Mechanisms Linking Postpartum Metabolism with Reproduction in Dairy Cows

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Introduction

Milk production per cow is increasing in the United States. The period of peak milk production is in early lactation, usually within 30 to 60 days after calving when the cow's uterus is involuting and the cow's ovary is returning to estrous cyclicity. The competing processes of milk production, uterine involution, and the restoration of ovarian activity can be at odds, particularly if the unique homeorhetic processes that typify early lactation become imbalanced and the cow experiences negative energy balance and (or) metabolic disease during early lactation. A potential end result is that the cow does not become pregnant during the breeding period. Understanding the mechanisms that link the first 60 days of lactation with the subsequent reproductive success or failure is an important area of research for the dairy industry.

This paper will specifically focus on glucose because of its dual purpose as a major component of cow's milk and also a molecule that coordinates homeorhetic mechanisms that could possibly impinge upon postpartum uterine health and the subsequent establishment of pregnancy.

Why Glucose Is Involved in Both Lactation and Reproduction

Glucose metabolism presents an interesting challenge for the cow. 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 g of glucose are required for each kg of milk produced (Bell, 1995). Most of this glucose is converted directly into the milk sugar lactose. Although glucose is a major product of carbohydrate digestion in the rumen, it is rapidly fermented to VFA. Glucose, therefore, must be resynthesized in the liver of the postpartum cow via gluconeogenesis (Figure 1). An early lactation cow will produce 50 to 100 kg of milk per day. This equates to a glucose requirement for milk synthesis alone of 3.6 to 7.2 kg per day. The cow undergoes a series of homeorhetic adaptations 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 redirects glucose to the mammary gland (Giesy et al., 2012). In spite of these mechanisms, the postpartum cow has chronically low blood glucose concentrations because she fails to meet the glucose requirement.

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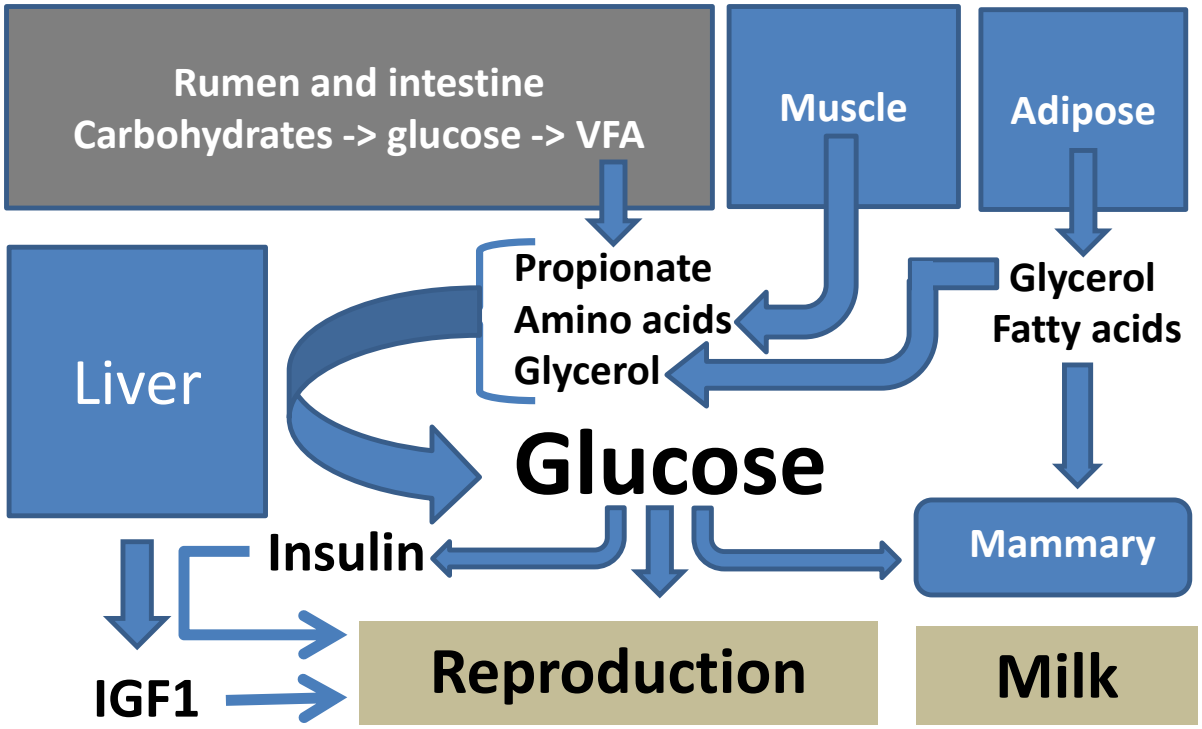

Figure 1. Metabolic processes in the early postpartum cow with potential to link glucose to the reproductive system. Glucose is synthesized in the liver via gluconeogenesis from substrates arising from rumen fermentation and the catabolism of muscle and adipose tissue. Glucose may ultimately control 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 may coordinate whole animal metabolism through its capacity to orchestrate changes in endocrine hormones such as insulin and insulin-like growth factor 1 (**IGF1**) (Lucy, 2008). Glucose causes insulin release and insulin partitions nutrients toward adipose tissue and muscle. Insulin also stimulates the liver to release IGF1 into the circulation (Butler et al., 2003). As long as glucose remains low, insulin and IGF1 remain low, and the cow remains in a catabolic (tissue-losing) state during lactation. Glucose deficiency is only corrected when the mammary gland produces less milk in later lactation, blood insulin and IGF1 increase, and the cow partitions glucose toward adipose tissue and muscle (an anabolic state). The switch from the catabolic state to the anabolic state is a key regulator of the reproductive axis (Kawashima et al., 2012).

Associations Between Early Postpartum Blood Glucose and Reproduction

The blood concentrations of glucose decrease after calving. The decrease in blood glucose is theoretically caused by the glucose requirement for milk production. When we examined blood glucose concentrations in early postpartum cows we found that those that became pregnant after first artificial insemination (**AI**) had greater blood glucose concentrations on the day of calving and at 3 days postpartum

when compared with cows that did not become pregnant (Garverick et al., 2013). A relationship between serum nonesterified fatty acid (**NEFA**) concentrations and subsequent pregnancy also existed (cows that became pregnant at first AI had lesser postpartum NEFA concentrations when compared with cows that did not become pregnant at first AI).

Additional studies have established a link between early postpartum glucose and subsequent reproduction. For example, in the study Green et al. (2012), cows that did not get pregnant after first AI at approximately 60 days postpartum had lesser plasma glucose concentration during the first 30 days postpartum when compared with pregnant cows. Interestingly, the differences in blood glucose in cows that subsequently became pregnant or did not become pregnant were observed in both lactating and non-lactating cows (Green et al., 2012). Later postpartum (30 to 60 days postpartum) there was no relationship between plasma glucose concentration and pregnancy.

In separate studies performed in Ireland (Moore et al., 2014), blood glucose concentrations were examined in dairy cows that were known to have either high (**Fert+**) or low (**Fert-**) fertility. The Irish studies demonstrated greater glucose in Fert+ cows on the day of calving and one week later. Later postpartum, Fert+ and Fert- cows were similar for blood glucose concentrations. Finally, in their recent pooled analysis of studies of prepartum nutrition and subsequent postpartum reproduction, Cardoso et al. (2013) determined that greater blood glucose concentrations at weeks 3 and 4 postpartum were associated with shorter days to pregnancy.

The described relationships between blood glucose and pregnancy were for early postpartum blood glucose concentration, generally within the first month of lactation, and the establishment of pregnancy several months after the glucose measurements were made. The suggestion is that the early postpartum metabolic profile that includes blood glucose concentrations is predictive of subsequent postpartum fertility. A key question is how the metabolic profile of the early postpartum cow controls the reproductive processes leading to pregnancy that occur several months after the early postpartum period.

Blood Glucose Entry Rate Controls Other Metabolites in the Postpartum Cow

Glucose may be a mediator of postpartum reproduction because it acts as a substrate for the production of milk and is also essential for reproductive processes. It is impossible to say, however, whether any change in reproductive function is a consequence of a single hormone/metabolite or the collective action of several hormones or metabolites that change in a coordinated manner postpartum.

In attempt to address the possibility that glucose is the primary metabolic driver of the entire system we infused glucose into early postpartum cows in a physiologically relevant manner. Increasing daily doses from 500 to 1,500 g/d glucose were administered via jugular infusion by using a constant rate of glucose infusion (Lucy et al., 2013). Glucose infusion increased blood insulin concentrations. There was a marked decrease in both NEFA and beta-hydroxybutyric acid (**BHBA**) in response to glucose infusion. In addition to changes in insulin and circulating metabolites the glucose infusion increased circulating IGF1 concentrations. Insulin

may have mediated the stimulatory effects of glucose on IGF1 through its capacity to recouple the somatotropic axis. The infusion studies demonstrated that a single molecule such as glucose could rapidly reverse the metabolic profile that typifies early lactation (greater NEFA and BHBA with lesser insulin and IGF1). Based on these results, it is possible that glucose entry rate relative to demand in early lactation is coordinating the homeorhetic mechanisms. These same mechanisms may be impacting the reproductive systems that are undergoing restoration during the first 30 days postpartum.

How Can Early Postpartum Glucose Affect Reproduction Later Postpartum?

Inadequate blood glucose during early lactation theoretically compromises the function of tissues that depend on glucose. Metabolites such as NEFA and BHBA as well as insulin and IGF1 may also play a role in controlling tissue function. The first 30 days postpartum may be the most critical in terms of the impact that metabolites and metabolic hormones have on reproduction. Two essential processes occur during the first 30 days postpartum – the restoration of ovarian cyclicity and uterine involution. These two essential processes may be directly affected by glucose.

Restoration of ovarian cyclicity postpartum. The bulk of the research performed on metabolites and metabolic hormones has focused the re-initiation of ovarian cyclicity. Cows that are not cycling are infertile. Furthermore, fertility generally improves with each successive estrous cycle before the breeding period. There has been a traditional focus on understanding the mechanisms that control the timing of the restoration of ovarian activity before the breeding period. A common topic is the positive association between insulin, IGF1, and the day postpartum that the cow begins to cycle (Velazquez et al., 2008).

A variety of metabolites and metabolic signals can act at the level of the hypothalamus to increase gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) pulsatility (LeRoy et al., 2008). LeRoy et al. (2008) concluded that glucose and insulin were the most-likely molecules to exert an effect on hypothalamic GnRH secretion in the postpartum dairy cow. At the level of the ovary, both insulin and IGF1 promote the proliferation, differentiation, and survival of follicular cells (Lucy, 2008; Lucy, 2011). The most important actions of insulin and IGF1 are observed when either hormone acts synergistically with the gonadotropins [either follicle-stimulating hormone (FSH) or LH]. Glucose does control insulin secretion in the animal and ultimately controls hepatic IGF1 secretion via insulin release. Circulating glucose and the insulin/IGF1 systems, therefore, are functionally linked in the whole animal (Lucy 2011; Kawashima et al., 2012).

The associations between postpartum hormone and metabolites and subsequent reproduction are found early postpartum when the most-extreme homeorhetic states are known to occur. The early postpartum metabolic profile, therefore, may have the capacity to imprint ovarian tissue either through permanent effects on the genome (epigenetic mechanisms) or by changing the chemical composition of the cells themselves. Perhaps the best-studied example of this metabolic imprint is the relationship between early postpartum NEFA and its effect on the composition of the oocyte and function of follicular cells (Leroy et al., 2011). The possibility that there are permanent epigenetic modifications to the genome

during the early postpartum period that affect long-term developmental competence of follicular cells has not been demonstrated at this time

Uterine health and immune function. The re-initiation of ovarian activity postpartum is a traditional focus of studies of postpartum metabolism. Recently, however, greater emphasis has been 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; Wathes, 2012). Under normal circumstances, uterine involution is completed during the first month postpartum. During involution, the uterus shrinks in size, reestablishes 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 et al., 2011). The postpartum cow has a depressed immune system particularly during the first month after calving. With respect to uterine involution and disease, the current theory is that the metabolic environment in postpartum cows suppresses the innate immune system through effects on PMN function (Graugnard et al., 2012; 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. 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).

Glucose is the primary metabolic fuel that PMN use to generate the oxidative burst that leads to killing activity. The glucose is stored as glycogen within the PMN. PMN undergo a brief period (approximately 14 days) of maturation and differentiation from progenitor cells within bone marrow prior to their release. It is during this time that glycogen is stored within the PMN. Glycogen concentrations in PMN within the postpartum cow decrease in a manner that is similar to the decrease in blood glucose postpartum (Galvão et al., 2010). Galvão et al. (2010) observed that cows developing uterine disease had lesser glycogen concentration in their PMN. Their conclusion was that the lesser glycogen reserve led to a reduced capacity for oxidative burst in PMN that predisposed the cow to uterine disease.

Most of the available data indicate that metabolic profile of the *prepartum* cow is equally important to that of the postpartum cow for subsequent uterine health and (or) the establishment of pregnancy (Castro et al., 2012). 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.

Implications of the Metabolic Profile Later Postpartum (During the Breeding Period)

Assuming that uterine involution is complete and the cow has began cycling then 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 BHBA have typically normalized.

Estrous cyclicity during the breeding period. Patterns of estrous cyclicity for the lactating cows are less regular when compared with estrous cycle of nulliparous heifers. The same hormones that control when the cow begins to cycle (insulin, IGF1, and LH) also have an effect on cyclicity which relates to the functionality of the follicle and corpus luteum. 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. 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 (Berlinguer et al., 2012). In their recent study of bovine follicles, Walsh et al. (2012) concluded that steroidogenic acute regulatory protein (**STAR**) gene expression, the rate limiting enzyme in steroidogenesis, was specifically down-regulated by the metabolic profile found in early lactation, i.e. low glucose, insulin, and IGF1. 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 (Wiltbank et al., 2011). Lesser circulating estradiol from the preovulatory follicle can lead to abnormal patterns of follicular growth, anovulatory conditions, multiple ovulation and also reduced estrous expression (Figure 2).

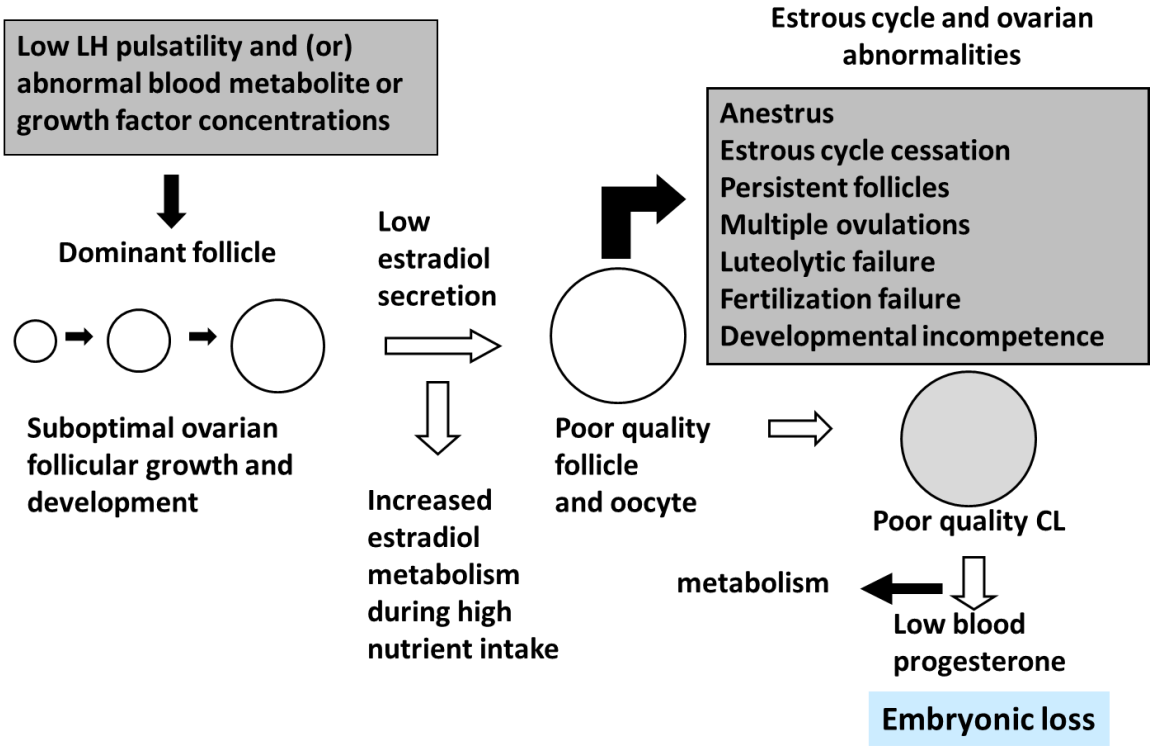

Figure 2. Mechanisms that link metabolism, metabolic hormones and metabolites to estrous cycle abnormalities, infertility, and embryonic loss in postpartum

cows. The cells of the follicle and the corpus luteum respond to changing concentrations of blood metabolites and growth factors. Steroids produced by the follicle and corpus luteum can have reduced circulating concentrations because they are metabolized by the highly metabolic liver of the lactating cow. An ovarian follicle may not be able to orchestrate the endocrine physiology of the estrous cycle because of reduced steroidogenic capacity and greater steroid metabolism. Endocrine failure by the follicle can lead to estrous cycle and ovarian abnormalities as well as a poor quality oocyte that may not develop after fertilization. The corpus luteum arises from the cells of the follicle. If the follicle is compromised then the corpus luteum may be compromised as well leading to low blood progesterone and embryonic loss.

Subnormal luteal function. Greater steroid metabolism has been implicated as a mechanism leading to low circulating progesterone in lactating cows. Low progesterone during the first weeks after insemination leads to slower embyronic development that predisposes the cow to embyronic loss (Lonergan, 2011). Progesterone stimulates uterine histotroph secretion and lesser uterine histotroph secretion, caused by low progresteorne concentrations, leads to slow embyronic development. The slowly developing embryos fail to reach adequate size to generate an adequate interferon-tau (**IFNT**) signal to the dam (Robinson et al., 2008). The pregnancy is lost because the mother fails to recognize the pregnancy and undergoes luteal regression as if she is not pregnant. Several authors have recently reviewed the mechanisms assoicated with subnormal luteal development and early embryonic loss (Pursley and Martins, 2011; Wiltbank et al., 2011; Bridges et al., 2013).

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 the milk sugar lactose. Likewise, in the uterus and placenta the bulk of the glucose is used to supply carbons for the synthesis of cellular components such as nucleotides, amino acids, lipids, etc. This latter phenomenon is known as the “Warburg effect” and typifies proliferating cells (Vander Heiden *et al.,* 2009).

In the study of Green et al. (2012) cows were either milked normally or dried off (not milked) immediately after calving. One major conclusion from the study was that for a given day of pregnancy, the fetus and placenta from a lactating cow were lighers and smaller than the fetus and placenta from a nonlactating cow. It was demonstrated that less glucose reached the fetus in a lactating compared with nonlactating cow, perhaps because maternal glucose concentrations were less 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 (Battaglia and Meschia, 1978).

The growth of the fetus and placenta, therefore, depends on the metabolic milieu of the cow (Figure 3). Low concentrations of glucose in postpartum cows may predispose the cow to pregnancy loss because the placenta may not have adequate

substrate for the creation of new cells. The incompetent and slowly developing placenta may eventually compromise the fetus. Once the fetus dies then the placenta dies and the corpus luteum regresses. The mammary gland has priority for glucose but neither the mammary gland nor the uterus/placenta has the capacity to concentrate glucose via a glucose transporter. Greater blood flow to the mammary gland dictates its greater capacity to extract glucose from the circulation.

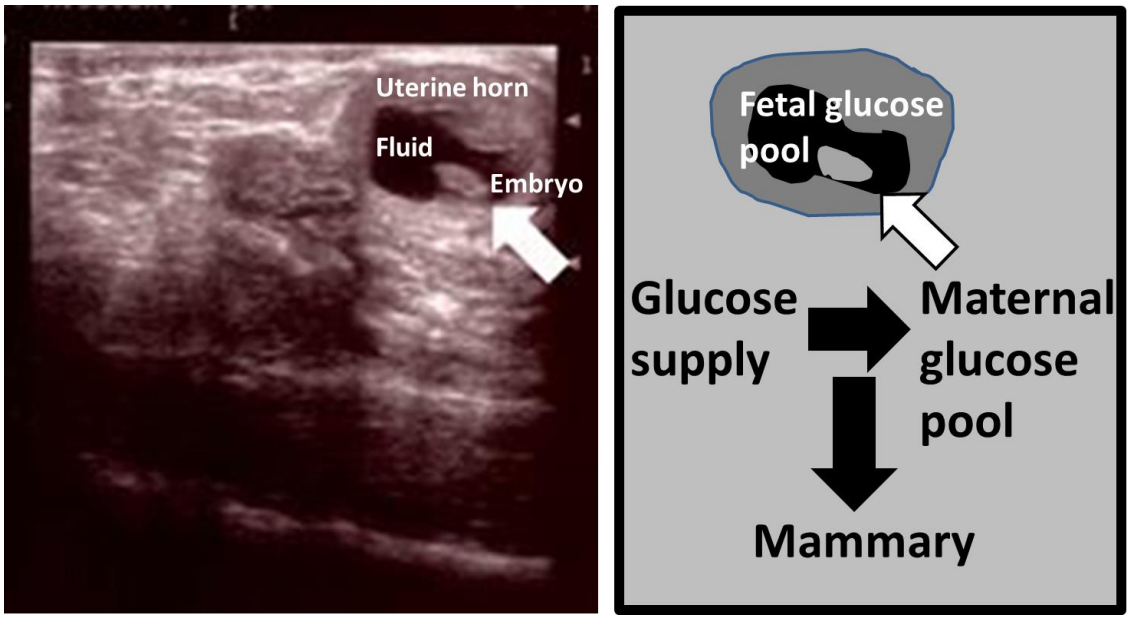

Figure 3. Ultrasound image of a bovine embryo in a lactating cow on day 27 (left) and model for glucose in the pregnant cow (right). The embryo is the small ovoid echogenic structure (arrow) floating within fluid inside the uterine horn. The embryo uses glucose as its primary carbon source for growth. Lactation causes a decrease in blood glucose concentrations because the mammary gland uses glucose for lactose synthesis. Glucose concentrations in placental fluids are less than glucose concentrations in the maternal circulation. The lesser blood glucose in lactating cows is associated with lower glucose concentrations in placental fluids compared with nonlactating cows (Lucy et al., 2012). Lesser glucose reaching the embryo may explain slower embryonic development in lactating cows.

Few published studies in cattle have asked the question “does slower growth of the fetal/placental unit lead to pregnancy loss?” In the horse, delayed development of the embryonic vesicle generally leads to embryonic loss (Carnevale et al., 2000). Several recent studies in the bovine have demonstrated that pregnant cows that undergo pregnancy loss have lesser blood concentrations of PAG leading up to the time that the pregnancy is aborted (Thompson et al., 2010; Pohler et al., 2013). The lesser blood PAG concentration may indicate that the cow is pregnant with a small embryo or fetus.

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. The specific mechanism through which the metabolic environment of early lactation deposits a lasting imprint on uterine and ovarian function is less clear. Also less clear are the mechanisms that link lactation to a predisposition for pregnancy loss in the lactating cow. The slow rate of embryonic or fetal growth in lactating cows with low blood progesterone and low blood glucose concentrations may be an important mechanism explaining pregnancy loss.

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SESSION NOTES