

Nutritional- and suckling-mediated anovulation in beef cows¹

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ABSTRACT: Nutrient intake, body energy reserves, and suckling are major regulators of reproductive performance of beef cows. Inadequate body energy reserves at parturition increase the interval to first estrus and ovulation, and postpartum nutrient intake can influence the duration of the interval in cows with thin to moderate body condition score. Suckling can increase the postpartum anestrous interval in thin cows, but has little effect on mature cows with adequate body energy reserves. The purpose of this review is to evaluate signals by which nutrient intake and body energy reserves may regulate ovarian function in postpartum beef cows. Nutritional restriction causes decreased secretion of GnRH and LH, reduces follicular growth, and decreases concentrations of estradiol in plasma.

In addition to direct and indirect effects of decreased energy intake on the hypothalamus and pituitary, nutrition may influence ovarian function. Metabolic signals that communicate the adequacy of body energy reserves and nutrient intake may stimulate changes several weeks before ovulation occurs, have a permissive role, be regulated by binding proteins or receptors, or interact with stimulatory or inhibitory factors produced by adipose tissue. Metabolic signals may also have autocrine and/or paracrine effects. Adequate body energy stores and sufficient plasma concentrations of metabolic signals are prerequisites for ovulation in postpartum cows. Complex interactions between hormones, metabolic compounds, and other factors control follicular maturation, estrus, and ovulation in postpartum beef cows.

Key Words: Cow, Insulin-Like Growth Factor, Ovulation, Postpartum Period, Reproduction

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J. Anim. Sci. 81(E. Suppl. 2):E48–E59

Introduction

Profitability of beef production is greatly influenced by reproductive efficiency. Beef cattle are frequently not pregnant at the end of the breeding season because of the absence of normal estrous cycles. The anestrous condition in heifers and postpartum cows is caused by reduced ovarian follicular growth and the absence of luteal activity (Wettemann, 1980). Two major factors that regulate duration of the postpartum anestrous period are suckling and nutrient intake before and after calving. If nutrient intake is inadequate and body energy reserves are depleted, the interval from calving to the first estrus is extended (Wiltbank et al., 1962; Dunn and Kaltenbach, 1980; Short et al., 1990). Suckling also inhibits the resumption of normal estrous cycles after parturition (Short et al., 1972; Edgerton, 1980; Williams, 1990).

Relationships between body energy reserves and weight loss (before and after parturition) with the dura-

tion of the postpartum anestrous period have been established (Dunn and Kaltenbach, 1980; Selk et al., 1988). The most important factor that influences pregnancy rate is body energy reserves at calving. When beef cows had a BCS (1 = emaciated, 9 = obese; Wagner et al., 1988) of five or greater at calving, the number of days from calving to first estrus and ovulation was 15 to 35% fewer than if cows calved with a BCS of less than 5 (Richards et al., 1986; Looper et al., 1997; Lents et al., 2000).

Body condition score of primiparous cows at calving influences the response to postpartum nutrient intake (Spitzer et al., 1995). When cows with a BCS of 6 were fed to gain 0.85 vs. 0.44 kg/d after calving, the percentage of cows in estrus during the first 20 d of the breeding season increased from 40 to 85%. However, when cows had a BCS of 4, the greater daily gain only increased the percentage of cows in estrus from 33 to 50%.

Energy intake and body energy stores influence concentrations of energy substrates and metabolic hormones in the blood of cattle. Chronic and acute alterations in substrates and metabolic hormones may signal the hypothalamic-pituitary-ovarian axis as to the metabolic status of the animal. However, the metabolic signals between body energy reserves and follicular maturation and ovulation have not been determined.

¹Approved for publication by the Director, Oklahoma Agric. Exp. Stn. This research was supported under project H-2331.

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Received August 8, 2002.

Accepted December 9, 2002.

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Discussion

Postpartum Follicular Development

Although follicular waves are recurrent during early and mid-pregnancy (Ginther et al., 1989), they are not detectable during the last weeks of pregnancy (Ginther et al., 1996). The first dominant follicle (**DF**) occurs within 10 to 12 d after parturition in beef and dairy cows (Murphy et al., 1990; Savio et al., 1990; Stagg et al., 1995). Thus, a lack of follicular waves after parturition is not the limiting factor for the onset of estrus and ovulation.

The first postpartum DF ovulated in few (11%) beef cows (Murphy et al., 1990), whereas the first DF ovulated in most (74%) dairy cows (Savio et al., 1990). Beef cows with inadequate body energy reserves and/or suckling calves had several follicular waves before the first ovulation (Murphy et al., 1990; Stagg et al., 1995) and the number of DF before ovulation was greater with reduced postpartum nutrient intake.

Frequent pulses of LH are needed for maturation of preovulatory follicles (Roberson et al., 1989; Savio et al., 1993; Stock and Fortune, 1993). Mean concentrations of LH and frequency of pulses increase with time before the first postpartum ovulation (Stagg et al., 1998). Inadequate pulses of LH may cause recurring follicular waves and atresia of the DF. Nutritionally induced anovulation is associated with decreased secretion of LH (Wettemann and Bossis, 2000). The first DF after parturition was prolonged or ovulated when beef cows were given hourly pulses of LH (Duffy et al., 2000). Treatment of nutritionally induced anovulatory cows with one pulse of GnRH each hour will initiate ovarian luteal activity (Bishop and Wettemann, 1993; Vizcarra et al., 1997).

The ability of DF to produce estradiol is limited during the postpartum anovulatory period and increases with time after parturition (Spicer et al., 1986). Postpartum anovulatory follicles produced less estradiol than preovulatory follicles (Braden et al., 1986). Although the amount of IGF-I in follicular fluid was not influenced by time postpartum or whether a follicle was estrogen-active (Spicer et al., 1988; Rutter and Manns, 1991), amounts of IGF binding proteins in follicles could regulate the availability of IGF-I to follicular cells. Factors that increase the postpartum interval to first ovulation probably decrease steroidogenesis in follicles.

Abnormal luteal function after the first ovulation occurs frequently in beef cows. The luteal phase after the spontaneous first postpartum ovulation is usually less than 10 d (Corah et al., 1974; Werth et al., 1996; Looper et al., 1997). Similarly, a short luteal phase also occurs after early weaning (Odde et al., 1980; Copelin et al., 1987; Breuel et al., 1993) or treatment with GnRH

Table 1. Concentrations of LH in the serum of nutrient-restricted and control steers before (d 0) and during (d 3) restriction^a

| Item | Treatment | | | | SE |
|------------------------|-----------|-----|------------|-----|-----|
| | Control | | Restricted | | |
| | d 0 | d 3 | d 0 | d 3 | |
| Concentration, ng/mL | 3.9 | 4.2 | 4.4 | 4.7 | 0.1 |
| Pulse frequency, 8 h | 6.3 | 6.8 | 6.0 | 5.8 | 0.8 |
| Pulse amplitude, ng/mL | 3.3 | 2.8 | 3.3 | 3.1 | 0.3 |

^aOjeda et al., 1996.

(Kesler et al., 1980; Wettemann et al., 1982). Short-lived corpora lutea (**CL**) cannot maintain pregnancy since they regress before d 15 when maternal recognition of pregnancy occurs (Northey and French, 1980). A premature luteolytic signal causes short-lived CL (Garverick et al., 1992).

Estrous behavior usually does not occur before the first postpartum ovulation in beef (Murphy et al., 1990; Perry et al., 1991; Looper et al., 1997) and dairy cows (Graves et al., 1968; Savio et al., 1990). The duration of the luteal phase after the first estrus in beef cows is usually normal (Corah et al., 1974; Odde et al., 1980; Looper et al., 1997).

Secretion of Gonadotropin

Secretion of LH is a rate-limiting step for the initiation of follicular growth and estrus after calving. Pulsatile secretion of LH is associated with secretion of GnRH in cows (Gazal et al., 1998; Yoshioka et al., 2001) and increased frequency of exogenous GnRH pulses increased pulse frequency and mean concentrations of LH in anovulatory cows (Bishop and Wettemann, 1993; Vizcarra et al., 1997).

Nutritional effects on LH secretion in ruminants are dissimilar to monogastric animals. Short-term nutritional restriction or fasting reduces LH secretion in rats (Campbell et al., 1977) and primates (Cameron and Nosbisch, 1991), but not in cattle (Khireddine et al., 1998; Mackey et al., 2000; Amstalden et al., 2002a). To determine if products of rumen fermentation are involved in control of LH secretion, total rumen contents of fistulated steers (440 kg) were removed and either all the fluid and particulate material were replaced (control) or only 15% of the rumen contents were replaced (restricted; Ojeda et al., 1996). Restricted steers were fed 2 kg of low-quality hay each day and control steers were fed a diet of hay and soybean meal to maintain weight. Mean concentration of LH and pulse frequency and amplitude were similar in control and restricted steers before and after 3 d of feed restriction (Table 1). Although the nutritional restriction resulted in a decrease in substrate and microbes for rumen fermentation, mobilization of body fat, and a twofold increase in plasma concentration of NEFA, LH secretion was unaltered.

Secretion of estrogens and progesterone during pregnancy reduces concentrations of LH in the pituitary at parturition (Nett et al., 1987) and the concentration of LH increases in serum within a week after calving (Erb et al., 1971; Ingalls et al., 1973). The interval from calving until pulsatile secretion of LH is sufficient for maturation of the ovulatory follicle is influenced by factors such as body energy reserve, nutrient intake, and suckling. During the early postpartum period, a pulse of LH is secreted every 3 to 6 h (Walters et al., 1982; Humphrey et al., 1983; Nett et al., 1988), and the frequency increases to 1 to 2 pulses/h before the first ovulation (Peters et al., 1981; Terqui et al., 1982). Reduced pulsatile secretion of LH during the early postpartum period is probably associated with decreased GnRH secretion because the number and affinity of GnRH binding sites on the pituitary do not change during the postpartum period (Moss et al., 1985) and pulsatile treatment with GnRH causes pulsatile secretion of LH.

Concentrations of FSH increase within a week after parturition (Schallenberger et al., 1982; Peters and Lamming, 1984) and are constant until ovulation (Convey et al., 1983; Nett et al., 1988). Postpartum anestrous beef cows have adequate FSH for development of DF (Stagg et al., 1998). Similar secretion of FSH in restricted and maintenance diet heifers before the onset of nutritionally induced anovulation, and increased concentrations of FSH in serum after the onset of anovulation (Bossis et al., 1999), indicate that secretion of FSH is not limiting for follicular growth in energy-restricted cattle.

The effect of inadequate nutrition and/or minimal body fat reserves on the sensitivity of the hypothalamus to the negative feedback of estradiol has not been established. During 93 d of nutritional restriction and weight loss, heifers treated continuously with estradiol were more sensitive to the negative effects of estradiol on the number of pulses of LH and mean concentrations of LH (Imakawa et al., 1987) compared with heifers that gained body weight.

When diets of cows were restricted and they lost 1% of their body weight per week for 26 wk, ovulation ceased. Mean concentrations of LH and the number of pulses of LH were not different for intact and ovariectomized nutritionally induced anovulatory cows during the first 10 d after ovariectomy; however, amplitude of LH pulses was greater in ovariectomized than intact cows (Richards et al., 1991). Garcia-Winder et al. (1984) suggested that ovarian factors might interact with suckling intensity to inhibit secretion of GnRH from the hypothalamus of postpartum cows. Further evaluation of the role of estradiol in the regulation of hypothalamic function in postpartum anovulation is needed.

Secretion of Progesterone and Estradiol

Plasma concentrations of progesterone are minimal at parturition (Henricks et al., 1972; Smith et al., 1973) and increase after the first ovulation (Lauderdale, 1986;

Perry et al., 1991; Werth et al., 1996) or luteinization (Donaldson et al., 1970; Corah et al., 1974) of a follicle. The first increase in plasma concentrations of progesterone in beef cows after calving usually persist for 3 to 9 d (Perry et al., 1991; Werth et al., 1996; Looper, 1999). This transient increase in progesterone is usually not preceded by estrus.

Plasma concentrations of estrogens decrease rapidly after parturition (see review, Wettemann, 1980). During the postpartum anovulatory period, concentrations of estradiol may increase in plasma for a short duration, but these increases may not be associated with growth and maturation of follicles (Murphy et al., 1990; Stagg et al., 1995). Concentrations of estradiol in plasma increase before the first postpartum ovulation (Echternkamp and Hansel, 1973; Perry et al., 1991; Stagg et al., 1995).

Suckling and Anovulation

Suckling prolongs postpartum anovulation, and the effect is of greatest magnitude in primiparous and thin cows (Short et al., 1990). (See Williams [1990] for a detailed review of the effect of suckling on neuroendocrine control of postpartum ovarian function.) Cows develop a bond with their calf (Silveira et al., 1993; Stevenson et al., 1997), and the effect of suckling by a cow's calf is greater than suckling by a foster calf. Although twice-daily suckling is adequate to increase the duration of the postpartum anestrous interval, twice-daily milking does not prolong anovulation (Lamb et al., 1999). Fewer cows with ad libitum suckling had ovulated by 80 d postpartum (43%) compared with cows that had calves isolated and only allowed to suckle once per day (90%; Stagg et al., 1998). However, if calves were allowed to suckle once per day and calves were adjacent to cows continuously, only 65% of the cows had ovulated by 80 d postpartum. Thus, development of the cow-calf bond prolongs the postpartum anovulatory interval even with a reduced suckling stimulus.

Body energy reserves at calving influence the effect of suckling on ovarian function. If cows had a BCS greater than or equal to 5 at calving, and calves were weaned at 35 d postpartum, all cows ovulated by 25 d after weaning (Bishop et al., 1994). In contrast, only 40% of cows with a BCS less than 5 had ovulated by 25 d after weaning. Although the interval from weaning to ovulation is greater in thin cows than in cows with greater BCS, weaning is a useful management option to increase pregnancy rates in thin cows.

Potential Metabolic Signals

Macronutrients or their metabolites can regulate gene expression and influence growth and body functions in addition to their roles as sources of energy. Glucose can influence expression of genes in cells independent of insulin (Jump, 2001), and low concentrations of cholesterol in cells increase the amount of low-

density lipoprotein receptor and synthesis of cholesterol (Brown and Goldstein, 1997). Fatty acids are also regulators of gene expression in cells, and type of fat in the diet, amount consumed, and duration of consumption can influence responses in cells by alteration of transcription factors (Jump and Clarke, 1999).

Insulin. Consumption of a meal and long-term dietary treatments have minimal effects on plasma glucose in cattle (Yelich et al., 1996; Vizcarra et al., 1998). Although plasma concentrations of glucose in cattle are extremely constant compared with monogastric animals, insulin regulates utilization of glucose by bovine cells.

There are receptors for insulin in the brain, pituitary gland (Lesniak et al., 1988), and ovarian tissue (Poretzky and Kalin, 1987). Insulin stimulates release of GnRH from hypothalamic fragments in vitro when glucose is available (Arias et al., 1992) and infusion of insulin into the cerebroventricles of nutritionally restricted ewes increased LH secretion (Daniel et al., 2000). Insulin also stimulates steroid production by bovine ovarian cells (Spicer and Echterkamp, 1995). Systemic treatment of cows with insulin may increase follicular development (Harrison and Randel, 1986) and estradiol production by large follicles (Simpson et al., 1994).

The hypothalamus, unlike other areas in the central nervous system, expresses an insulin-dependent glucose transporter (Livingstone et al., 1995). This may allow the hypothalamus to respond to increased concentrations of glucose in blood. During nutritionally induced anestrus, cows become resistant to insulin (Richards et al., 1989) and entry of glucose into hypothalamic cells may be reduced.

Early studies demonstrated that 2-deoxy-D-glucose, a glucose antagonist, induced anestrus and anovulation in cows (McClure et al., 1978), and secretion of LH was reduced by treatment of ewes (Funston et al., 1995b) and ram lambs (Bucholtz et al., 1996) with 2-deoxy-D-glucose. Phlorizin-induced hypoglycemia prevented LH and insulin secretion after early weaning of beef cows (Rutter and Manns, 1987).

Insulin-Like Growth Factor-I. Insulin-like growth factor-I is produced by the liver and has effects on many cell types to regulate carbohydrate, fat, and protein metabolism. It is also produced by other tissues and can have autocrine and paracrine effects. Concentrations of IGF-I in blood of cattle are decreased during feed restriction (Richards et al., 1991, 1995; Armstrong et al., 1993) and concentrations of GH are increased (Bossis et al., 1999). Restriction of protein and/or energy intake reduces the increase in blood IGF-I that usually occurs in response to treatment with GH (Brier et al., 1988; Ronge and Blum, 1989; Armstrong et al., 1993). The reduction in IGF-I in serum during nutrient restriction is associated with reduced binding of GH to hepatic membranes in restricted steers (Brier et al., 1988). At least six high-affinity IGFBP in biological fluids can influence the functions of IGF-I (Jones and Clemmons,

1995). Degradation of IGFBP by proteases also influences the biological activity of IGF-I (Maile and Holly, 1999).

Hypothalamic and other neural cells in rats have IGF type-I receptors (Lesniak et al., 1988; Hiney et al., 1996), and IGF-I stimulated expression of the GnRH gene in neural cells (Longo et al., 1998) and GnRH secretion (Anderson et al., 1999). Body energy reserves are related to amounts of IGFBP in hypothalami of ewes (Snyder et al., 1999).

Gene expression for type-I IGF receptors and IGFBP-5 occur in the pars tuberalis and pars distalis of the ovine pituitary and are greater than expression for IGF-II, type-2 receptor, and IGFBP-3 (Adam et al., 2000). Treatment of ovine pituitary cells with IGF-I increases LH release (Adam et al., 2000). Insulin-like growth factor-binding protein-2, -3, and -5 are present in bovine pituitary glands (Funston et al., 1995), and their activity is associated with the stage of the estrous cycle (Roberts et al., 2001).

Antral follicle development in mice requires IGF-I (Zhou et al., 1997). Follicles synthesize IGF-I, and systemic IGF-I could also influence ovarian function (Spicer and Echterkamp, 1995). Specifically, ovarian cell proliferation and steroidogenesis are stimulated by IGF-I (Spicer et al., 1993; Spicer and Chamberlain, 1998). Steroidogenesis is stimulated by IGF-I binding to type-I receptors on cells, and IGF-I is also bound to high-affinity binding proteins in extracellular fluids. Concentrations of IGF-I in follicular fluid and its receptor in granulosa cells of dominant and subordinate follicles are similar; however, dominant follicles have less IGFBP activity than subordinate follicles (Stewart et al., 1996; Yuan et al., 1998). The decrease in intrafollicular concentrations of IGFBP during terminal development of follicles (de la Sota et al., 1996; Funston et al., 1996; Stewart et al., 1996) may increase availability of IGF-I to follicular cells. Concentrations of IGFBP-4 may determine which follicle becomes dominant during selection in cattle (Mihm et al., 2000). Increased energy intake resulted in reduced concentrations of mRNA for IGFBP-2 and -4 in small follicles of heifers (Armstrong et al., 2001).

Nonesterified Fatty Acids. Adipose tissue of ruminants is metabolized and NEFA and glycerol are released and can be used as sources of energy during negative energy balance. Concentrations of NEFA in nutritionally induced anovulation of heifers are maximal during anestrus, decrease dramatically during re-alimentation, and then gradually increase before resumption of ovulation (Bossis et al., 1999, 2000). Plasma concentrations of NEFA do not appear to be directly involved in nutritional regulation of ovarian function in heifers. A direct effect of NEFA on the hypothalamus and/or pituitary gland has not been established in cattle and infusion of FFA did not alter LH secretion in lambs (Estienne et al., 1990).

Leptin. Concentrations of leptin in plasma are related to amounts of body fat in humans (Considine et al.,

1996; Ostlund et al., 1996) and rodents (Maffei et al., 1995; Schneider et al., 2000), but the relationship between plasma concentrations of leptin and body fat or BCS is not well established in ruminants. Nutrient intake influences amounts of messenger RNA (mRNA) for leptin in fat of cattle (Tsuchiya et al., 1998; Amstalden et al., 2000) and concentrations of leptin in plasma (Ehrhardt et al., 2000). Concentrations of leptin in the plasma of dairy cows are decreased by a negative energy balance (Block et al., 2001). These effects of nutrition on plasma leptin increase the difficulty of determining the effect of body fat reserves on plasma leptin. Concentrations of leptin in plasma respond in 2 d to fasting (Amstalden et al., 2000) or in 4 d to reduced nutrient intake (Ciccioli et al., 2001b). Studies have determined positive correlations between body fat and plasma leptin in calves and dairy cows (Ehrhardt et al., 2000) and ewes (Delavaud et al., 2000; Thomas et al., 2001), but minimal numbers of animals were sampled and in the studies with calves and ewes amount of body fat was confounded with dietary intake.

Since the discovery of leptin, there has been much interest as to its potential function as a signal to inform brain targets about body energy stores (Spicer, 2001; Smith et al., 2002). Receptors for leptin have been identified in the brain (Dyer et al., 1997) and pituitary (Iqbal et al., 2000) of sheep, and feed restriction increases expression of leptin receptor in hypothalamic nuclei of ewes (Dyer et al., 1997). Administration of leptin into the brain of sheep reduces feed intake and suppresses LH pulse frequency (Blache et al., 2000; Morrison et al., 2001). However, the effect of leptin on LH secretion cannot be separated from the effect of leptin on feed intake. Treatment of nonruminants with leptin increases secretion of gonadotropins (Barash et al., 1996). Fasting of cows (Tsuchiya et al., 1998) or heifers (Amstalden et al., 2000) for 48 h decreased leptin mRNA in adipose tissue and concentrations of leptin in plasma (Amstalden et al., 2000) without altering concentration or amplitude of LH pulses. Central infusion of leptin did not influence pulsatile secretion of LH in well-fed ewes (Henry et al., 1999), but did prevent the fasting-induced decrease in LH pulse frequency in wethers. Exogenous leptin prevented the fasting-induced suppression of plasma concentrations of LH in castrated rams treated with estradiol (Nagatani et al., 2000), and LH secretion in fasted ovariectomized estradiol treated cows was increased by leptin treatment (Zieba et al., 2002). Leptin has a direct inhibitory effect on the bovine ovary (Spicer and Francisco, 1997). Greater than adequate nutritional intake could result in abundant concentrations of leptin in plasma that could prevent the production of excessive amounts of estradiol by follicles (Spicer, 2001).

Nutrition and Postpartum Endocrine Function

The influence of BCS at calving and postpartum nutrient intake on endocrine and ovarian functions was

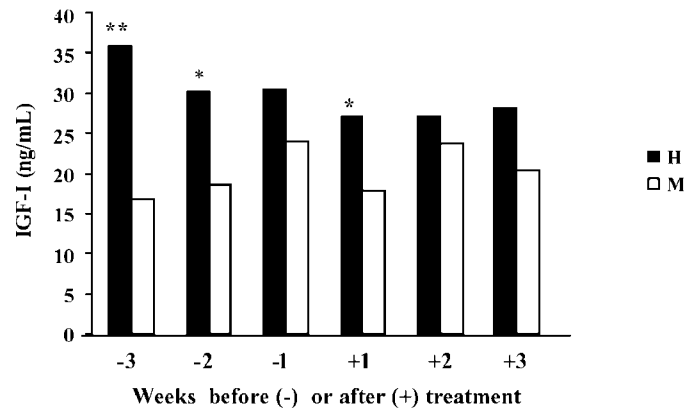


Figure 1. Concentrations of IGF-I in plasma of postpartum primiparous cows during the last 3 wk of nutritional treatment and 3 wk after treatment (adapted from Ciccioli et al., 2001b). * $P < 0.05$, ** $P < 0.01$.

evaluated in Angus \times Hereford primiparous cows (Ciccioli et al., 2001a,b). During the last third of gestation, cows were fed different amounts of protein supplement to produce cows with BCS of 4 or 5 at calving. At parturition, thin (BCS = 4.4 ± 0.1) and moderate (BCS 5.5 ± 0.1) cows were allotted to diets for gains of 0.45 kg/d (M; $n = 17$) or 0.90 kg/d (H; $n = 17$) for the first 70 d after calving. Cows on the H diet weighed about 45 kg more and had greater BCS than M cows after 63 d of treatment. Ovarian and reproductive functions were not influenced by BCS at calving. Duration of ovarian cycles before and after the first postpartum estrus was not influenced by BCS at calving or postpartum nutrient intake. Eighty-eight percent of cows had short luteal phases before the first estrus and all cows had a normal luteal phase after the first estrus. The interval to first estrus and ovulation was shorter ($P < 0.01$; 100 ± 8 d) for H than M cows (120 ± 8 d). The size of the DF, determined by ultrasonography at 4 to 16 h after the onset of estrus (determined by HeatWatch), was larger ($P < 0.01$) for H (14.8 ± 0.3) than M cows (13.5 ± 0.3). Pregnancy rate from artificial insemination at 14 to 20 h after onset of first postpartum estrus was also greater ($P < 0.03$) for H (76%) than for M cows (58%).

Concentrations of glucose and insulin in plasma during the last 3 wk of nutritional treatment (wk 8 to 10 postpartum) and the 3 wk after treatment, when all cows received the same diet, were influenced by treatment \times week ($P < 0.01$). During treatment, concentrations of glucose were 5 to 10 mg/dL greater in H than M cows. However by 2 wk after treatment, concentrations of glucose in plasma of H and M cows were not significantly different. Similarly, concentrations of insulin in plasma during treatment were 40 to 50% greater in H than M cows, but were not different 1 wk after cessation of the nutritional treatment.

Concentrations of IGF-I in plasma during the last 3 wk of treatment and the first 3 wk after treatment were influenced by treatment ($P < 0.01$; Figure 1). Cows on

Table 2. Changes in hormones and metabolites in plasma of beef cattle preceding the first ovulation in postpartum cows and nutritionally induced anovulatory heifers that were realimented

| Constituent | Weeks change occurred before ovulation | |
|-------------|--|-----------------------------------|
| | Postpartum anestrus | Nutritional anestrus ^a |
| Glucose | >7 | >3 |
| Insulin | >7 | >3 |
| IGF-I | >7 | >3 |
| NEFA | >7 | >3 |
| Leptin | >7 | >3 |

^aBossis et al. (2000).

H treatment had greater plasma concentrations of IGF-I on wk 2 and 3 before the end of treatment and on the first week after treatment. Effect of greater nutrient intake on IGF-I in plasma decreased with time after treatment.

Leptin concentrations in plasma were 2.6-fold greater ($P < 0.01$) in H than M cows during the last 3 wk of nutritional treatment. However, within 4 d after the end of nutritional treatment, concentrations of leptin in plasma were similar for M and H cows. At the end of treatment, H cows had about a 0.75 greater BCS than M cows. This indicates that leptin is associated with feed intake and not amount of body fat.

Concentrations of insulin, IGF-I, and leptin were greater in H than M cows during nutritional treatment, but were not significantly different by 1 or 2 wk (approximately 90 d postpartum) after the end of treatment. Ovulation and estrus occurred in most cows after the end of treatment; only 32% of H cows were in estrus by 80 d postpartum. Concentrations of insulin, IGF-I and leptin during 7 wk before the first postpartum estrus were not influenced by time. Changes in concentrations of these hormones and glucose and NEFA occurred more than 7 wk before ovulation (Table 2). Similarly, when nutritionally induced anovulatory heifers were realimented, concentrations of glucose and insulin were similar in control ovulatory and realimented anovulatory heifers during at least 3 wk before ovulation of realimented heifers (Bossis et al., 2000). In realimented heifers, concentrations of IGF-I and NEFA in plasma were greater at 3 wk before ovulation than during the consumption of the restricted diet, and concentrations continued to increase until ovulation.

The stable concentrations of insulin, IGF-I, and leptin in plasma of primiparous cows during the 7 wk before the first postpartum estrus indicate that immediate changes in these constituents may not stimulate the first postpartum ovulation. These hormones could be metabolic signals by which nutrient intake and body fat stores regulate ovulation, but have a delayed effect, a permissive role, and/or the effect could be mediated by alterations in binding proteins or specific receptors, so that absolute changes in concentrations of hormones may not be necessary for the response to occur.

Nutrient Intake, Body Condition Score, and Plasma Insulin and Insulin-Like Growth Factor-I

Recently, we evaluated the roles of nutrient intake and BCS on concentrations of insulin and IGF-I in plasma of gestating cows (Lents et al., 2002). Commencing at 2 to 4 mo of gestation, cows ($n = 73$) were fed one of four diets for 109 d. High (H) cows received a 50% concentrate diet in a drylot, and moderate (M), low (L), and very low (VL) cows grazed native range pasture and received 2.5, 1.5 or 0.5 kg of a 42% CP supplement each day. After 109 d of treatment, all cows grazed a common pasture and received 1.5 kg of a 42% CP supplement daily. By 109 d of treatment, BCS were 6.7^a, 4.8^{bc}, 5.0^b and 4.7^c (means without a common superscript differ; $P < 0.05$) for H, M, L, and VL cows, respectively. On d 123, after cows were on the same diets for 14 d, BCS were 6.4^a, 4.8^b, 4.8^b and 4.5^c (means without a common superscript differ; $P < 0.05$) for H, M, L, and VL cows, respectively. Body condition scores of cows ranged from 4 to 7.5 on d 109 and 3.5 to 7.5 on d 123. The relationship between BCS and concentration of insulin in plasma on d 109, after cows had access to feed, was best fit by linear regression with $R^2 = 0.34$ ($P < 0.05$). However, concentrations of insulin in plasma after cows were fasted (no water and feed for 18 h) were not related to BCS ($R^2 = 0.01$). On day 123 of the experiment, after cows were on the same diets for 14 d, concentration of insulin in plasma was not influenced by BCS after either feeding or fasting. These results indicate that concentrations of insulin in plasma of gestating cows are influenced by nutrient intake more than by BCS.

On day 109 of gestation, the relationship between BCS and plasma concentrations of IGF-I was best fit by a quadratic equation ($P < 0.05$) with $R^2 = 0.36$ for samples collected after cows had access to feed and $R^2 = 0.27$ ($P < 0.05$) after an 18-h fast (Figure 2). After all cows were on the same diet for 14 d (d 123), BCS did not influence concentration of IGF-I in plasma samples after feeding ($R^2 = 0.01$) or after an 18-h fast ($R^2 = 0.01$) (Figure 2). Similar to the relationship between BCS and concentrations of insulin in plasma, concentrations of IGF-I in plasma of gestating cows are influenced by nutrient intake more than by BCS.

Nutritional Effect on Postpartum Follicular Growth

Mature Angus \times Hereford cows were fed amounts of supplemental protein during the last 4 mo of pregnancy so they would have a BCS of 4 or 5 at calving. Follicular growth was monitored by ultrasonography to measure growth of the DF between d 27 and 33 or d 47 to 53 postpartum. When the diameter of the DF increased less than 0.75 mm in 24 h, it was aspirated using a transvaginal, ultrasound-guided needle. Concentrations of IGF-I, estradiol, and IGFBP were quantified in follicular fluid. Proestrus DF were aspirated from postpartum cows with normal estrous cycles at 48 h

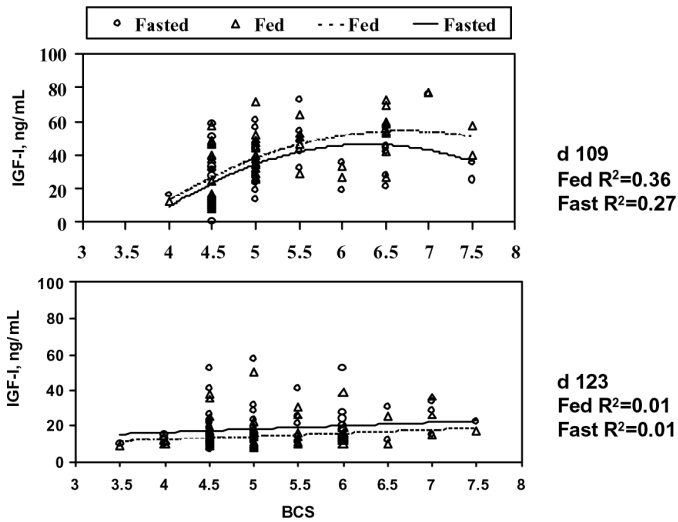


Figure 2. Relationships between BCS and concentrations of IGF-I in plasma of fed and fasted (18 h) beef cows, when cows received different diets (d 109) and after all cows received the same diet for 14 d (adapted from Lents et al., 2002).

after treatment with prostaglandin $F_{2\alpha}$. BCS at calving did not influence any of the postpartum follicular characteristics. Time of aspiration of DF was classified as either less than (short) or greater than 35 d (long) before the first estrus and ovulation. Follicles from short cows were aspirated an average of 42 d postpartum and estrus and ovulation occurred about 55 d postpartum. Follicles from long cows were aspirated about 39 d postpartum, and estrus and ovulation occurred about 85 d postpartum (Table 3). Diameters of the aspirated DF were similar (12.8 ± 0.6 mm) for short, long, and proestrous cows. Concentrations of IGF-I in follicular fluid were not influenced by estrus/ovulation classification and averaged 25.4 ± 3.6 ng/mL. Concentration of estradiol in the fluid from proestrous follicles was greater (435 ± 79 ng/mL) than the concentration in short (95 ± 56 ng/mL) or long cows (72 ± 59 ng/mL). Amounts of IGFBP-3 and -4b were greater in the DF of short than long cows. In addition, the amount of IGFBP-3 and -4b in short cows was similar to amounts in proestrous

follicles. Amounts of IGFBP-2 and -4a were not different in follicles from short, long, and proestrous cows. Follicular fluid concentrations of IGF-I are not different between DF and first subordinate follicles (Stewart et al., 1996). Changes in amounts of IGFBP in follicles during several weeks before the first postpartum estrus and ovulation may result in similar total concentration of IGF-I within follicles, but may result in different biological effects on follicular growth and maturation.

Leptin Receptors in the Hypothalamus and Pituitary

We used acute nutritionally restricted anovulatory heifers to evaluate the possible role of leptin in the regulation of the onset of anestrus (White et al., 2001). When postpubertal heifers were fed $0.4 \times$ maintenance (M) for 14 d, 58% became anovulatory and concentrations of IGF-I were reduced ($P < 0.001$) compared with heifers fed $1.2 \times$ M. Concentration of leptin in plasma of heifers fed $0.4 \times$ M tended to be reduced ($P < 0.10$) compared with heifers fed $1.2 \times$ M. The amount of leptin receptor in the median eminence, arcuate nucleus, and anterior pituitary as determined by quantitative RT-PCR were not significantly different for $0.4 \times$ M and $1.2 \times$ M heifers. In agreement with our results, secretion of GnRH by medial basal hypothalamic explants from ovariectomized estradiol-treated cows was not influenced by leptin (Amstalden et al., 2002b). If acute nutritional restriction signals hypothalamic or pituitary function via leptin, we have no evidence that the effect is by alteration in the amount of message for synthesis of leptin receptor.

Conclusions

Body energy reserve at calving is the most important factor that influences the interval from parturition to the first estrus and ovulation in beef cows. Postpartum nutrient intake can modulate the duration of the postpartum anestrus interval; however, even if thin cows gain great amounts of weight after calving, ovulation occurs later than for cows that calve in good body condition and maintain body weight.

Decreased pulsatile secretion of GnRH is the major cause of reduced pulsatile secretion of LH and extended

Table 3. Influence of days before first postpartum (PP) estrus and ovulation on dominant follicle size and concentrations of insulin-like growth factor-I, estradiol, and insulin-like growth factor binding proteins in follicular fluid

| Estrus and ovulation, d | Cows, no. | Aspiration PP, d | Follicle diameter, mm | IGF-I, ng/mL | Estradiol, ng/mL | IGFBP | |
|-------------------------|-----------|------------------|-----------------------|--------------|------------------|------------------|------------------|
| | | | | | | 3 | 4 b |
| <35 | 10 | 42 | 13.2 | 24.1 | 95 ^a | 42 ^a | 0.4 ^c |
| ≥35 | 9 | 39 | 12.3 | 22.6 | 72 ^a | 32 ^b | 0.1 ^d |
| Proestrous | 6 | 47 | 13.0 | 28.3 | 435 ^b | 40 ^{ab} | 0.5 ^c |
| SE | — | — | 0.6 | 3.6 | 63 | 3.9 | 0.1 |

^{a,b}Means within a column that do not have a common superscript differ ($P < 0.06$).

^{c,d}Means within a column that do not have a common superscript differ ($P < 0.05$).

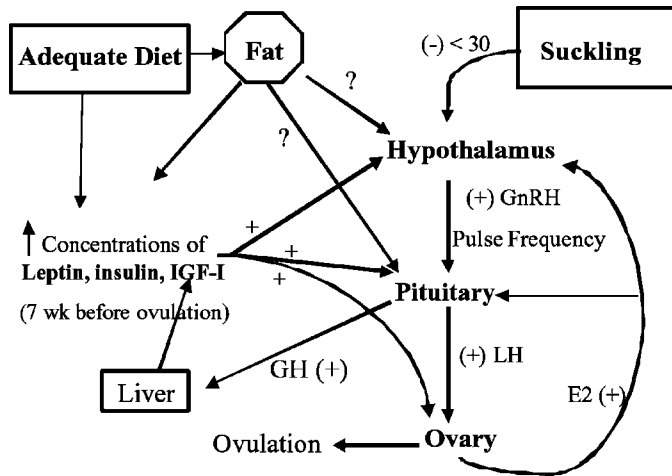


Figure 3. Control of reproductive function in postpartum beef cows.

postpartum anovulatory intervals in beef cows (Figure 3). With inadequate secretion of LH, DF do not become estrogen active and secrete insufficient estradiol to induce an ovulatory surge of LH and estrus. Adequate nutrient intake results in increased concentrations of insulin, IGF-I, and leptin in plasma and increased body fat reserves. If fat stores are sufficient (BCS greater than 5) and nutrient intake is not adequate, mobilization of fat can occur and alter plasma concentrations of insulin, IGF-I, and leptin. Secretion of growth hormone by the anterior pituitary stimulates synthesis of IGF-I by the liver except during inadequate nutrient intake when GH receptors on the liver are inadequate and the GH-IGF-I system is disconnected. Under these circumstances, tissue-specific synthesis of IGF-I may have important autocrine or paracrine effects. A stimulatory role of leptin in control of GnRH secretion in cattle is not established, however, insulin and IGF-I may enhance GnRH secretion. Leptin, IGF-I, and insulin may have direct effects on the pituitary to increase secretion of LH and on the ovary to regulate steroidogenesis.

Although concentrations of insulin, IGF-I, and leptin in plasma are relatively constant during the 7 wk before the first postpartum estrus and ovulation, this does not mean they are not metabolic signals that regulate reproduction. The hormones could a) influence early follicular or oocyte development and have delayed effects, b) have a permissive role to facilitate the effect of other hormones or factors, or c) have effects that are modulated by amounts of binding proteins or specific receptors. It is probable that unidentified compounds produced by adipose tissue have stimulatory or inhibitory effects on hypothalamic, pituitary or ovarian function since adequate body energy reserves, as well as secretion of insulin and IGF-I, are a prerequisite for postpartum ovulation.

Suckling has an inhibitory effect on pulsatile GnRH secretion during the early postpartum period, and in

thin cows. If cows have adequate body energy reserves and nutrient intake, the suppressive effect of suckling on GnRH secretion is greatly diminished by 30 d postpartum.

We conclude that both body fat reserves and nutrient intake regulate anovulation in beef cows. Effects of BCS and nutrient intake on concentrations of IGF-BP, as well as receptors for IGF-I and leptin, must be evaluated in the hypothalamus, pituitary, and ovary to elucidate metabolic signals that control postpartum ovulation in beef cows.

Implications

The interval from calving to conception greatly influences profitability of beef production. Inadequate body fat stores at calving and reduced postpartum nutrient intake increase the interval from calving until ovulation. Suckling suppresses ovulation during the early postpartum period in cows with moderate body fat stores, and the suppression is longer in thin cows. Restricted suckling or early weaning of calves can be used to improve reproductive efficiency in very thin cows. Insulin, insulin-like growth factor-I, and leptin may be metabolic signals or permissive cues; however, other interactive factors must be involved. Determination of metabolic signals by which body energy stores and nutrient intake regulate the interval from calving to first ovulation will allow development of management strategies to increase pregnancy rates in beef cows.

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