Nutrition and Reproduction Loss—Can We Feed Our Way Out of It?

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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.
- Maintain energy intake through the prepartum period to calving and increase intake rapidly thereafter in order to minimize negative energy balance.
- Feeding, nutrition, and health of lactating cows for improved reproductive performance begins in the transition period and continues through early lactation.

Introduction

Over the last several decades, large increases in milk production capability among dairy cows have been associated with declining fertility (Figure 1). Conception rate in large commercial dairy herds stands at only 35-40% for mature cows as compared with 51% in first lactation cows or normally 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?
- What nutritional strategies are available to minimize the metabolic effects associated with high milk yield on reproductive performance?

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. 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 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 progesterone profiles during early postpartum cycles (Lucy and Crooker, 2001). Together these important relationships have focused concern on the NEBAL condition controlling the timing of first postpartum ovulation.

Resumption of ovulation in postpartum cows

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

**Ovary** —
1. Re-establishment of full follicular development with ovulation.
2. Healthy oocyte and fully functional corpus luteum- progesterone.

**Hypothalamus/pituitary gland** — Gonadotropins – LH & FSH, pulsatile mode

**Uterus** — Complete involution and lack of inflammation.
Liver – Supports heavy metabolic load (Gluconeogenesis, fatty acid oxidation, insulin-like growth factor-I production).

The recovery of each of these tissue functions is negatively influenced by NEBAL (Butler, 2000; 2001). NEBAL acting perhaps through the combined metabolic signaling of low blood glucose and insulin concentrations along with elevated nonesterified fatty acids (NEFA) and ketones delays increases in LH pulses necessary for stimulation of ovarian follicles (Figure 2). Low blood insulin concentrations are also responsible for low IGF-I production from the liver (Butler et al., 2003), which together reduces responsiveness of the ovary to gonadotropins. Low or delayed production of ovarian steroids, estradiol from follicles and progesterone after ovulation, slows the rate of involution and recovery of normal uterine function. 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 6-8 days postpartum. 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 as shown in Table 1. More detailed description of the regulation of postpartum ovulation is reviewed elsewhere (Beam and Butler, 1999).

Beginning about one to two weeks before calving, feed intake declines (Hayirli et al., 2002b) resulting in NEBAL that will worsen over the next 2-3 weeks with the onset of lactation and reach its lowest point (nadir) about two weeks postpartum. NEBAL results in mobilization of body fat and release of NEFA into the blood. 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). Increasing body condition score (BCS) is a major cow factor causing decreased dietary intake during the close-up dry period approaching 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.

During the immediate prepartum period, depressed feed intake and endocrine changes result in NEFA mobilization from adipose tissue. The liver extracts NEFA in direct proportion to circulating concentrations and is the major site of further metabolism and processing of NEFA as follows: 1) esterification and secretion as very-low density lipoproteins; 2) esterification and intracellular storage as triglycerides; 3) complete oxidation to CO2; 4) partial oxidation to acetate or ketone bodies. During the transition period, plasma concentrations of NEFA and B-hydroxybutyrate (BHBA) and hepatic accumulation of triglycerides were higher for cows in which the first postpartum 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 with ovulatory status of the DF 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 (eg. insulin and IGF-I). Thus, liver metabolism of NEFA seems to play a central role in relation to the timing of first ovulation.

**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 3). Significant numbers of cows (28-50%) remain anovulatory beyond 50 days of lactation and into the breeding period (Staples et al., 1990; 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%/0.5 unit BCS loss (see review by Butler, 2001). Cows remaining anovulatory after 50 days of lactation will have a higher risk for not becoming pregnant during lactation and, therefore, of being culled (Figure 4).

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 reflects
increased metabolism by the liver (Lucy and Crooker, 2001; Sangsritavong et al., 2002). The initial critical period for optimum progesterone influence related to conception appears to be days 5-7 after insemination (Butler et al., 1996). The successful maternal recognition of pregnancy depends on the presence of a sufficiently well developed embryo producing sufficient quantities of interferon-α, which in turn, is dependent on appropriate stimulation by circulating progesterone concentrations (Mann and Lamming, 2001).

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 60-80 days (Britt, 1991). Severe NEBAL impaired oocyte developmental competence at 80-120 days of lactation suggesting toxic effects of high periparturient NEFA concentrations (Kruip et al., 2001). Another study conducted in normal healthy high-producing cows in early lactation also demonstrated inferior embryo quality and viability (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 ongoing metabolic effects associated with lower BCS (<2.5) in high genetic merit cows (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 follicular development during early lactation and may be continuously manifested during high milk yield.

In summary, NEBAL during early lactation delays the timing of first ovulation and exerts delayed carryover consequences on fertility during the breeding period. These effects include reduced or sub-optimum 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.

**Dietary protein intake and reproductive performance**

Dietary strategies for meeting the nutritional requirements of high producing dairy cows have been adjusted in response to genetic gains in milk yield. Diets high in crude protein (17 to 19%) are typically fed during early lactation to both stimulate and support high milk production. Feeding high protein diets does not appear to have a strong impact on the re-initiation of ovulatory activity in postpartum cows; however, high protein diets have been associated with reduced reproductive performance (Butler, 1998; Westwood et al., 1998).

The intake of high dietary protein can result in elevated blood concentrations of ammonia, urea, or both, depending upon the balance of protein fractions present in the rumen and the availability of fermentable carbohydrates. Increased plasma or milk urea nitrogen concentrations are highly correlated with decreased fertility in cows (Butler, 1998; Westwood et al., 1998; Wittwer et al., 1999). Plasma urea is inversely related to uterine luminal pH and sequential measurements in lactating cows have demonstrated that uterine pH is dynamically attuned to changes in plasma urea with a time lag of several hours (Butler, 1998). Successful embryo development depends upon the nature of the uterine environment. The uterine luminal milieu is dynamic and exhibits marked differences between the stages of the estrous cycle as a consequence of ovarian steroidal regulation of endometrial secretion. Intake of high protein diets by lactating cows has been shown to alter the pH and the concentrations of other ions in uterine secretions, but only during the luteal phase and not at estrus. As a result of feeding high protein, increased plasma urea concentrations may interfere with the normal inductive actions of progesterone on the microenvironment of the uterus and, thereby, cause suboptimal conditions for support of embryo development (Butler, 2001).

*In vitro* studies of bovine endometrial cell cultures have shown that urea alters both the pH gradient across the polarized cells and increases secretion of prostaglandin F2α that may interfere with embryo development and viability (Butler, 1998). Embryo quality and development was reduced in lactating cows fed excess rumen degradable protein (Butler, 1998; Bode et al., 2001), but embryo transfer and superovulation experiments in beef heifers found no detrimental effect of high dietary crude protein (urea) on embryo viability, fertilization rate, or embryo quality (Gath et al., 1999). Since the energy balance status of the dairy and beef cattle were different, the effects of high dietary protein in lactating cows may exacerbate metabolic or hormonal mediated processes that would result in impaired embryo development. For example, the long-term effect of NEBAL might be to impair the health of preovulatory oocytes and follicles and reduce progesterone concentrations.
after ovulation (Britt, 1991), in addition to which some aspect of protein metabolism would further compromise successful embryo development. Additional research on the interactions of energy balance and dietary protein metabolism that may impact embryo developmental processes should further aid our understanding of poor fertility in high producing dairy cows.

Overall, the interactions of nutrition on reproductive performance in dairy cattle involve the most important dietary components, energy and protein, and their adequacy relative to requirements for high milk yield. The observed decline in fertility may be attributed to the combined effects of a uterine environment that is dependent on progesterone, but has been rendered suboptimal for embryo development by antecedent effects of negative energy balance and can be further compromised by the effects of urea resulting from intake of high dietary protein.

What nutritional strategies are available to minimize the metabolic effects associated with high milk yield on reproductive performance?

Due to NEBAL that begins prepartum, mobilization of body fat as NEFA results in accumulation of triglycerides in the liver that can impair important functions such as glucose synthesis (Overton, 2001). Ketone levels in blood are also increased. Both hepatic triglyceride accumulation and increased blood ketones are associated with delayed first postpartum ovulation. Regardless, managing the transition cow to reduce fat mobilization and to increase metabolism of NEFA for improved metabolic health also benefits the recovery of ovarian activity after calving. A WIN-WIN situation!

- Maintaining energy intake to minimize NEBAL is a major aspect of nutritional modulation of the reproductive system. Since BCS is a major cow factor decreasing dietary intake during the closeup period, use feeding management of dry cows to achieve neither gain nor loss in body condition and a score of 3.25 to 3.5 at calving. Feeding a higher energy ration (34-36% NFC) for 3 weeks prepartum is recommended (NRC 2000; Doepple et al., 2002) and improves both pre- and postpartum dry matter intakes. Energy availability determines insulin secretion that inhibits lipolysis (ie. minimizes NEFA). Improving energy metabolism and insulin availability during the transition period and early lactation improves liver function, cow health, and subsequent fertility (Duffield et al., 2002; Hayirli et al., 2002a; Gong et al., 2002; Westwood et al., 2002). Good closeup and fresh cow nutritional programs to achieve high levels of dry matter intake throughout the transition period should always be the first area of focus, but further metabolism research and dietary recommendations are needed as NEBAL problems remain. Quite often short -term measures such as providing glucogenic precursors (propylene glycol, glycerol) are employed. Propylene glycol must be drenched to be effective in reducing NEFA and ketones and although labor intensive, improved ovarian activity has been reported (Formigoni et al., 1996; Miyoshi et al., 2001).

- Reducing NEBAL is beneficial, but very difficult to achieve in cows being managed for high milk yield. Supplemental dietary fats have been proposed as a means to increase dietary energy density and improve energy status during the period of low intake in early lactation, but have generally been unsuccessful. Feeding fats after 30 days of lactation has been beneficial on reproduction in a number of studies (Staples et al., 1998). The benefit on fertility may be due to lipids reducing the metabolic clearance rate of progesterone by the liver (Hawkins et al., 1995) or to effects on fatty acid metabolism in tissues.

- Feed unsaturated fatty acids to manipulate uterine fatty acid composition and prostaglandin production. A high proportion of embryonic losses in establishment of early pregnancy in cattle is coincident with the period of embryonic inhibition of uterine prostaglandin F2a (PGF2a) secretion (day 15-17), suggesting that some losses may be occurring because certain embryos are unable to inhibit secretion of PGF2a. Therefore, strategies to further inhibit secretion of PGF2a may result in increased embryonic survival and pregnancy rates. Fish meal contains oil (8% of DM) with relatively high concentrations of two long chain polyunsaturated fatty acids (PUFA) of the n-3 family, eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6) that in the uterus act to reduce synthesis of PGF2a (Mattos et al., 2002). PUFA such as linoleic, linolenic, EPA, and DHA may inhibit uterine PGF2a synthesis through mechanisms such as decreased availability of the precursor arachidonic acid; increased competition by
these fatty acids with arachidonic acid for binding to prostaglandin H synthase (PGHS); and inhibition of PGHS synthesis and activity (Mattos et al., 2000).

The production of endometrial prostaglandins is mainly governed by the rate-limiting enzyme cyclooxygenase (COX-2), a component of PGHS. COX-2 mRNA and protein were expressed at low and high levels on Days 1–12 and 13–21 of the estrous cycle, respectively (Arosh et al. 2002). The most potent COX-2 inhibitor was EPA followed by DHA (Ringbom et al., 2001). Evidence for the incorporation of dietary fatty acids such as EPA and DHA into uterine lipids has been reported by Burns et al. (2000). Inhibiting uterine secretion of PGF2α by feeding EPA and DHA (Burke et al., 1997; Staples et al., 1998; Mattos et al., 2000) may prevent regression of the corpus luteum in concert with the actions of embryonic interferon- (Thatcher et al., 2001) and increase pregnancy rates.

Goals for nutritionally managing postpartum reproductive issues

- Maintain energy intake through the prepartum period to calving and increase intake rapidly thereafter.
  - reduces NEBAL and the detrimental effects on coordinated ovarian and liver function
  - reduces BCS loss, effects of NEFA on oocytes and liver, and delay to first ovulation
- Selectively incorporate fats into lactating cow rations to enhance steroid concentrations and to target decreased uterine prostaglandin production.

References


Table 1. Onset of postpartum ovarian follicular activity and first ovulation.

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<thead>
<tr>
<th>Outcome</th>
<th>Incidence</th>
<th>Days to Ovulation</th>
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<tbody>
<tr>
<td>Ovulation</td>
<td>45%</td>
<td>20</td>
</tr>
<tr>
<td>Regression/Atresia</td>
<td>35%</td>
<td>51</td>
</tr>
<tr>
<td>Cystic</td>
<td>20%</td>
<td>48</td>
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Figure 1. The inverse relationship between conception rate (CR) and annual milk production of Holstein dairy cows in New York.

Figure 2. Negative energy balance inhibits recovery of the reproductive system after parturition.
Figure 3. Body condition score loss delays first ovulation in lactating dairy cows.

Figure 4. Delayed first ovulation until after 50 days in milk decreases pregnancy rate during lactation.