# Relationships of Negative Energy Balance with Fertility

**W. Ronald Butler**

**Department of Animal Science, Cornell University**
**203 Morrison Hall, Ithaca, NY 14853**
**Email: wrb2@cornell.edu**

## 1. Take Home Message

- ➢ Negative energy balance during early lactation is the major nutritional link to low fertility in lactating dairy cows.
- ➢ Negative energy balance delays recovery of postpartum reproductive function and exerts carryover effects that reduce fertility during the breeding period.
- ➢ Feeding, nutrition, and health of lactating cows for improved reproductive performance begins in the transition period and continues through early lactation.
- ➢ Maintain energy intake through the prepartum period to calving and increase intake rapidly thereafter to reduce NEBAL and the detrimental effects on coordinated ovarian and liver function.

## 2. Introduction

Over the last several decades, large increases in milk production capability among dairy cows have been associated with declining fertility. Conception rate in large commercial dairy herds stands at 25 to 40% for mature cows as compared with 65+% in virgin heifers. These differences within a herd indicate that fertility declines with each calving until cows reach maturity.

- Since milk production increases each lactation, what part of the decrease in fertility is due to metabolic effects linked to high milk yield?

The onset of lactation is associated with a prolonged period of negative energy balance (NEBAL) during which energy intake lags behind the energy requirements of rapidly increasing milk production. NEBAL usually begins a few days before calving as intake decreases and becomes visible and apparent during early lactation as loss in body condition. Depending upon the length of the elective waiting period, many cows may still be in NEBAL at first breeding. With regard to fertility to AI, there is a very positive association between conception rate and early commencement of postpartum ovulatory cycles (Butler, 2001). Conception rate increases with successive cycles and this probably is related to improvement in plasma progesterone levels during early postpartum cycles. Together these important relationships have focused concern on the extent of the NEBAL condition that controls the timing of first postpartum ovulation and their effects on fertility later during breeding.

## 3. Resumption of Ovulation in Postpartum Cows in Relation to NEBAL

In considering what factors may affect the ability of cows to become pregnant again in early lactation, it is important to understand that all the organs associated with reproduction must recover from pregnancy and parturition:

### *Ovary*

— The elevated levels of hormones produced in late pregnancy suppress ovarian activity. After calving, full follicle development must be re-established leading to first ovulation and estrous cycles.

— Oocytes carried in the follicles must remain healthy and ovulation must result in fully functional corpus luteum for high progesterone.

***Hypothalamus/pituitary gland***

— The peak of hormone production in late pregnancy suppresses the release of gonadotropins (LH & FSH) and secretion of LH pulses must be reestablished to stimulate development of large ovarian follicles.

***Liver***

— Supports heavy metabolic load (gluconeogenesis, fatty acid oxidation, insulin-like growth factor-I production [IGF-I]).

The recovery of each of these tissue functions is negatively influenced by NEBAL that occurs in periparturient dairy cows (Butler, 2003; Overton, 2001). NEBAL, acting perhaps through the combined metabolic signaling of low blood glucose and insulin concentrations along with elevated nonesterified fatty acids (NEFA), delays increases in gonadotropin (LH and FSH) pulses necessary for stimulation of ovarian follicles. Low blood insulin concentrations are also responsible for low IGF-I production from the liver, which together reduces responsiveness of the ovary to gonadotropins. By way of these various interactions, NEBAL shifts the course of postpartum ovarian activity and strongly influences the resumption of ovulatory cycles. At least one large follicle develops on the ovaries in all cows by 6 to 8 days after calving. What is different among cows is that this first large follicle has three outcomes which determine the variation among cows in days to first ovulation:

a. Ovulation occurs successfully in about 45% of cows around day 20 of lactation.
b. Atresia (death) of the follicle occurs <u>or</u> the follicle becomes cystic and in either case ovulation is delayed an additional 3 to 4 weeks.

Beginning about one week before calving, feed intake (DMI) declines; resulting in NEBAL that will worsen over the next 2 to 3 weeks with the onset of lactation and reach its lowest point (nadir) about two weeks postpartum. The different pattern of changes in NEBAL for cows that ovulate (OV) early after calving and those with delayed ovulation (NOV) is shown in Figure 1. NEBAL results in mobilization of body fat and release of NEFA into the blood. Variation between cows in the extent of NEBAL is directly related to differences in DMI and whether decreases in DMI occur early or late relative to calving (e.g., -9 days vs. -1 day). Body condition score (BCS) is a major cow factor related to decreased dietary intake during the close-up dry period approaching calving. Overconditioning (BCS > 4) greatly increases the risk of metabolic disorders, but loss of BCS during the dry period also increases the risk of retained placenta and metabolic problems (Kim and Suh, 2003; Markusfeld et al., 1997). A recommended management strategy is to maintain moderate BCS (3.25 to 3.5) until calving. Metabolic adaptations to the emerging NEBAL surrounding the onset of lactation are both dynamic and complex with the condition changing daily throughout the transition period.

An emerging issue is that the pattern and timing of decreased DMI before calving is predictive of changes in liver function and other upcoming health disorders. These relationships are shown in Figure 2. In cows with early decline in DMI from day -9, liver release of acute phase proteins (haptoglobin and ceruloplasmin) increased during the same interval, likely as a consequence of cytokine release (Trevisi et al., 2002). Cytokines are usually released during injections and depress intake, but the reason for their release in otherwise healthy cows could not be explained. In a recent preliminary report, DMI was decreased from 1 week before calving in cows with postpartum retained placenta, subclinical endometritis, or fever compared to normal cows (Hammon et al., 2004). The authors suggested that some health disorders are preceded by NEBAL that begins prior to calving. It is well accepted that postpartum health disorders are associated with reduced fertility later during breeding.

During the immediate prepartum period, depressed DMI and endocrine changes result in increased NEFA in blood. The liver extracts NEFA in direct proportion to circulating concentrations and is the major site for further metabolism and processing of NEFA (Drackley, 1999) as follows: 1) intracellular storage as triglycerides; 2) oxidation for energy; 3) partial oxidation to ketone bodies. Accumulation of triglycerides in the liver occurs to some degree in all cows, but is especially problematic in overconditioned cows. Overconditioning interferes with hepatic fatty acid oxidation, thereby contributing to triglyceride accumulation (Murondoti et al., 2004b). Secondly the activity of crucial enzymes for hepatic gluconeogenesis is already decreased before calving (Murondoti et al., 2004a) and contributes to potential metabolic problems.

During the transition period, plasma concentrations of NEFA and â-hydroxybutyrate (BHBA) and hepatic accumulation of triglycerides were higher for cows in which the first dominant follicle failed to ovulate in comparison with cows that had ovulatory follicles (Marr et al., 2002). The strong negative relationship of NEFA and BHBA concentrations indicates that higher circulating levels may act to inhibit follicular estradiol production and ovulation. Potential sites of inhibition are at the hypothalamus on LH pulse frequency and on follicular sensitivity to metabolic stimuli (e.g. insulin and IGF-I). Thus, liver metabolism of NEFA seems to play a central role to the timing of first ovulation.

In postpartum dairy cows the extent of NEBAL is apparent from degree of BCS loss. Cows with more severe NEBAL lose more body condition during the first 30 days of lactation and experience longer intervals to first ovulation. The variation in the degree of NEBAL among individual cows is explained largely by differences in energy intake rather than milk yield (Villa-Godoy et al., 1988; Zurek et al., 1995). Differences in DMI and its regulation are directly related to NEBAL and the timing of first ovulation. NEBAL is minimized in cows that maintain high DMI until the day of calving and rapidly increase their intake thereafter, over the first several weeks of lactation (Butler et al., 2006). It is well established that DMI on day 28 of lactation is directly related to DMI on the day before calving (Grummer, 1995; Trevisi et al., 2002). Figure 3 summarizes the changes in DMI and body weight loss for cows ovulating early after calving (OV) or delayed (NOV).

The importance of DMI is further demonstrated by grouping cows by days to first postpartum ovulation and calculating gross efficiency of milk production. Cows with the lowest efficiency ratio (milk production/DMI) have the shortest interval to first ovulation. Conversely, the most efficient cows (highest milk production compared to DMI) have extended delays to first ovulation (Figure 4). Since the energy efficiency of milk production is similar in all cows, the cows producing more milk per unit DMI have worse NEBAL because more of the energy requirement for milk is coming from body reserves rather than dietary intake. This is an unusual situation where high efficiency is not beneficial because another important aspect, fertility, is negatively affected. The bottom line is high producing cows that better increase DMI to match milk production will have better energy status and likelihood of higher fertility during breeding.

BCS loss during early lactation is paralleled by reduced back fat thickness and decreased muscle mass (Bruckmaier et al., 1998). Mobilization of muscle protein as measured by plasma 3-methylhistidine concentrations was highest during the first week following parturition, but was not related to days to first ovulation (Phillips et al., 2003; Zurek et al., 1995). Although first postpartum ovulation was especially delayed in lean primiparous cows (Meikle et al., 2004), dynamic changes in NEBAL and BCS are more consistently associated with the inhibition of ovulation after parturition than the rate of muscle protein degradation (Beam and Butler, 1999; Butler and Smith, 1989; Zurek et al., 1995).

## 4. Carryover Effects of Early NEBAL on Fertility

Monitoring NEBAL in dairy herds is done by observing changes in BCS. Greater NEBAL/BCS loss during the first 30 days postpartum delays first ovulation (Figure 5). Significant numbers of cows (28 to 50%) remain anovulatory beyond 50 days of lactation and into the breeding period (Stevenson, 2001). Obviously, cows that fail to resume ovulatory cycles are infertile, but even cows with delayed first ovulation will lack the benefit of multiple ovarian cycles and will express lower fertility to insemination. There is strong agreement among many studies that conception rate decreases with increased BCS loss. For example, conception rate decreases about 10% per 0.5 unit BCS loss (see review by Butler, 2001). When the results of 11 large studies were reanalyzed (López-Gatius et al., 2003), low BCS (< 2.5) at first AI extended the days open by 12 days. Comparison of differences in BCS loss during early lactation on average days open was as follows: 0.5 to 1 BCS loss = +3.5 days open; > 1 BCS loss = +11 days open. Cows remaining anovulatory after 50 days of lactation will have a higher risk of not becoming pregnant during lactation and, therefore, are more likely to be culled (Figure 5).

Progesterone is essential for pregnancy after breeding and must be present in blood in adequate amounts to support embryo development and survival (Butler, 2001). The levels of progesterone increase over the first three ovulatory cycles in postpartum cows with less improvement in cows with greater NEBAL (Villa-Godoy et al., 1988). Lower progesterone levels normally observed in high producing cows probably also reflect increased metabolism by the liver. The initial critical period for optimum progesterone influence appears to be days 5 to 7 after insemination, but research attempts at progesterone supplementation after insemination have had mixed success.

Another possible carryover effect of early NEBAL may be that oocytes are imprinted by deleterious conditions within the follicle during their development over a period of 60 to 80 days. Severe NEBAL impaired oocyte developmental competence at 80 to 120 days of lactation, suggesting toxic effects of high periparturient NEFA concentrations (Kruip et al., 2001). Another study found a high incidence of inferior embryo quality and viability in normal, healthy, high-producing cows in early lactation as compared to non-lactating cows (Sartori et al., 2002). While these results support concerns about early NEBAL affecting oocytes, results of another study showed that early embryo development is compromised even later during mid-lactation by the ongoing metabolic effects associated with low BCS (≤ 2.5; (Snijders et al., 2000). Therefore, these collective results indicate a detrimental impact of NEBAL on oocyte competence for embryo development, but metabolic effects are not limited to follicles during early lactation and may be exerted continuously during high milk yield.

## 5. Feeding Strategies Related to the Effects of NEBAL on Fertility

The transition period for dairy cows, from 3 weeks precalving to 3 weeks post calving, is the most critical phase of the lactation cycle, affecting both milk production and reproductive performance. During the transition period, there is a decline in DMI around parturition, mobilization of both body fat and protein, and hormone changes for calving and onset of lactation. As detailed previously, the increases in NEFA from fat stores can lead to liver and metabolic problems. Feeding prepartum diets with higher energy density may offset the negative effects of lower DMI by reducing plasma NEFA concentrations and liver triglyceride accumulation. This idea was tested in a recent study as outlined in Figure 6. The higher energy density diet contained added fat and 32% NFC. The results demonstrate that increased prepartum energy intake provided carryover benefits after calving including improved energy balance, reduced NEFA, and less accumulation of triglycerides in the liver. These effects would all be supportive of good cow health and early first ovulation; however, these items were not reported.

Another recent trial (Frajblat and Butler, 2003) has also considered the effects of adding fat to the prepartum diet as outlined in Figure 7. The inclusion of prilled saturated fatty acids had little measurable effect on DMI or metabolic and hormonal parameters throughout the transition period. The most striking carryover effects of prepartum fat were a reduction in days open for pregnant cows and overall higher pregnancy rate resulting in less culling at end of lactation.

Although more studies need to be done on the effects of feeding supplemental fat to prepartum cows, the results of the two recent studies seem very promising. More work is required to understand whether benefits are simply due to greater energy density or specific type and fatty acid composition of the fat supplements.

## 6. Summary

NEBAL occurring early during lactation delays the timing of first ovulation and exerts other carryover consequences on fertility during the breeding period. These effects include reduced or suboptimum levels of progesterone in blood that influence fertility through alteration of uterine function and inadequate rate of early embryo development. In addition, NEBAL may detrimentally impact the oocyte that is released after ovulation. Reducing NEBAL is beneficial, but very difficult to achieve in cows being managed for high milk yield. Maintaining dietary intake during the transition period is <u>most important</u> for achieving better energy status during the early weeks of lactation. Including fat in the prepartum diet appears useful in formulating higher energy density rations and appears to exert a carryover benefit on pregnancy rate during lactation.

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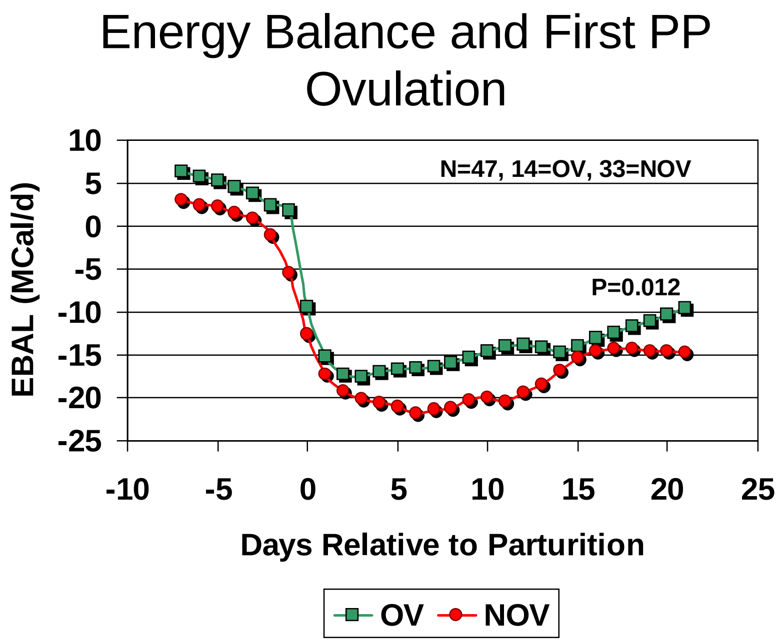


**Figure 1.** Energy balance becomes negative before calving and remains more negative longer in cows with delayed ovulation (NOV) compared to early ovulating cows (OV).

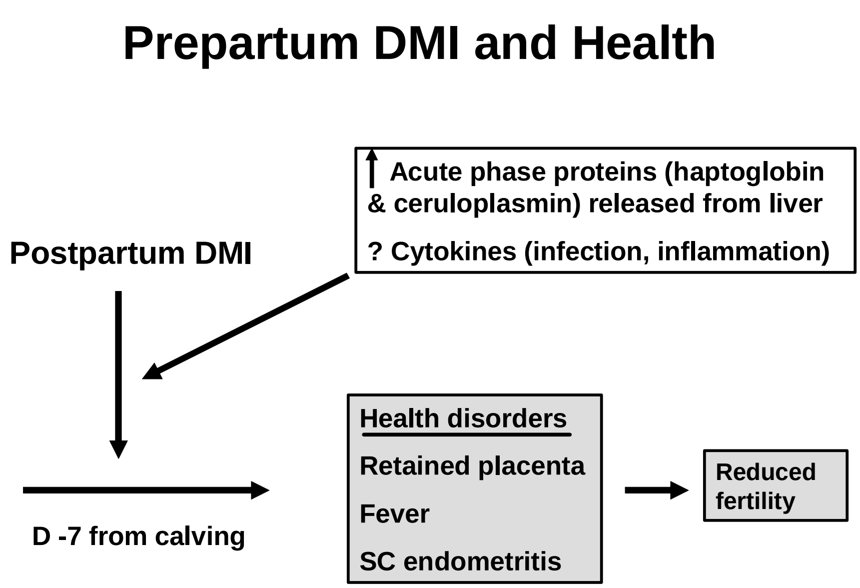


**Figure 2.** Relationships between reduction in DMI before calving and health disorders.

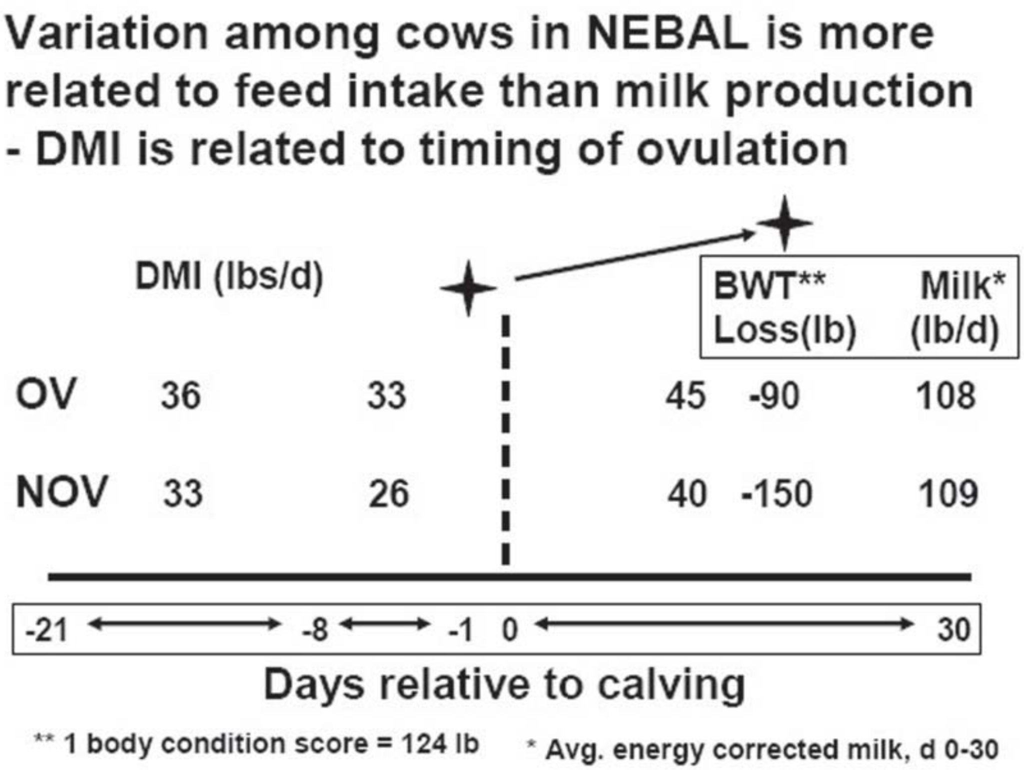


**Figure 3.** Comparison of changes in pattern of DMI and body weight (BWT) for cows with early (OV) or delayed (NOV) ovulation after calving.

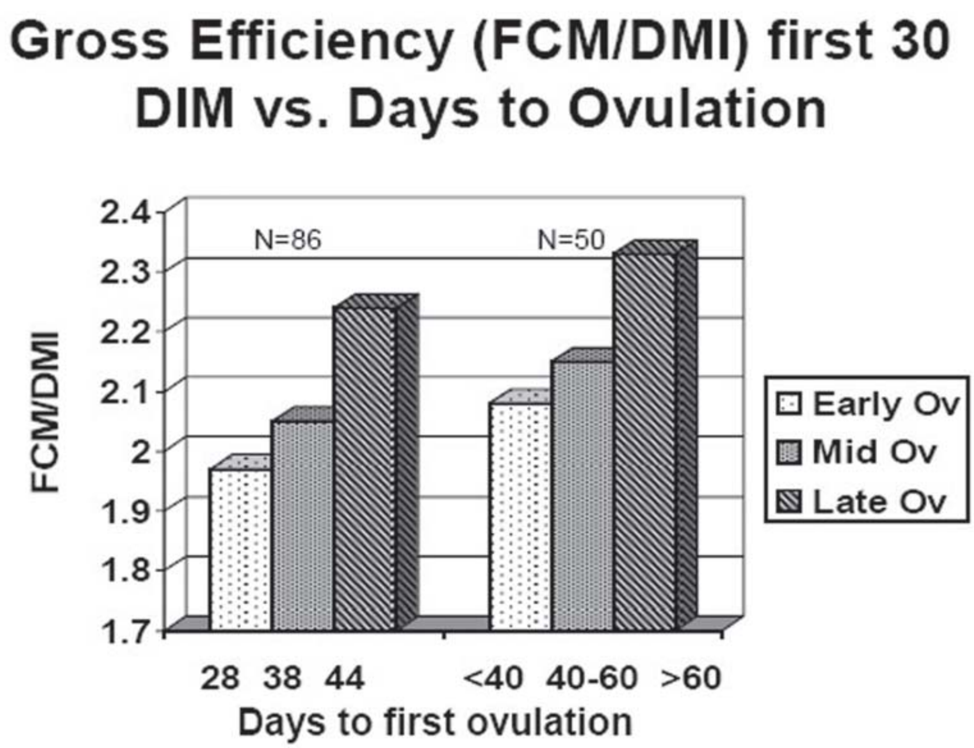


**Figure 4.** Gross efficiency of milk production (fat corrected milk, FCM) compared to feed intake (DMI) in early lactation dairy cows in two studies. Cows were divided into groups by days from calving to first ovulation. Cows with the highest apparent efficiency had delayed ovulation because they were in greater negative energy balance and used more body reserves for energy required to produce milk.

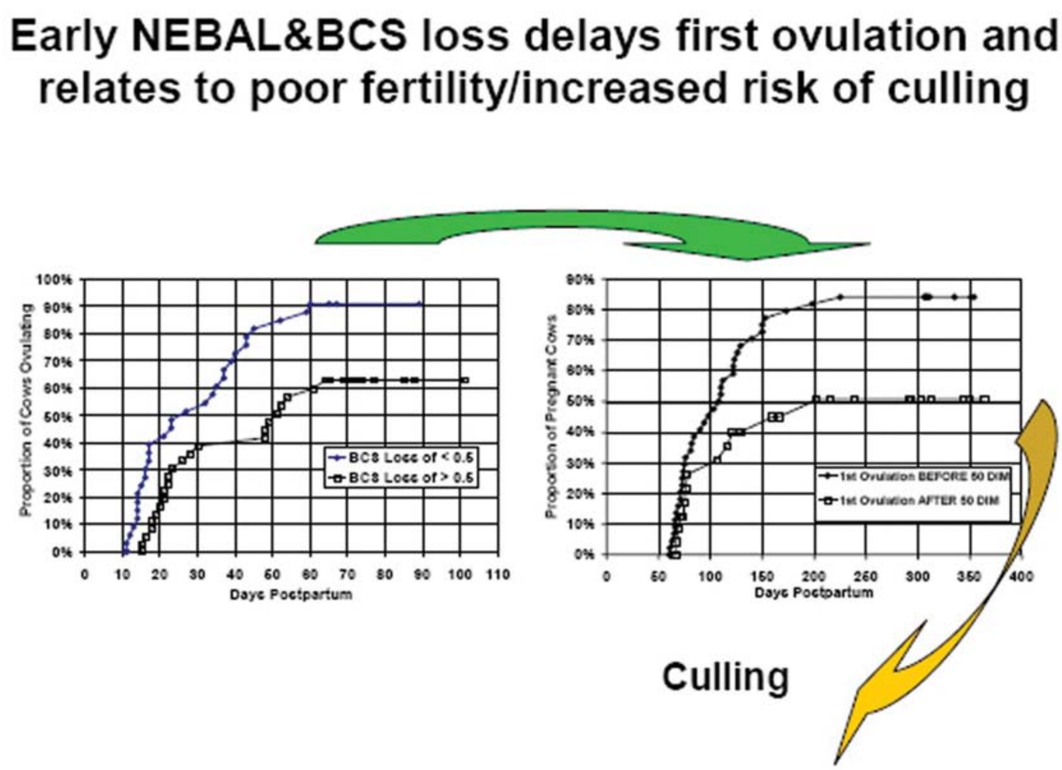


**Figure 5.** Negative energy balance (NEBAL) results in body condition score loss in early lactation dairy cows. Greater BCS loss (> 0.5 score) delays the timing of first ovulation. Among the cows that have delayed ovulation until after 50 days postpartum, pregnancy rate during lactation is reduced and cows remaining open after 200 days are likely to be culled.

## Prepartum energy intake

**Multiparous cows were fed diets from 21 d before expected calving then fed common PP diet.**
**•Energy levels: 1.65 or 1.30 Mcal/kg NEL**
**– High diet had 2.2% tallow**

**Doepel et al., JDS 85:2315, 2002**

| | High vs Low Energy |
|---|---|
| Prepartum DMI | n.s. |
| Postpartum DMI | ↑ |
| EB | ↑ |
| Milk yield | ↑ |
| NEFA | ↓ 354 vs 440 μM/l |
| Liver triglycerides | ↓ |

**Good closeup and fresh cow nutrition to achieve high levels of DMI throughout the transition period should always be the first area of focus!**

**Figure 6.** A research trial was conducted comparing two levels of dietary energy fed to close-up dry cows for the last 21 days before calving. The high energy diet contained higher fat (4.8%) and NFC (34%) and provided beneficial carry-over effects after calving of higher DMI, milk production, and energy balance.

## Prepartum dietary fat

**Multiparous cows (n=81) were fed two diets from 21 d before expected calving and a similar diet postpartum.**

**•Prepartum diets were isoenergetic (2.9 or 4.6% fat) and equal metabolizable protein yielding NEL of 1.48 and 1.53 Mcal/Kg).**

| | High Fat vs. Low Fat |
|---|---|
| Prepartum DMI | n.s. |
| Postpartum DMI | n.s. |
| Postpartum EB | n.s. |
| Milk yield | n.s. |
| Days to I$^{st}$ ovulation | n.s. |
| Days open (average) | 110 vs. 141 |
| Pregnancy rate @ 225 DIM | 86% vs. 58% |

**Figure 7.** A research trial was conducted comparing two levels of dietary fat fed to close-up dry cows for the last 21 days before calving. The diets were designed to be isoenergetic. Cows that had consumed the diet containing supplemental fat expressed higher fertility during lactation.