The Role of Glucose in Dairy Cattle Reproduction

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Take Home Messages

- Glucose is an important nutrient for the dairy cow because there is a high demand for milk production and it must be synthesized de novo in the liver.
- Glucose controls circulating concentrations of nonesterified fatty acids (NEFA) and beta-hydroxybutyrate (BHBA) in part through its effects on blood insulin concentrations.
- Improved immune function and shorter interval to first ovulation are 2 potential benefits to increasing circulating blood glucose, insulin, and insulin-like growth factor–1 (IGF1) and reducing NEFA and BHBA.
- Treating ketotic cows with propylene glycol (and thus providing substrate to increase blood glucose and lower blood ketones) improves their postpartum reproduction.
- Optimizing all aspects of herd nutrition beginning with the dry period is the best way to maintain adequate glucose supply so that postpartum reproduction is not compromised.

Introduction

Glucose is a critical nutrient in the postpartum cow because it is a major component of cow's milk and also is a coordinator of the endocrine mechanisms controlling homeorhesis (Lucy et al., 2014). The sum of the affected mechanisms can impinge upon the cow's immune system, perhaps affecting postpartum health by affecting immune cells that combat common postpartum diseases such as metritis, endometritis, mastitis, and pneumonia (Moyes, 2015). The endocrine axes controlling the ovary are also affected to potentially influence the return to normal cyclicity (Lucy, 2008). This paper will

specifically focus on glucose because of the requirement for de novo synthesis in liver combined with its high demand in early lactation.

▪ Glucose in the Postpartum Cow

General Aspects of Glucose Metabolism

The microorganisms in the rumen ferment carbohydrates to volatile fatty acids (VFA) that can be oxidized for energy. In addition to VFA, protein and fat passing into the lower digestive tract are absorbed and used for the synthesis of milk protein and fat. Seventy-two grams of glucose are required for each kg of milk produced (Bell, 1995). Most of this glucose is converted directly into lactose (milk sugar). Glucose is rapidly fermented to VFA in the rumen and gastrointestinal tract and these VFA enter the circulation of the cow. Glucose is then resynthesized in liver from VFA as well as amino acids and glycerol by using a process called gluconeogenesis (Figure 1).

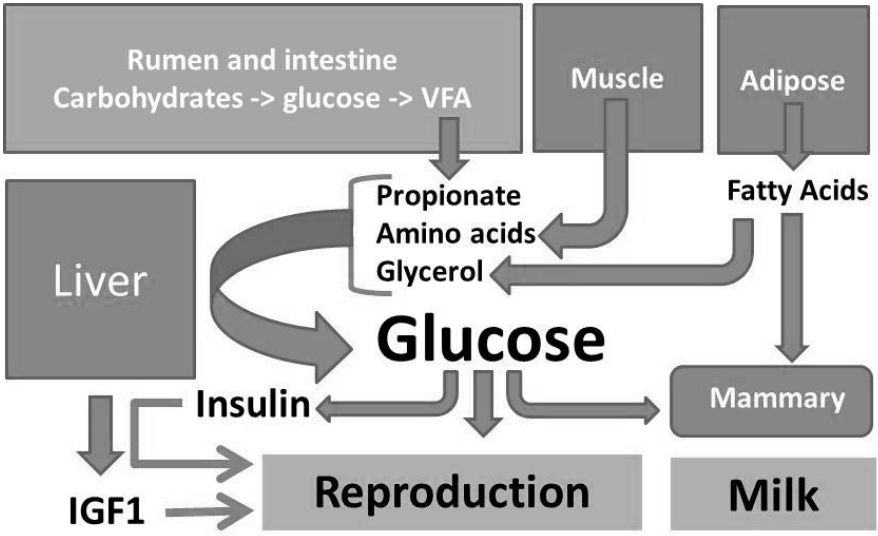

Figure 1. Metabolic processes in the early postpartum cow with potential to link glucose to the reproductive system (Lucy et al., 2014). Glucose is synthesized in the liver via gluconeogenesis from substrates arising from rumen fermentation and the catabolism of muscle and adipose tissue. Glucose may ultimately control both circulating insulin (directly) and liver IGF1 production (via insulin-stimulated IGF1 synthesis and secretion). Glucose is also a required substrate for lactose synthesis during the production of milk. Low circulating glucose may impair reproductive processes that are needed to re-establish pregnancy during early lactation.

Glucose Demand and Associated Homeorhetic Mechanisms

An early lactation cow will produce 50 to 100 kg of milk per day. This equates to a glucose requirement for milk production alone of 3.6 to 7.2 kg per day. The cow undergoes a series of homeorhetic mechanisms that are aimed toward elevating glucose supply (Bauman and Currie, 1980). In addition to a large increase in hepatic gluconeogenesis shortly after calving, the cow assumes a state of insulin resistance that prevents glucose storage as glycogen in muscle or liver, or to use glucose for lipogenesis in adipose tissue. The insulin resistant state conserves glucose for the synthesis of lactose in the mammary gland. In spite of the increase in gluconeogenesis and the development of insulin resistance, the postpartum cow has chronically low blood glucose concentrations because she fails to meet the glucose requirement for lactation.

Glucose as a Regulator of Postpartum NEFA and BHBA

Cows will break down glycogen in liver and muscle to release glucose early postpartum. The glycogen stores are quickly depleted. Cows also break down triglycerides in adipose tissue to yield glycerol (a substrate for glucose synthesis) and NEFA that can be used for energy. Typically, an excess of ketones are formed leading to elevated BHBA in blood. Increasing the circulating concentration of glucose by increasing glucose supply or decreasing demand rapidly decreases circulating NEFA and BHBA. This is because glucose can cause the release of insulin which will antagonize lipolysis and promote lipogenesis. Glucose also provides substrate to the tricarboxylic acid cycle so that BHBA can be fully metabolized (White, 2015). Thus, circulating glucose is an important regulator of both NEFA and BHBA.

Glucose as a Regulator of Postpartum Endocrine Function

In addition to its effects on metabolites, glucose can orchestrate changes in endocrine hormones such as insulin and IGF1 (Lucy, 2008). Glucose causes insulin release, and insulin partitions glucose toward adipose tissue and muscle by causing glucose transporters to move to the cell surface. Insulin also stimulates the liver to increase the expression of growth hormone receptors and release IGF1 into the circulation. As long as glucose remains low, insulin and IGF1 remain low, and the cow remains in a catabolic (tissue-losing) state during lactation. When the glucose supply increases (generally through greater gluconeogenic capacity) or the mammary gland produces less milk (gradually throughout lactation), then blood insulin increases. The increase in insulin causes the cow to partition glucose toward adipose tissue and muscle (an anabolic state). The switch from the catabolic state (low glucose, low insulin, and low IGF1) to the anabolic state (high glucose, high

insulin, and high IGF1) is a key regulator of the reproductive axis (Kawashima et al., 2012).

▪ Association Between Early Postpartum Glucose and Fertility Later Postpartum

The blood concentrations of glucose decrease after calving. The decrease in blood glucose is theoretically caused by the rapid and sustained increase in glucose demand for milk production. Cows that become pregnant after first insemination have greater blood glucose concentrations on the day of calving and during the first 3 weeks after calving compared with cows that do not become pregnant (Garverick et al., 2013). The relationship between blood glucose around the time of calving and improved reproduction is seen for cows in confinement (Garverick et al., 2013) and also for cows in pasture systems (Moore et al., 2014).

Mechanisms that determine the circulating concentration of blood glucose at or near the time of calving are not very well understood. Circulating blood glucose concentration is determined by entry rate, exit rate and pool size. Exit rate is largely determined by the amount of milk produced by the cow and also the circulating concentration and sensitivity to insulin. Entry rate is a function of her stored glucose and also gluconeogenic capacity. When cows differ in blood concentrations of glucose on the day of calving and shortly thereafter, this may simply reflect her capacity to store glycogen during the dry period and release it rapidly postpartum. Later, differences in blood glucose may reflect the cow's insulin sensitivity as well as her capacity to acutely adapt to lactation and synthesize a large amount of glucose within liver tissue.

The intriguing feature of the aforementioned studies of blood glucose is that the authors were describing relationships between blood glucose and pregnancy when the insemination was occurring several weeks after the differences in blood glucose. The suggestion is that the early postpartum metabolic profile that includes blood glucose concentrations is predictive of subsequent postpartum fertility.

Mechanisms Through Which Early Postpartum Glucose Can Affect Reproduction

Inadequate blood glucose during early lactation theoretically compromises the function of tissues that depend on glucose as a substrate for carbon skeletons and intracellular energy supply. Metabolites such as NEFA and BHBA, as well as the hormones insulin and IGF1, all of which are controlled by glucose, may also play a role in controlling tissue function. The first 30 days postpartum is a

critical time for the cow with respect to the impact that metabolites and metabolic hormones can have on reproduction. Two essential processes that may be directly affected by glucose, the restoration of ovarian cyclicity and uterine involution, will be discussed.

Restoration of Ovarian Cyclicity Postpartum

The bulk of the research performed about metabolites and metabolic hormones in postpartum cows has focused on the re-initiation of ovarian cyclicity. There is a positive association between insulin, IGF1, and the day postpartum that the cow begins to cycle (Velazquez et al., 2008). LeRoy et al. (2008) concluded that glucose and insulin were the most likely molecules to exert an effect on hypothalamic gonadotropin releasing hormone (GnRH) secretion in the postpartum dairy cow. Increasing glucose supply so that both circulating insulin and IGF1 are increased, therefore, should theoretically cause an earlier resumption of cyclicity postpartum by causing the cow to release more GnRH and have more luteinizing hormone (LH) in the system, which is stimulatory to the ovary. There is also strong synergism for insulin, IGF1 and LH at the ovarian level that shortens the interval to first postpartum ovulation (Kawashima et al., 2012; Lucy 2011).

Uterine Health and Immune Function

Great emphasis is now placed on uterine health and the central place that uterine immune cell function occupies in determining the reproductive success of the postpartum cow (LeBlanc, 2012). Under normal circumstances, uterine involution is completed during the first month postpartum. During involution, the uterus shrinks in size, re-establishes the luminal epithelium, and immune cells (primarily polymorphonuclear neutrophils or PMN) infiltrate the uterus to clear residual placental tissue as well as infectious microorganisms (LeBlanc, 2012).

The postpartum cow has a depressed immune system particularly during the first month after calving. The current theory is that the metabolic environment in postpartum cows suppresses the innate immune system through effects on PMN function (LeBlanc, 2012). In most cases, changes in circulating concentrations of nutrients and metabolites that occur in the postpartum cow are exactly opposite to those that would benefit the function of PMN. For example, glucose is the primary metabolic fuel for PMN (Moyes, 2015). The glucose is stored as glycogen within the PMN. Galvão et al. (2010) observed that cows developing uterine disease had less circulating glucose and lower glycogen concentration in their PMN. Their conclusion was that the lower glycogen reserve led to a reduced capacity for oxidative burst in PMN that predisposed the cow to uterine disease. There is good agreement between in vitro analyses of PMN function and epidemiological evidence that indicates

that an abnormal metabolic profile during the periparturient period predisposes the cow to uterine disease during the early postpartum period and infertility later postpartum (Chapinal et al., 2012).

When is the Metabolic Profile Affecting Immune Function Established?

In their work in which an index for physiological imbalance was created, Moyes et al. (2013) concluded that an index that included NEFA, BHBA, and glucose was predictive of postpartum uterine disease especially when the prepartum index was used. In all likelihood, the metabolic profile associated with uterine disease is initiated before or shortly before calving. This is not surprising given the relatively acute nature of the physiological events at the time of calving and the homeorhetic mechanisms at the initiation of lactation. A cow's homeorhetic capacity (i.e., capacity for gluconeogenesis, lipid mobilization, etc.) and her inherent resistance to disease are largely manifested after calving, but the underlying biology is theoretically in place before she calves.

▪ Blood Glucose Concentrations Later Postpartum (During the Breeding Period)

Assuming that uterine involution is complete and the cow has begun cycling, what are the implications of the metabolic profile of the cow during the breeding period? The metabolic profile of the later postpartum cow (greater than 30 days postpartum) still involves relatively low concentrations of glucose, insulin, and IGF1, although concentrations of NEFA and BHBAA have typically normalized.

Estrous Cyclicity During the Breeding Period

Patterns of estrous cyclicity for lactating cows are less regular compared with the estrous cycle of nulliparous heifers (Remnant et al., 2015). The hormonal environment created by lactation (in this example, low blood glucose, insulin and IGF1 concentrations) may potentially affect the capacity for ovarian cells to respond to gonadotropins (FSH and LH). In the cycling cow, this could potentially affect estradiol production by the follicle as well as progesterone production by the corpus luteum. Low blood glucose could potentially compromise a variety of essential metabolic processes in ovarian cells including the oocyte that depends on glucose for energy. There is also the potential for greater steroid metabolism in lactating compared with nonlactating cows that can be explained by greater dry matter intake in cows that are lactating. Lower circulating estradiol from the preovulatory follicle can lead to abnormal patterns of follicular growth, anovulatory conditions, multiple ovulation and reduced estrous expression.

Glucose as a Substrate for the Developing Embryo and Fetus

Glucose is typically thought of as a key energy source for ATP production through mitochondrial oxidative phosphorylation. Glucose is not used primarily for metabolic fuel production, however, by either the mammary gland or the pregnancy. In the mammary gland, the bulk of the glucose is used to produce lactose. Likewise, in the uterus and placenta the bulk of the glucose is used to supply carbons for the synthesis of cellular components (nucleotides, amino acids, lipids, etc.). This latter phenomenon is known as the "Warburg effect" and typifies proliferating cells.

In a study performed by Green et al. (2012), the major conclusion was that for a given day of pregnancy, the fetus and placenta from a lactating cow were smaller (weighed less) than the fetus and placenta from a nonlactating cow. Less glucose reached the fetus in a lactating compared with a nonlactating cow, perhaps because maternal glucose concentrations were lower during lactation (Lucy et al., 2012). The reduction in glucose reaching the pregnancy can potentially affect how the pregnancy develops because the pregnancy depends on glucose as a substrate for tissue synthesis and metabolic energy.

A recent study in dairy cows demonstrated that pregnant cows that undergo pregnancy loss have lower blood concentrations of pregnancy-associated glycoproteins (PAG) leading up to the time that the pregnancy is aborted (Pohler et al., 2015). The lower blood PAG concentration may indicate that the cow is pregnant with a small embryo or fetus. Perhaps this small embryo or fetus is created when the cow has inadequate glucose or growth factor concentrations.

We recently completed 2 separate studies where we attempted to correlate blood glucose concentrations as well as a variety of other metabolic indicators with size of the fetus and amnion vesicle (Stratman and Lucy, unpublished). In these studies we only found minimal effects of circulating blood glucose, insulin, and IGF1 concentrations on the development of the pregnancy. Our conclusion was that the conceptus is fully capable of developing in a low glucose and growth factor (insulin and IGF1) environment that typifies the cow after 100 days postpartum. Other factors must lead to poor embryonic development and embryonic loss in lactating dairy cows.

▪ Practical Methods to Increase Glucose Supply Postpartum

Glucose is a difficult molecule to study postpartum because of the numerous homeorhetic mechanisms that tightly control its concentration. Two cows with similar blood glucose may have a vastly different metabolic profile (BHBA,

NEFA, insulin, IGF1, and insulin resistance). The fastest and most dependable method to change blood glucose concentrations is reduce demand, for example, by changing milking frequency (3 times daily to 2 or 1 time daily; Stelwagen et al., 2013). Reducing the milking frequency may not be practical or economical for most dairies. Alternative methods for improving circulating blood glucose concentrations postpartum begin during the dry period and extend into early lactation.

Fewer or Zero Days Dry

Cows that do not have a dry period produce less milk. They also have improved metabolic status postpartum as indicated by lower NEFA and greater glucose, insulin, and IGF1 concentrations (Chen et al., 2015; Jolicoeur et al., 2014). However, van Knegsel et al. (2013), in their review of the literature, concluded that the evidence for improved reproduction in cows with a reduced dry period was inconsistent. The greatest benefit to reducing dry period length may be in the prevention of over-conditioned dry cows that have an undesirable metabolic profile postpartum.

Appropriate Dry Cow Feeding and Nutrition

Dry cow nutrition is essential for maintaining a healthy liver postpartum and maintaining good reproduction (Drackley and Cardoso, 2014). Cows that are overweight (BCS >3.75) at calving will develop fatty liver. The inflammation associated with fatty liver inhibits liver metabolism and gluconeogenesis (Garcia et al., 2015). Cows with fatty liver are incapable of achieving the high rates of gluconeogenesis that are needed to maintain adequate glucose supply (McCarthy et al., 2015c). Inadequate glucose supply leads to ketosis and negative downstream effects on reproduction (LeBlanc, 2015).

Treating ketotic cows with propylene glycol will elevate glucose and normalize BHBA (Bjerre-Harpøth et al., 2015; Piantoni and Allen, 2015). The improvements in reproduction that are observed after ketosis treatment demonstrate the important relationship between metabolite concentrations early postpartum and subsequent reproductive function (LeBlanc, 2015).

Less is known about appropriate methods to achieve a large glycogen supply in liver and muscle at calving. Although glycogen is typically depleted rapidly postpartum, a larger glycogen store could perhaps enable the cow to achieve greater blood glucose concentrations in the short term postpartum as is seen for cows with better reproduction. Although it is tempting to think that increasing energy prepartum will increase glycogen stores, this feeding strategy typically leads to overweight cows that are predisposed to fatty liver.

Postpartum Starch and Monensin

A logical approach to address inadequate glucose supply postpartum is to feed starch and monensin. Starch hydrolysis in the rumen and small intestine yields glucose and a greater proportion of propionate (relative to acetate) that can be used to synthesize glucose via gluconeogenesis in liver. Monensin feeding also increases the amount of propionate produced by the rumen which will also support the synthesis of glucose via gluconeogenesis.

In general, an effect of monensin is seen on BHBA (reduced) (Duffield and Bagg, 2000). Cows fed monensin have a greater capacity to convert propionate to glucose (via gluconeogenesis) which could explain the reduction in BHBA (McCarthy et al., 2015b). Starch feeding also reduces BHBA and may increase glucose and insulin concentrations (McCarthy et al., 2015b). These improvements in glucose and insulin associated with starch and monensin feeding have been linked to improved immune cell function in one study (Yasui et al., 2016).

Although the effects of starch feeding and monensin on postpartum metabolites have been demonstrated, there is less information concerning the reproduction in these cows. Dyck et al. (2011) reduced interval to first ovulation by feeding starch but did not show additional improvements in reproduction. Their data were similar to Gong et al. (2002) who showed a shorter interval to first ovulation in cows fed a diet designed to increase blood insulin concentrations postpartum. In their meta-analysis, Duffield et al. (2008) concluded that monensin feeding in postpartum cows reduced the risk of ketosis but had no effect on first service conception.

Starch and monensin generally normalize herd-level metabolic indicators but reproduction is not necessarily improved. When ketotic cows, however, are treated there is clearly a benefit to reproduction (LeBlanc, 2015). This probably indicates that when cows are metabolically balanced postpartum (appropriate concentrations of NEFA and BHBA) there is no benefit to reproduction through normalizing further their metabolite concentrations by additional starch or monensin feeding. This statement does not negate other benefits of monensin feeding that include increased milk production (McCarthy et al., 2015a). In cows that are metabolically imbalanced as evidenced by ketosis, there is a benefit to normalizing NEFA and BHBA concentrations with respect to improving postpartum reproduction.

▪ Conclusions

The endocrine and metabolic environment of the lactating cow affects the capacity of the cow to become pregnant postpartum. There is ample evidence that the hormones responsible for the homeorhetic mechanisms that support

lactation can also act on the uterus and ovary to affect their function prior to and during the breeding period. In addition to the hormonal environment, the metabolic environment created by lactation that includes low blood glucose and elevated NEFA and BHBA impinges upon the ovary as well as the immune system that plays a critical role in restoring uterine health in the postpartum cow. Glucose controls many aspects of the system. Postpartum reproduction in ketotic cows clearly benefits from treatments designed to normalize blood glucose and correct ketosis. Feeding strategies that are designed to increase glucose supply at the herd level (starch and monensin) will reduce BHBA but may not necessarily improve reproduction for the entire herd. This may be because the majority of the cows adapt to early lactation successfully and function within acceptable norms for glucose, NEFA, BHBA and IGF1. Optimizing all aspects of herd nutrition beginning with the dry period is the best way to maintain adequate glucose supply so that postpartum reproduction is not compromised.

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