchronization typically inseminate any cow that is seen in estrus (essentially terminating the program until pregnancy examination; Stevenson & Phatak 2005).

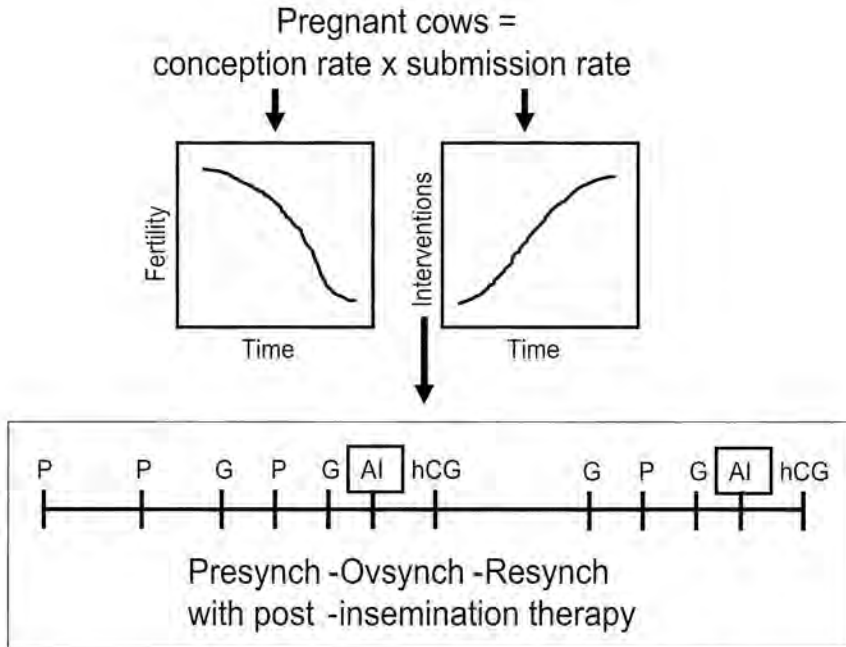


Fig. 4. The number of pregnant cows is a function of conception rate and submission rate. As conception rates (fertility) have declined over time, farmers have increased submission rates by intensive reproductive intervention such as timed AI. An example of a timed AI program is the Presynch-Ovsynch-Resynch program that includes a post-insemination treatment (hCG) to increase fertility. In this system a cow receives six injections before or shortly after first AI (P = PGF_{2a}; G = GnRH). If she is not pregnant for first AI then she will receive four additional injections for second AI. The success rate of the program is about 35% for first AI and somewhat less for second AI so that only 50 to 60% of cows are pregnant after two AI. Repeated hormonal injections that return relatively low pregnancy rates may not be a sustainable option for maintaining fertility on dairy farms.

An average of fifteen injections per dairy cow pregnancy is a troublesome number. A question raised by Macmillan *et al.* (2003), and restated here, concerns the effectiveness of our current programs for estrous synchronization. When is the point of diminishing returns reached? Estrous synchronization and timed AI programs have become the primary method to combat the declining trend in fertility within North American dairy herds. What was once a method to control the estrous cycle and to group cows in estrus is now the only possible means of achieving acceptable submission rates in large confinement dairies. The situation for dairy cows contrasts greatly from that of beef cows where timed AI programs with fewer injections can achieve conception rates above 60% (Schafer *et al.* 2005). Improving the underlying fertility of dairy cattle (see below) may increase pregnancy rates for timed AI in dairy cows and simplify timed AI programs because fewer injections will be needed.

Treating cows after insemination

Treatments can be applied to dairy cows after insemination in an effort to improve fertility. The reader is referred to several recent reviews of the subject (Macmillan *et al.* 2003; Thatcher *et*

al. 2006). There are three primary strategies. The first strategy addresses low progesterone during the first week after breeding. An injection of GnRH or hCG given between days 5 to 8 of the estrous cycle will cause the ovulation of accessory CL in some cows and may also improve CL function (hCG through its LH-like activity). A progesterone-containing device may also be inserted during this period and left in place for approximately one week. The aforementioned treatments may increase progesterone in blood and there is a positive correlation between blood progesterone and fertility (see above). The second strategy involves GnRH treatment later in the estrous cycle. Turning over or ovulating the dominant follicle decreases estradiol and blocks the luteolytic mechanism. Delaying luteolysis will increase the amount of time that the embryo has to signal the mother. In practice, the two strategies described above suffer from herd by treatment interactions where there is a positive response in some herds but not others. The underlying cause of the herd effect is unknown. The treatments may be most-successful when they are applied to lactating cows in low body condition (i.e., targeting cows with the greatest risk of infertility; Thatcher *et al.* 2006). It may be necessary to periodically retest these treatments as dairy cattle continue to evolve in the future. What was not effective in the past may be effective in the future because dairy cows have changed genetically.

The third strategy is the administration of recombinant bovine somatotropin (rbST) around the time of insemination. Recombinant bST is inexpensive in the United States and is approved for the purpose of increasing milk production. An injection of rbST increases blood IGF-I concentrations. Embryonic and uterine tissues typically respond positively to IGF-I (Thatcher *et al.* 2006). Cows with elevated blood IGF-I are more fertile. For example, Taylor *et al.* (2004) reported that dairy cows with blood IGF-I concentrations greater than 50 ng/ml had a five-fold increase in pregnancy rate. Application of rbST at AI has been shown to be efficacious for increasing pregnancy rate for cows inseminated by timed AI and at estrus (Thatcher *et al.* 2006).

Feeding diets that are designed to improve fertility

Developing diets that increase the fertility of dairy cows has always been an attractive option to scientists and farmers. In North American confinement-style herds and in pasture-based systems, farmers have some flexibility in terms of the diets and supplements that they feed. The diet is mixed and fed along a fence-line or in the milking parlor so there is no need to handle individual cows when feeding a specially-designed diet.

Negative energy balance, weight loss, and decreased body condition score occur during early lactation when nutrient requirements for maintenance and lactation exceed the ability of the cow to consume energy in the feed. Cows in negative energy balance have lower blood concentrations of insulin and IGF-I (Lucy 2004). Low blood IGF-I causes reduced negative feedback on growth hormone (GH) and an increase in blood GH concentrations (Lucy 2000). Greater blood GH increases liver gluconeogenesis and promotes lipolysis (NEFA release) from adipose tissue. High blood GH and NEFA concentrations antagonize insulin action and create a state of insulin resistance in postpartum cows. The insulin resistance blunts glucose utilization by non-mammary tissues and conserves glucose for milk synthesis. The cycle described above (low IGF-I, high GH, low glucose, low insulin, and insulin resistance) is gradually reversed during the first 4 to 8 weeks of lactation.

The aforementioned endocrine hormones (insulin and IGF-I) that are metabolically controlled can influence GnRH and LH secretion (Lucy 2003). Insulin and IGF-I can also act directly on the ovary to increase the sensitivity of the ovary to LH and FSH. Postpartum dairy cows are thought to be less sensitive to LH and FSH because their insulin and IGF-I concentrations are low. Although typically thought to affect ovarian function, the insulin/IGF system is clearly resident within the

uterus and embryo (Watson *et al.* 1999). Therefore, insulin and IGF-I may be tied to an effect of body condition on the uterus and embryo.

Roche *et al.* (2006) found that cows with North American pedigrees in a New Zealand system increased milk production (and not body condition) when fed additional energy. Likewise, North American dairy cows consume feed *ad libitum* but nevertheless use all available nutrients for milk production at the expense of body condition (Bauman & Currie 1980). Nutrient partitioning prevents the transition out of the catabolic state because all of the available glucose is consumed, primarily for milk synthesis (Lucy 2004). Feeding more energy may not solve reproductive problems in dairy cows selected for milk production because the cows will partition additional nutrients toward milk production and not toward adipose or reproductive tissues. The metabolic state of low insulin, low IGF-I and elevated GH is maintained despite the higher level of feeding.

Perhaps a more realistic approach to feeding dairy cows for fertility is to provide specific nutrients that are designed to impinge upon the endocrine system of the cow (nutraceutical-type approach). Examples of this include feeding hyperinsulinemic diets (Gong *et al.* 2002) and supplementing with propylene glycol (Miyoshi *et al.* 2001; Butler *et al.* 2006). In each case, blood glucose and insulin concentrations are strategically increased and fertility may be improved because the cow is "tricked" into thinking that she is anabolic. It is also possible to tailor the fatty acid composition of the diet. Feeding polyunsaturated fatty acids may improve reproduction in dairy cows because the $PGF_{2\alpha}$ -synthesizing luteolytic mechanism is attenuated (Mattos *et al.* 2000).

Long-term strategies for increasing fertility in dairy cows

The problems facing reproduction in dairy cattle are not simple. A reversal in the current trends can be achieved only through a variety of approaches. The short-term solutions provided above should be pursued. In the long-term, the current trend in inbreeding needs to be attenuated and cows should be actively selected for improved reproductive efficiency.

Inbreeding in dairy cows

Inbreeding in dairy cattle breeds has increased dramatically since 1980 and may play a role in reproductive decline (Funk 2006). Present levels of inbreeding for United States cows are greater than 5% and continue to increase in most breeds. Inbreeding negatively affects reproductive and longevity traits in dairy cows (Sewalem *et al.* 2006; VanRaden & Miller 2006). One way to correct inbreeding is through crossbreeding. Dairy farmers in New Zealand routinely crossbreed their cows; so much so that crossbred cows may soon outnumber purebred Holstein-Friesian (Harris 2005). Crossbreeding in the United States is practiced by a small number of farmers. The major limitation is that the Holstein breed is superior to all others in terms of milk production. Thus, although there is heterosis for milk production, the crossbred cow produces less milk than the Holstein (Heins *et al.* 2006a). Holstein-Jersey crossbred cows had better fertility than Holstein cows when studied within a university research herd (Heins *et al.* 2006b). In the long-term, it may be necessary to develop multiple lines of dairy cattle with equivalent capacity for milk production so that crossbreeding can be used to maintain genetic diversity and capitalize on heterosis.

Improving dairy cattle genetics for reproduction traits

Genetic selection programs for dairy cattle have capitalized on partitioning nutrients away from adipose tissue. This was not a preplanned strategy of genetic selection (i.e., cows were not pur-

posely selected for low body condition in early lactation) but instead was a consequence of the genetic selection for milk production (the highest producing cows had genetics that supported the low body condition phenotype). The homeorhetic mechanisms that supported the low body condition phenotype were viewed as positive and highly desirable, particularly in the North American system. Low body condition during lactation, however, antagonizes reproduction (Pryce & Harris 2006). Dairy fertility has economic value but how much value does it have relative to the value of milk? Reproduction will not improve if it is undervalued relative to other traits in the selection index but reproduction should not be over-valued relative to other traits simply to correct a perceived problem.

There has clearly been a change in the way we select dairy cattle. A historical examination of the primary selection indices in the United States clearly shows a shift toward longevity and functional traits since the mid-1990's (Fig. 5). The worldwide decline in dairy fertility is being addressed by including fertility traits in selection indices (Lucy 2005). The Scandinavians were the first to do this, and other countries followed in the past decade (Lindhé & Philipsson 1998). It is impossible to capture each of the individual fertility components listed above. Instead, time to pregnancy, i.e. the most meaningful outcome, is measured. The United States has adopted daughter pregnancy rate (DPR) for fertility weightings (VanRaden *et al.* 2004). The DPR is based on days open, i.e. the number of days from calving to conception. A 1% increase in DPR is equivalent to a 4-day reduction in days open. In untreated cattle, the DPR captures cyclicality, expression of estrus and fertility (conception rate), in a single measure. The DPR breeding value for North American Holstein and Jersey cows has declined since 1957 but appears to have stabilized (Lucy 2005). The correlation between DPR and NM\$ for United States dairy sires is nearly zero; meaning that sires at the top of the selection index are neutral for DPR (Fig. 6). There is clearly a negative correlation between DPR and milk traits such as protein yield. Thus, the selection index (that theoretically reflects profitability) may be the best method for selecting future sires because balanced selection does not place reproductive traits at a disadvantage.

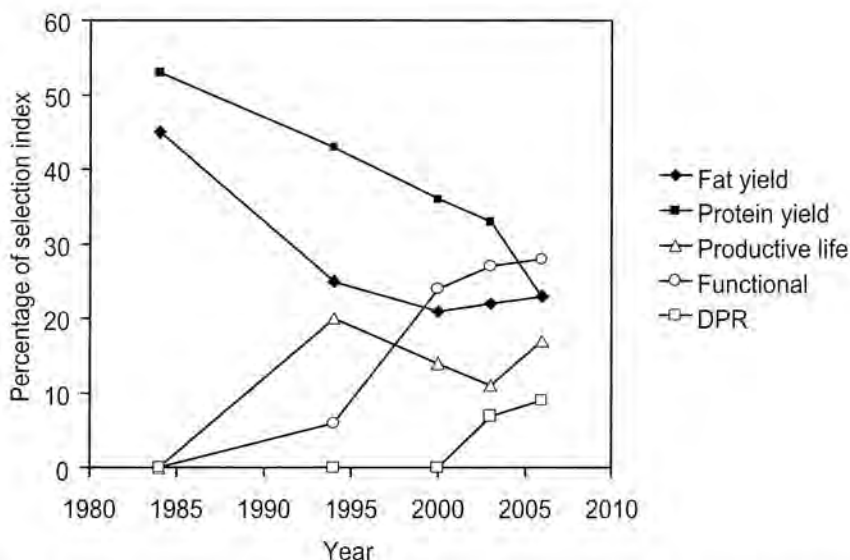


Fig. 5. Relative emphasis of different traits in United States dairy selection indexes (Animal Improvement Programs Laboratory, Beltsville, Maryland, USA). Since 1994, the weightings for fat and protein yield have decreased whereas the weightings for productive life, functional traits (somatic cell score, udder, feet and legs, etc.) and daughter pregnancy rate (DPR) have increased.

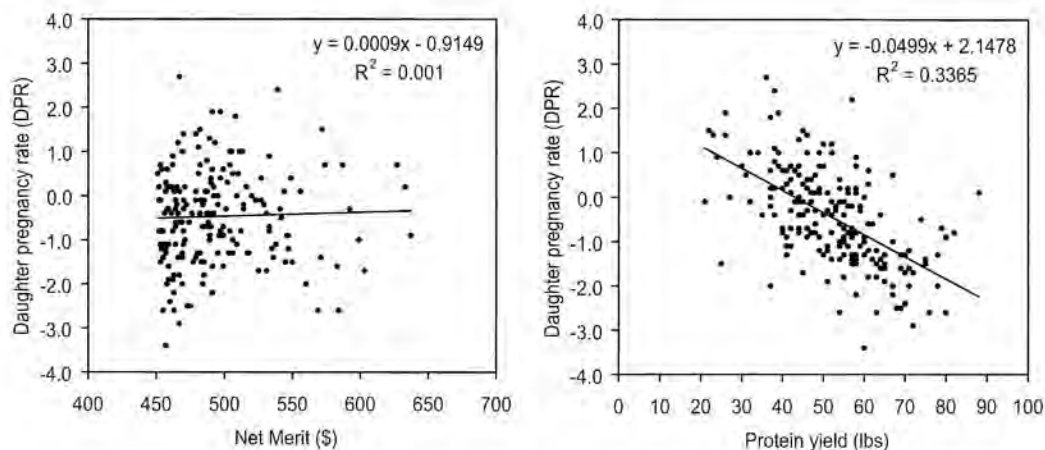


Fig. 6. Regression of daughter pregnancy rate (DPR) on Net Merit (left panel) and protein yield (right panel) for Holstein sires (Animal Improvement Programs Laboratory, Beltsville, Maryland, USA). There is no relationship between DPR and Net Merit. This indicates that DPR does not change across sire rankings within the Net Merit index. Using a single trait such as protein yield, however, clearly leads to lower DPR when the top sires are selected.

Most of the available literature suggests that dairy cattle have a genetically-determined set point for body condition during lactation (Stockdale 2001). Once dairy cows begin lactation, they will migrate toward their body condition set point through the coordinated depletion of adipose tissue. The magnitude of adipose tissue loss does not depend on nutrient demands *per se* but instead depends on the available adipose tissue mass and the genetically-determined set point for the individual cow. There is wide-spread consensus that the genetically-determined set point for body condition during lactation affects the reproductive performance of dairy cows (Berry *et al.* 2003; Pryce & Harris 2006). The lower body condition of modern dairy cows reflects the genetic predisposition to direct nutrients away from body fat during lactation (homeorhetic mechanism that supports milk production).

Since there are strong positive genetic trends between body condition and reproductive performance then selection programs based on postpartum body condition score should alleviate some reproductive loss (Pryce *et al.* 2002). Milk that is made in early lactation could be made in later lactation if selection indices emphasized a persistent lactation instead of a high peak milk yield. This change in emphasis would improve the body condition of cows during the breeding period and could improve reproductive success simply because cows are in better body condition when they are inseminated. There has been little attention paid to residual feed intake (RFI; the difference between an animal's actual feed intake and its expected feed intake based on nutrient requirements; Crews 2005). Such an energetic efficiency measure may have utility particularly when feed has limited availability (pasture systems) or represents a high percentage of costs (confinement systems). If RFI were applied to lactating dairy cows then the RFI calculation would have to account for the milk energy gained from adipose tissue mobilization. Otherwise, cows that lose excessive adipose tissue would have a low RFI but also a low body condition.

Reproductive traits have low heritabilities but the coefficient of variation for reproductive traits is large. Therefore, genetic selection for good fertility is possible in dairy cattle (Weigel

& Rekaya 2000). The current situation with dairy reproduction genetics is not a blind alley. The problem can be corrected without retrenching in terms of milk production. It is, of course, scientifically appealing to predict how dairy cows will change if they are simultaneously selected for both milk production and reproduction traits. The above discussion implies that high fertility cows will have lactation curves that are flatter so that the cow maintains better body condition throughout lactation. An alternative and equally reasonable possibility is that high-producing cows with good fertility will have reproductive systems that function efficiently under conditions of high milk production. There is no biological reason that this cannot occur in as much as some species reproduce naturally under extreme metabolic conditions. For example, Bauman & Currie (1980) described the work of Miescher who in 1880 noted that the reproductive organs of salmon developed extensively during their migration up the Rhine River when 55% of muscle mass was lost. Selection for milk production was done without any preconceived notion as to how it would change the cow. Likewise, genetic selection for reproductive traits should be practiced in the same manner with the sole objective of achieving better fertility through a balanced approach. Simply maintaining current fertility levels may be unacceptable because pregnancy rates are low and the level of reproductive intervention is high on modern dairy farms.

Conclusions

Single-pronged approaches will probably not reverse the current decline in dairy fertility because the underlying causes are multi-faceted and appear to affect the reproductive process at nearly every level. In the short-term, aggressive reproductive management (treatment of anestrus, use of high fertility sires, estrous synchronization and re-synchronization, post-insemination treatments, etc.) should maintain current reproductive rates. Routine treatment of food animals with hormones will likely become a concern to the public so these approaches may become unavailable to farmers. In the United States, for example, we have recently witnessed the removal of a popular estrous synchronization product from the market (estradiol cypionate). Formulating diets to improve reproduction is perhaps a more sustainable option because farmers are used to changing diets to suit their management objectives. A long-term solution is to improve the reproductive genetics of the dairy cow. This includes addressing the potential impact of inbreeding and also reversing the genetic trends that underlie the current pattern of reproductive decline. Although progress toward greater milk production may be less, the cow will be healthier and easier to manage because she will become pregnant more easily.

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