Inhibition of ovulation in the postpartum cow and the lactating sow

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Abstract

Increased genetic selection and capacity for milk production in dairy cows has been associated with a decline in fertility. Following parturition, nutritional requirements increase rapidly with milk production and the resulting negative energy balance (NEBAL) extends for 8–10 weeks of early lactation. NEBAL delays the timing of first ovulation through attenuation of LH pulse frequency and low levels of blood glucose, insulin and IGF-I that collectively limit oestrogen production by dominant follicles. NEBAL results in mobilization of adipose tissue and loss of body condition score (BCS), which is strongly associated with the length of the postpartum anovulatory period. Failure of ovulation of the first wave dominant follicle is associated with elevated nonesterified fatty acids and ketones in plasma and greater accumulation of triglycerides in the liver during the first 3 weeks of lactation. NEBAL is related to lower fertility in dairy cows both through inhibition of ovulation in early lactation and effects exerted later during the breeding period. Management strategies to minimize the inhibitory effects of NEBAL on first ovulation should begin during the prepartum transition period and include maintaining moderate BCS and energy intake through parturition.

Modern sows have been improved genetically for higher productivity including ovulation rate, litter size and milk production. Peak milk yield is achieved within 10 days after farrowing with consequent massive mobilization of body fat and protein mass. Conservation of body protein mass (<12% loss) during the first lactation minimizes the weaning to estrus interval by advancing ovarian follicular development toward ovulation. The lysine requirement in early lactation is extraordinary. Plasma insulin and IGF-I concentrations seem unrelated to the observed differences in ovarian follicular development. Overall, NEBAL inhibits ovulation in both high producing cows and sows, but there are species differences in response to protein losses and hormonal interactions.

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Keywords: Cows; Sows; Energy balance; Insulin; IGF-I; Ovulation; Protein

1. Introduction

The modern dairy cow and the modern sow have been intensively selected for high milk production. For the cow, high milk production for human consumption represents the primary economic trait, whereas in the nursing sow, greater milk production provides a high level of weaned pig output for subsequent growth and meat production. Both the modern cow and sow have a larger mature size and are leaner than their predecessors two or more decades
ago. Additionally, modern pigs have been improved to increase growth rate, feed efficiency, ovulation rate and litter size. Common to both cows and sows, milk production increases rapidly after parturition to peak yields, within 10 days for the sow or about 30 days for the cow, but dietary energy intake lags behind requirements with consequent negative energy balance (NEBAL). The onset of lactation shifts the prioritization of nutrient utilization toward the mammary gland and further reproduction is delayed. Associated with NEBAL are characteristic metabolic and hormonal changes that contribute to understanding the inhibition of ovulation in the early postpartum (PP) cow or to the delay of ovulation following weaning in the sow and provide the main direction for this review. For the sow, however, protein balance or loss during lactation appears more significant toward inhibition of ovulation and is considered further.

2. Factors affecting the timing of first ovulation in the lactating dairy cow

Resumption of ovulation in PP dairy cows requires that all the organs associated with reproduction must recover from the previous pregnancy and parturition: ovary—re-establishment of full follicular development with ovulation; hypothalamus/pituitary gland—gonadotropins, LH and FSH, are secreted in an appropriate manner to stimulate ovarian follicles; liver—supports heavy metabolic load (gluconeogenesis, fatty acid oxidation, insulin-like growth factor-I [IGF-I] production). The recovery of each of these tissue functions is negatively influenced by NEBAL that occurs in periparturient dairy cows (Butler, 2003; Overton, 2001). Comprehensive reviews including the physiological effects of energy balance related to ovarian follicular development and ovulation in PP dairy cows are available (Jolly et al., 1995; Beam and Butler, 1999; Webb et al., 1999, 2004; Butler, 2000, 2001; Lucy, 2003; Wathes et al., 2003).

Beginning about 1–2 weeks before calving, feed intake declines (Hayirli et al., 2002) resulting in NEBAL that will worsen over the next 2–3 weeks with the onset of lactation and reach its lowest point (nadir) usually within the first 2 weeks PP. 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; Zurek et al., 1995). High body condition score (BCS) is a major cow factor causing decreased dietary intake during the close-up dry period approaching calving. Recommended management strategies include maintaining moderate BCS (3.25–3.5) until calving and feeding a higher energy ration from 3 weeks prepartum (Doepel et al., 2002). 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 continued NEFA mobilization from adipose tissue. 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) esterification and secretion as very low-density lipoproteins; (2) esterification and intracellular storage as triglycerides; (3) complete oxidation to CO₂; and (4) partial oxidation to acetate or ketone bodies. During the transition period, plasma concentrations of NEFA and β-hydroxybutyrate (BHBA) and hepatic accumulation of triglycerides were higher for cows in which the first PP 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 oestradiol 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 PP 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 (Fig. 1; Butler, 2001). BCS loss during early lactation is paralleled by reduced back fat thickness and decreased diameter of the longissimus dorsi muscle (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 (Zurek et al., 1995; Phillips et al., 2003). Although first PP 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 (Butler and Smith, 1989; Zurek et al., 1995; Beam and Butler, 1999). However, another potential signal linking body condition to ovarian activity in lactating cows is leptin (Wathes et al., 2003). Leptin is produced primarily by adipose cells and leptin concentrations in circulation are positively correlated to the size of the fat depot and nutritional status. Leptin receptors have been identified in the hypothalamus and bovine ovarian granulosa cells. In lactating cows, NEBAL during the first several weeks of lactation is linked to markedly decreased plasma leptin concentrations (Kadokawa et al., 2000; Block et al., 2001; Liefers et al., 2003), but any link to delayed resumption of ovulation is controversial (Kadokawa et al., 2000; Liefers et al., 2003).

The first ovulation PP reflects the resumption and completion of preovulatory ovarian follicular development and application of transrectal ultrasonography has been instrumental in monitoring follicular dynamics during this transition period. Following parturition and the clearance of gestational oestradiol from blood, a new follicular wave was initiated rather synchronously, 5–7 days PP in all cows regardless of NEBAL or diet (Beam and Butler, 1997, 1998). Follicular development occurred in response to increased plasma FSH concentrations that peaked on days 4 to 5 PP (Beam and Butler, 1997). Although dairy cows develop dominant follicles during the first weeks PP, three patterns of follicular development and outcome have been described: (1) ovulation of the dominant follicle of the first follicular wave; (2) development of a first-wave nonovulatory dominant follicle and turnover followed by an additional wave(s) of follicular development preceding first ovulation; and (3) development of a first-wave dominant follicle that becomes cystic. Compared to cows in which ovulation of the first dominant follicle occurs ~20 days PP (45% of cows), the development of non-ovulatory (35% of cows) or cystic (20% of cows) follicles prolongs the interval for first ovulation to 40 or 50 days PP (Beam and Butler, 1999).

Follicular growth in cattle is controlled by a combination of FSH and LH (Mihm et al., 2002) and is dependent on the concentrations of their respective receptors and also on the functional intracellular second messenger response systems. FSH is responsible for initiating follicular growth and LH is responsible for final maturation of the dominant preovulatory follicle. Successful ovulation of a dominant follicle during early lactation depends upon an appropriate pattern of LH secretion with the re-establishment of pulsatile LH secretion conducive to preovulatory follicular growth and oestradiol secretion being recognized as a key element (Lamming et al., 1982; Canfield and Butler, 1991; Hampton et al., 2003). Both LH pulse frequency (Canfield and Butler, 1990) and the ovarian responsiveness to LH pulse signaling (Lamming et al., 1982) increase during the first 2 weeks PP. In cows that develop a non-ovulatory dominant follicle compared to cows that develop an ovulatory dominant follicle, the frequency of LH pulses is significantly lower during the first follicular wave PP (days 8–12; Beam and Butler, 1999). This suggests that a low LH pulse frequency (3 pulses per 6 h) is apparently adequate to sustain morphological development, but that the failure of dominant follicles to continue development and to ovulate (i.e., atresia) may reflect insufficient LH pulse stimulation (Mihm et al., 2002).

Low energy availability during NEBAL may limit LH stimulation for follicular development (Butler, 2001); however, other evidence suggests that ovarian responsiveness to LH stimulation is also compromised. Canfield and Butler (1991) studied PP cows differing in NEBAL status. LH pulse frequency was similar on days 7 and 14 PP in NEBAL and positive EB cows, yet first ovulation occurred much earlier in the positive EB cows (average 14 days) compared
with NEBAL cows (average 27 days). During the first week PP in lactating dairy cows, plasma insulin concentrations were higher in cows that developed an ovulatory first-wave dominant follicle compared to cows in which the dominant follicle failed to ovulate (Beam and Butler, 1997).

Serum concentrations of growth hormone are elevated after parturition, but production of IGF-I by the liver in response to growth hormone is low and uncoupled due to NEBAL and the associated low blood insulin concentrations (Butler et al., 2003). NEBAL results not only in low serum IGF-I, but also in elevated IGF binding protein-2 levels that would be expected to limit IGF-I action (oestradiol production) in dominant ovarian follicles as they develop (Armstrong and Webb, 1997). Perhaps most importantly for PP ovarian activity in dairy cows, levels of plasma IGF-I were 40–50% higher during the first 2 weeks PP in cows in which the first dominant follicle would ovulate as compared to cows with non-ovulatory follicles (Beam and Butler, 1997, 1998; Wathes et al., 2003). Plasma IGF-I was already higher on day 1 PP, at a time before the establishment of follicular dominance and subsequent increases in peripheral oestradiol.

Insulin and IGF-I exert both separate actions and functional overlap during PP ovarian follicular development (see Wathes et al., 2003 for review). Systemic IGF-I is mitogenic and stimulates growth of small follicles and granulosa cell proliferation, whereas insulin is the primary regulator of oestradiol production. The actions of circulating IGF-I are modulated by IGF binding proteins that also vary in concentration according to nutritional status. The adverse conditions during NEBAL not only limit these important metabolic hormones, but also coordinately inhibit the LH pulse generator as described above.

3. Inhibition of ovulation in the lactating sow

The strong suckling stimulus from a large litter suppresses gonadotropin secretion in the lactating sow and effectively blocks ovarian function and estrus until after weaning (Britt et al., 1985; Varley and Foxcroft, 1990). Although the neural effects of suckling are more important inhibitors of LH secretion than the metabolic demands of milk production (Foxcroft, 1992; Zak et al., 1998), nutrition and body condition during lactation have effects on the weaning to oestrus/ovulation interval.

Considering first the effects of nursing and lactation on gonadotropin secretion, differential regulation of FSH and LH is evident. The excellent reviews by Foxcroft (1992), Williams (1998), and Kemp (1998) should be consulted regarding gonadotropin secretion. During mid- to late lactation, LH secretion is characterized by low-frequency, high-amplitude episodes. There is a strong functional relationship between the frequency of LH episodes and ovarian follicular development at the time of weaning and in the several days thereafter. Also, this association between episodic LH secretion during the course of lactation and ovarian follicular development seems to be the basis for the observed relationship between increased LH secretion in lactation and a shorter weaning to oestrus interval. It has been substantiated that LH pulsatility at and directly after weaning are related to restoration of LH pulsatility during lactation and consequently to the weaning to oestrus interval (Kemp, 1998). The importance of enhancing gonadotropin levels during lactation and weaning to stimulate ovarian activity is supported by the beneficial effect of exogenous gonadotropins in shortening the weaning to oestrus interval (Estienne and Hartsock, 1998). Soon after weaning, the pattern of LH secretion shifts to high-frequency pulses and an overall increased LH secretion (Foxcroft, 1992; Zak et al., 1998; Quesnel et al., 1998; Willis et al., 2003), therefore demonstrating the inhibitory effect of suckling during lactation on LH release.

It is difficult to design experiments in sows which clearly differentiate between the effects of suckling intensity and the associated metabolic demands of high milk production. In the sow as in the cow, there appears to be ample evidence for the concept that NEBAL results in changes in circulating metabolites and metabolic hormones that have the potential to inhibit episodic LH secretion independently of the suckling-induced inhibition (Foxcroft, 1992; Whittemore, 1996). Accepting the view that suckling is of primary importance in regulating LH secretion, the NEBAL catabolic state during lactation likely adds a further insult creating a more profound inhibitory effect on the reproductive axis. Not surprisingly then, feed restriction during lactation inhibits LH pulsatility and ovarian activity (Quesnel et al., 1998; Mao et al., 1999).
High voluntary feed intake during lactation is important for sustaining high milk production, but also to provide a basis for rapid return to oestrus after weaning and initiating the next pregnancy. Lactation feed intake is negatively related to gestation feed intake and the effect is mediated through excessive body fatness at parturition (Whittemore, 1996) and 70% higher plasma NEFA concentrations (Revell et al., 1998). Guidelines for optimizing body fatness at parturition, neither over-lean nor over-fat, have been established (refer to Whittemore, 1996 for review). Concern over reduced lactation feed intake has been especially focused on the primiparous sow as generally low intakes and greater NEBAL result in a longer weaning to oestrus interval. This problem in the modern sow appears to have been exacerbated by the response to genetic selection for leanness and feed efficiency as these traits are associated with reduced feed intake and made worse by reduced body reserves at parturition and increased milk production capacity (ten Napel et al., 1995).

Concern over feed intake during lactation is not only related to NEBAL and loss of body fat that delay ovulation following weaning, but loss of body protein may be even more important! As reviewed previously (Whittemore, 1996), “in addition to energy intake and body fatness, protein intake and body protein balance is importantly related to the weaning to oestrus interval.” Starting with King and Williams (1984), the direct relationship between lactation dietary protein intake and reproductive performance was clearly established. Low dietary protein intake in lactation and consequent-ly greater losses of body protein extended the weaning to oestrus interval in association with lower plasma LH levels (King and Martin, 1989). The effects of specific amino acid nutrition during lactation on LH secretion have been investigated more recently. Lysine is the first limiting amino acid and lysine requirement for the first 6 days of lactation is extraordinary (Boyd et al., 2000). Mean LH on day 21 of lactation is reduced by restrictions of either dietary lysine or energy intake (Kemp, 1998). Inadequate lysine intake in sows during early lactation resulted in reduced LH pulses by day 10 PP and extended the weaning to oestrus interval (Jones and Stahly, 1999; Yang et al., 2000). Nutritional strategies for managing body protein pools and amino acid status in lactating sows toward achieving high fertility have been reviewed (Boyd et al., 2000).

Dietary restriction, as well as combined dietary energy and protein formulations, has been used to investigate metabolites and metabolic hormones in circulation that also may be related to pulsatile LH secretion and ovulation. Koketsu et al. (1996) demonstrated that feeding restriction during any of the 3 weeks of lactation resulted in reduced LH pulsatility and subsequently oestrus after weaning was delayed. Energy restriction (to 50% of control intake) during lactation reduced follicle development after weaning due to decreased LH pulsatility, but nutritional modulation via decreased plasma insulin or IGF-I in follicular fluid further inhibited follicle growth (i.e., decreased sensitivity to gonadotropin action; Cosgrove and Foxcroft, 1996; Quesnel et al., 1998). A role for insulin has been proposed as a linkage between LH production and nutrition (Kemp, 1998) and plasma levels 25 min after feeding were positively correlated with LH pulse frequency (Yang et al., 2000). However, more detailed sampling in another study found no relation of insulin with LH traits (van den Brand et al., 2000). Also in another recent study, neither plasma insulin nor IGF-I seemed related to ovarian activity at weaning (Clowes et al., 2003a) nor did superalimentation (125% of ad libitum intake via gastric cannula) alter insulin, IGF-I, or LH pulses (Zak et al., 1998). Although the results of previous studies relating metabolic hormones to pulsatile LH secretion are mixed, there is a more convincing body of evidence suggesting a direct role for insulin in ovarian follicular development and, to a lesser extent, for IGF-I (Kemp, 1998; Williams, 1998).

In conjunction with the specific effects of dietary protein or lysine on LH secretion described above, the magnitude of body protein loss currently provides the most direct association with inhibition of ovulation post-weaning. Sows can sustain a loss of 9–12% of their body protein mass after parturition without a decline in ovarian function, but higher losses suppressed follicular development (Clowes et al., 2003a). In a companion study, pregnant gilts were fed to result in standard or high body protein mass at parturition and to lose differing amounts of protein in lactation (Clowes et al., 2003b). Ovarian function was higher at weaning in high body mass sows and in sows losing the least protein (10–11%) in lactation suggesting that a larger lean body mass will reduce the inhibitory
effects of lactation on ovulation after weaning. The means by which protein mass or loss is signaled to the reproductive axis is not apparent.

4. Summary and conclusion

Dietary intake related to NEBAL is important for understanding the regulation of ovarian activity and inhibition of ovulation in both lactating dairy cows and lactating sows. For the cow, differences in intake and energy balance begin prepartum and continue PP resulting in marked differences in plasma NEFA, BHBA, insulin, leptin and IGF-I, as well as liver triglyceride accumulation. All of these except leptin have been implicated as signals acting most likely on the ovary and interacting with increased LH pulse frequency for success or inhibition of ovulation in the early PP period. The relative importance and integration of the various signals continues to develop.

For the lactating sow, the suckling stimulus is the most inhibitory signal for LH pulse secretion and inhibition of ovulation until after weaning. Both extensive NEBAL and especially negative protein balance during lactation exacerbate the inhibitory effects of suckling on ovarian activity and extend the weaning to oestrus interval. The metabolic signals or factors relating depletion of energy reserves or protein mass to inhibition of ovarian activity and ovulation have not been clearly identified.

In conclusion, NEBAL is a strong metabolic signal for inhibition of ovulation in both the lactating cow and sow and, additionally, low body protein mass and negative protein balance delays ovulation, especially in the sow.

References


