

THE ROLE OF ENERGY BALANCE AND METABOLISM ON REPRODUCTION OF DAIRY COWS

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INTRODUCTION

Over the last several decades, large increases in milk production capability among dairy cows have been associated with declining fertility. Conception rate now stands at 40% in dairy herds in the eastern USA (Butler, 2003; DHI Raleigh Center, 2012).

In high genetic merit cows, feed intake and energy balance begin decreasing prepartum that results in mobilization of body fat as nonesterified fatty acids (**NEFA**) in blood (Butler et al., 2006). The onset of lactation after calving 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 and consequently delays ovarian cycles.

With regard to fertility to AI, there is a strong positive association between early commencement of postpartum ovulatory cycles and pregnancy during lactation (Butler, 2000; Galvao et al., 2010). This important relationship has focused research attention on the regulation and re-initiation of ovarian activity and ovulation in early lactation prior to the breeding period. Energy balance, re-initiation of ovarian activity, and metabolic health status are inter-connected in transition dairy cows.

ENERGY BALANCE RELATED FACTORS AFFECT RESUMPTION OF OVARIAN ACTIVITY IN TRANSITION COWS

Relationships during the Transition Period

The transition period extends from 3 weeks before calving through the first 3 weeks of lactation. During late pregnancy elevated plasma levels of steroid hormones (estradiol and progesterone) suppress the release of pituitary gonadotropins (LH and FSH) and ovarian follicular activity. Following calving, steroids are reduced and increased secretion of FSH and LH pulses become re-established to stimulate development of large ovarian follicles and ovulatory ovarian cycles. With the onset of lactation, the liver must support a heavy and rapidly increasing metabolic load for glucose production and fatty acid oxidation and processing. The liver also plays an important role as the primary source of insulin-like growth factor-I (**IGF-I**) that stimulates development of ovarian follicles. The functional activity of the ovary and liver is negatively influenced by NEBAL (Butler, 2003; Overton, 2001).

Negative energy balance, acting through the combined metabolic signaling of low blood glucose, insulin and IGF-I concentrations along with elevated NEFA, β -hydroxybutyrate, and liver accumulation of triglycerides delays the increases in LH and FSH necessary for stimulation of ovarian follicles, estradiol production, and ovulation (Butler et al., 2006). Low blood insulin concentrations are responsible for low IGF-I production from the liver (Butler et al., 2003) which together reduce responsiveness of ovarian follicles to gonadotropins. Physiologically the metabolic and gonadotropin signals controlling early follicle development are interrelated: FSH stimulates granulosa cells in follicles to develop receptors for insulin, growth hormone and IGF-I; insulin and IGF-I then provide the hormonal stimulus for full development of preovulatory ovarian follicles (Beam and Butler, 1999; Kawashima et al., 2007; Kawashima et al., 2012; Shimizu et al., 2008; Sudo et al., 2007).

By way of various metabolic factors, interactions and responses, 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 dairy cows by 6-8 d after calving. What is different among cows is that this first large follicle has 3 outcomes which relate to the variation among cows in days to first ovulation:

- a) Ovulation occurs successfully in about 45 % of cows by around d 20 of lactation;
- b) Atresia (death) of the follicle occurs; or
- c) c) The follicle becomes cystic.

In either case of b *or* c, first ovulation is delayed at least an additional 3-4 wk (Beam and Butler, 1999; Butler et al., 2006).

Prepartum Differences in DMI, Energy Balance and Metabolic Hormones Associated with Postpartum Ovarian Follicle Outcome

Following calving, ovarian follicle development in dairy cows was monitored for determination of ovulatory or nonovulatory outcome and for comparison, retrospectively, with differences in prepartum DMI, energy balance, and metabolic hormone profiles (Butler et al., 2006). The main difference between ovulatory or nonovulatory follicles is their capacity to produce large amounts of estradiol. As early as 3 weeks prepartum, the nonovulatory low estradiol cows would have lower DMI, energy balance, and plasma concentrations of insulin and IGF-I. The NEBAL was more severe for nonovulatory cows and NEFA concentrations were higher. Overall, 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. As reported previously, DMI on d 21 of lactation is directly related to DMI on the day before calving (Grummer, 1995). Figure 1 summarizes changes throughout the transition period in DMI, milk production, and body weight loss ie. NEBAL for cows ovulating (**OV**) early after calving or with nonovulatory follicles (**NOV**).

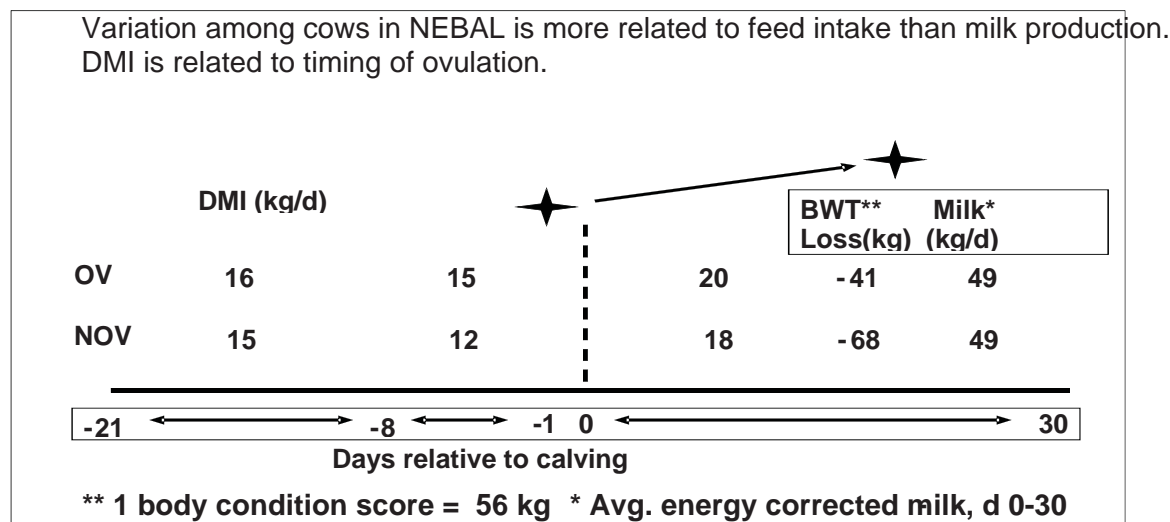


Figure 1. Comparison of changes in pattern of DMI and body weight (BWT) for cows with early (OV) ovulatory or nonovulatory (NOV) follicles after calving. + DMI d -1 is highly correlated to DMI at d 21.

Prepartum Decreases in DMI and Energy Balance Associated with Postpartum Health Problems that Impact Fertility

Over the past 10 years, it has become clear that prepartum declines in DMI and increased NEFA associated with delayed early ovulation also predispose cows to health problems after calving. Already one to two weeks prepartum, cows that would later develop uterine disease had lower DMI, higher NEFA, and decreased function of immune cells (neutrophils or **PMN's**) as compared to cows that remained healthy (Hammon et al., 2006). Thus, the decrease in PMN function and energy balance occurred prior to parturition and uterine health disorders. The negative effect of increased NEFA on PMN function is confirmed (Ster et al., 2012) and prepartum NEFA concentrations provides an important monitoring tool to assess health risks for retained placenta and metritis (Chapinal et al., 2011). Very importantly, NEFA ≥ 0.27 mEq/L also reduced the risk of pregnancy 19% by 130 DIM (Ospina et al., 2010).

During the transition period, shifts in metabolic profile appear to reflect responses associated with inflammation (Bertoni et al., 2008). Numerous factors can promote inflammation, but oxidative stress is a common initiator of metabolic inflammation and release of cytokines (reviewed by Bradford, 2011). In turn, the resulting inflammation may promote metabolic disorders through decreased DMI and maladaptive changes in liver metabolism of carbohydrates and lipids (Donkin, 2012). Uterine inflammation occurs during normal calving, regardless of whether or not a cow will develop metritis. With the onset of NEBAL, global gene expression and immune response to inflammation is altered in uterine tissue that affects the rate of repair and recovery (Wathes et al., 2009). Failure of complete uterine recovery represented by subclinical endometritis (**SCE**) is characterized by an increased proportion of PMN cells in uterine

fluid at 35-49 DIM. SCE is prevalent in high-producing dairy cows and has been associated with delayed resumption of ovarian cyclicity and extended intervals to pregnancy (Galvao et al., 2009).

NEBAL, DMI AND METABOLIC EFFECTS ON FERTILITY DURING LACTATION

In early lactation dairy cows, the extent of NEBAL is apparent from degree of BCS loss. Cows with more severe NEBAL lose more BCS during the first 30 d of lactation and experience longer intervals to first ovulation (Butler, 2005; Patton et al., 2007). 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) and DMI during the first 28 DIM is positively associated with earlier ovulation (Patton et al., 2007). Interestingly, milk protein % during the first 28 DIM is also related to earlier first ovulation, presumably because it is recognized as an important indicator of energy balance (Patton et al., 2007). 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 2). Since the energy efficiency of milk production is similar in all cows, the cows producing more milk per unit DMI experience more severe NEBAL as more of the energy requirement for milk is derived from body reserves rather than dietary intake. This is an unusual situation where **high efficiency is not beneficial** because delayed onset of ovulatory cycles results in lower fertility. The positive association of DMI during 28 DIM with daily energy balance, early ovulation and fewer days open lead Patton et al. (2007) to identify DMI as the principal component of energy balance influencing subsequent fertility in dairy cows.

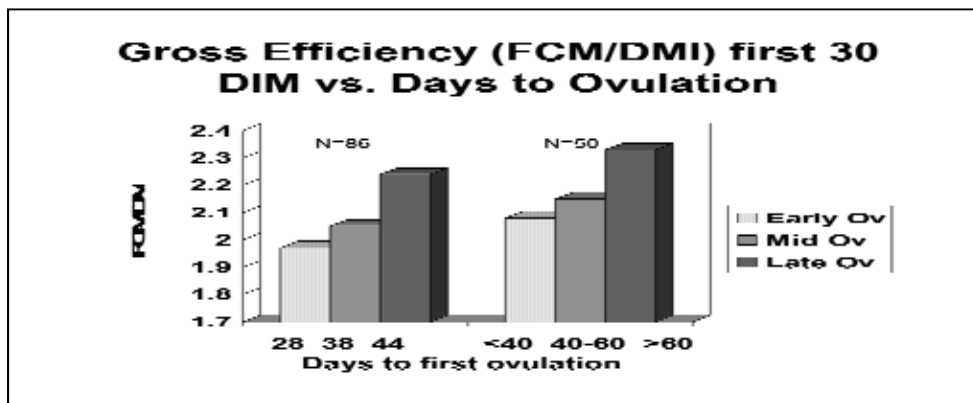


Figure 2. Gross efficiency: kg fat corrected milk (FCM) compared to kg DMI in early lactation dairy cows in two studies. Cows were grouped by days from calving to first ovulation. Cows with high efficiency had delayed ovulation because they were in more severe NEBAL and used more body reserves for energy requirement.

The bottom line - high producing cows that increase DMI to better match requirements for milk production will have better energy status and likelihood of higher fertility during breeding.

CARRYOVER EFFECTS OF EARLY NEBAL ON FERTILITY

Prolonged Anovulatory Periods

Using cows that lose ≤ 0.5 BCS during the first 30 d of lactation as an example, more than 90 % will initiate ovulatory cycles by 60 d of lactation (see Figure 3, left panel). However, by comparison as many as 30-40 % of cows losing more than 0.5 BCS in early lactation may remain anovulatory. Cows remaining anovulatory beyond 50 DIM have increased risk of non-pregnancy by 225 DIM with the consequence of being culled at the end of lactation (Figure 3, Right Panel).

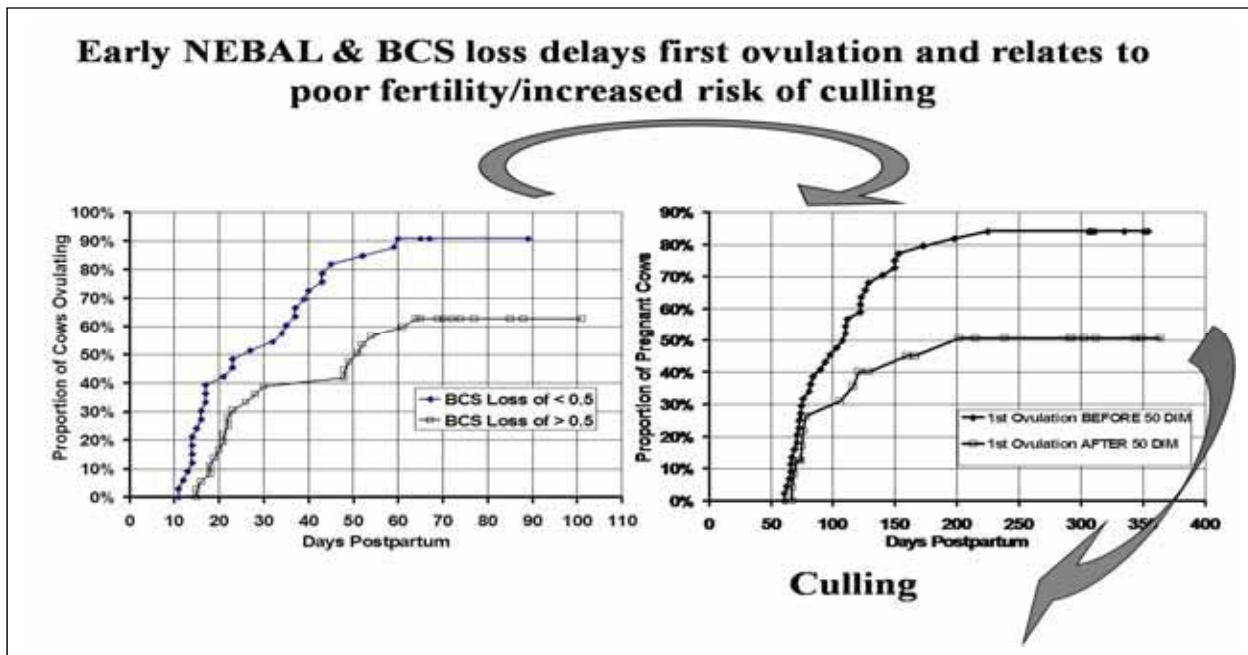


Figure 3: Negative energy balance (NEBAL) results in body condition score loss in early lactation dairy cows. Greater BCS loss (>0.5 score by 30 days in milk) delays the timing of first ovulation. Among the cows that have delayed ovulation until after 50 days postpartum, pregnancy rate during lactation is reduced and cows remaining open after 225 days are likely to be culled. $N = 72$ cows in study

Conception Rate to AI

Delayed ovulation and insemination provides some explanation for the observed low pregnancy rate; however, as loss of BCS becomes more extensive, the reduction in conception rate to AI becomes greater (See Butler, 2003; Roche et al., 2009 for reviews). Cows losing one unit or more BCS (5 point scale) during early lactation are at greatest risk for low fertility (Santos et al., 2009). As a guideline, conception rate

decreases about 10 %/0.5 unit BCS loss (Butler, 2001). Extended calving to conception intervals were associated with low BCS by week +7 and greater peak milk yield (Patton et al., 2007; Wathes et al., 2007).

Oocyte and Embryo Quality

Another possible carryover effect of early NEBAL may be that oocytes are imprinted by deleterious conditions within the follicle during their development period of 60-80 d. Evidence has been reviewed on the metabolic environment during NEBAL that may impair oocyte development and embryo quality (Leroy et al., 2008a; Leroy et al., 2008b). One consequence of more severe NEBAL on fertility is through reduced plasma IGF-I levels. Cows which failed to become pregnant despite multiple AI had low IGF-I in the week after calving and continuing low plasma IGF-I values through the breeding period (Taylor et al., 2004). Another study found a high incidence of inferior embryo quality and viability in normal healthy high-producing cows in early lactation as compared to embryos from non-lactating cows (Sartori et al., 2010). Metabolism associated with high milk production increases the rate of hepatic clearance of progesterone resulting in lower circulating levels compared to those in non-lactating heifers. Progesterone is essential for establishment and maintenance of pregnancy by effects on the oviduct and uterus that regulate embryo development and survival. Plasma progesterone during days 4-7 after AI seems especially important (Clemente et al., 2009; Forde et al., 2011; Lynch et al., 2010). Because of combined metabolic differences, the reproductive tract of lactating cows is less capable of supporting early embryonic development than that in heifers resulting in lower fertility (Rizos et al., 2010).

NUTRITIONAL AND MANAGEMENT STRATEGIES

Dietary Strategies During the Dry Period to Reduce NEBAL and Improve Fertility

Nutritional management of dairy cattle during the dry and transition period have important carryover effects on DMI, health and reproduction in early lactation. This topic area was reviewed at this conference in 2011 (Overton, 2011) and is only highlighted here. During late pregnancy, insulin resistance in adipose tissue contributes to increasing plasma NEFA concentrations and subsequent oxidation of NEFA by the liver is the cause of decreasing DMI as cows approach calving. Studies over the past few years suggest that energy nutrition during the dry period interacts with insulin resistance during the late prepartum period. Excess energy intake not only during the close-up period, but also during the far-off dry period exacerbates insulin resistance. Collectively, these reports indicate that overfeeding energy to dry cows results in changes in metabolism that, in turn, likely predispose cows to decreased DMI and higher NEFA in the periparturient period. Cows with high BCS scores are particularly at risk. Recommendations for energy nutrition of dairy cows during both the far-off and close-up periods have evolved over the past several years toward the goal of meeting, but not markedly exceeding energy requirements *ie.* no more than 110 to 120%. Controlling energy intake via high-bulk diets (containing straw) or moderately restricted feeding

prepartum result in similar metabolic profiles (Janovick et al., 2011), but limit feeding is difficult to manage successfully, especially when cows and heifers are co-mingled in pens with the associated social and behavioral interactions.

Future Opportunities

Currently, there is global interest and widespread research activity toward identifying genetic mechanisms regulating feed intake, feed efficiency, early ovulation and IGF-I production. Such studies seek to relate these characteristics to single nucleotide polymorphisms utilizing the tools of genomic analysis, data records on performance, and genetic selection. As an early example, Fert (+) cows express higher milk yield and higher conception rates to AI, but no difference in feed intake or energy balance (Cummins et al., 2012). Future benefits and opportunities from this type of research will have major impacts.

SUMMARY

Negative energy balance (NEBAL) may begin prepartum in association with declining feed intake. Excess body condition is one factor related to decreased feed intake. During the first 3 weeks of lactation, NEBAL delays early ovulation and recovery of postpartum reproductive function and provides the major nutritional link to low fertility in lactating dairy cows. NEBAL may detrimentally impact the oocyte that is released after ovulation and exert other carryover effects on uterine conditions resulting in reduced conception rate to insemination. Reducing NEBAL is beneficial, but very difficult to achieve in cows being managed for high milk yield. Maintaining intakes through the prepartum period to calving and increasing intake rapidly thereafter reduces NEBAL and the detrimental effects on coordinated ovarian and liver function. Management of feed intake, nutrition, and metabolic health of lactating cows for improved reproductive performance must begin prepartum in the dry period and continue through early lactation.

CONCLUSIONS

- Metabolic changes in periparturient cows associated with onset of NEBAL appear most responsible for the coordinated detrimental effects on metabolic health and reproductive performance.
- Negative energy balance during lactation is related to decreasing feed intake prepartum and delaying early ovulation that reduces fertility during the breeding period.
- Negative energy balance and metabolism during lactation impair postpartum reproductive function via effects on BCS loss, oocyte/embryo quality, and the uterine environment.

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