Mechanisms Linking Postpartum Metabolism with Reproduction

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Take Home Messages

- The reproductive and immune systems of the cow must function within the highly metabolic environment required to produce large volumes of milk in early lactation.
- The endocrine axes controlling reproduction respond to the hormones and metabolites that control the highly metabolic environment.
- Dairy cows are immunosuppressed after calving and this immunological state predisposes the cow to common diseases such as metritis and endometritis that can negatively affect reproduction.
- Genetic selection for high-producing healthy cows should reverse current trends and create a future cow that can transition well and reproduce successfully in a highly metabolic environment.

Introduction

Genetic selection has successfully increased milk production per cow (Berry et al., 2015). The increase in milk production per cow has been achieved by selecting for large cows with the capacity to consume and metabolize large volumes of feed. The modern cow is highly metabolic. Her great capacity to metabolize nutrients is supported by endocrine systems that control the flow of metabolites to the mammary gland for the synthesis of milk (Lucy, 2008). Genetic selection for traits other than milk production was not done during the latter half of the 20th century (VanRaden, 2004). The resulting cows were compromised with respect to health, reproduction, and longevity, perhaps because the highly metabolic environment that supports high production was incompatible with other processes that were not under genetic selection (Berry et al., 2015). This review will discuss the relationship between

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metabolism and reproductive function in early postpartum cows during the transition period.

▪ General Aspects of Metabolism Postpartum

An early lactation cow will produce 50 to 100 kg of milk per day. The cow undergoes a series of homeorhetic mechanisms to support the increase in milk production (Bauman and Currie, 1980; Bell, 1995). Several hormones are involved, but perhaps the best studied hormone is growth hormone (GH). Blood concentrations of GH increase shortly after calving (Lucy, 2008). The increase in GH orchestrates the homeorhetic mechanism that typifies early lactation. Growth hormone stimulates hepatic gluconeogenesis (glucose synthesis in the liver) to increase glucose supply to support that rapid increase in milk production shortly after calving. At the same time, GH antagonizes insulin action and creates an insulin resistant state so that circulating glucose cannot be used by liver, muscle or adipose tissue for the creation of glycogen or fat. Growth hormone also stimulates lipolysis. The mobilized lipid can either be incorporated directly into milk fat or used as an energy source in the postpartum cow. The end result is a large mass of glucose created through gluconeogenesis and fatty acids mobilized from lipid that are directly available for the synthesis of milk.

The Liver Coordinates the Homeorhetic Mechanisms Postpartum

A variety of tissues are involved in coordinating homeorhetic mechanisms that support milk production, including the brain (hypothalamus and pituitary), other endocrine glands (thyroid, adrenal, pancreas, etc.), the digestive tract (rumen, small and large intestines), adipose tissue (abdominal and subcutaneous stores), skeletal muscle, immune systems and liver. No endocrine gland or tissue can function alone to support the metabolic state of early lactation. This explains why the entire animal must be healthy to achieve high milk production. Although we traditionally thought that hormones controlling lactation arose exclusively from traditional endocrine glands, we now know that most tissues produce hormones with the capacity to control various aspects of the physiological state. This includes the liver, which functions as a highly metabolic organ with important endocrine functions.

Among the tissues that support milk production, the liver is pivotal because it coordinates nutrient metabolism with the endocrinology of the cow (Figure 1). There is a decrease in GH receptor expression in liver before calving. The decrease in GH receptor expression before calving is associated with a decrease in the release of insulin-like growth factor–1 (IGF1) from the liver. IGF1 is the primary negative feedback molecule for GH. The decrease in IGF1 from liver, therefore, explains the increase in GH that occurs early postpartum. The increase in GH early postpartum causes the increase in

gluconeogenesis and insulin resistance that supports the demand for large amounts of glucose postpartum. The increase in GH also drives lipolysis that mobilizes fatty acids (NEFA) from adipose tissue for incorporation directly into milk fat or for the generation of cellular energy. Incomplete metabolism of NEFA leads to an increase in blood ketone concentrations (primarily beta hydroxybutyrate or BHB).

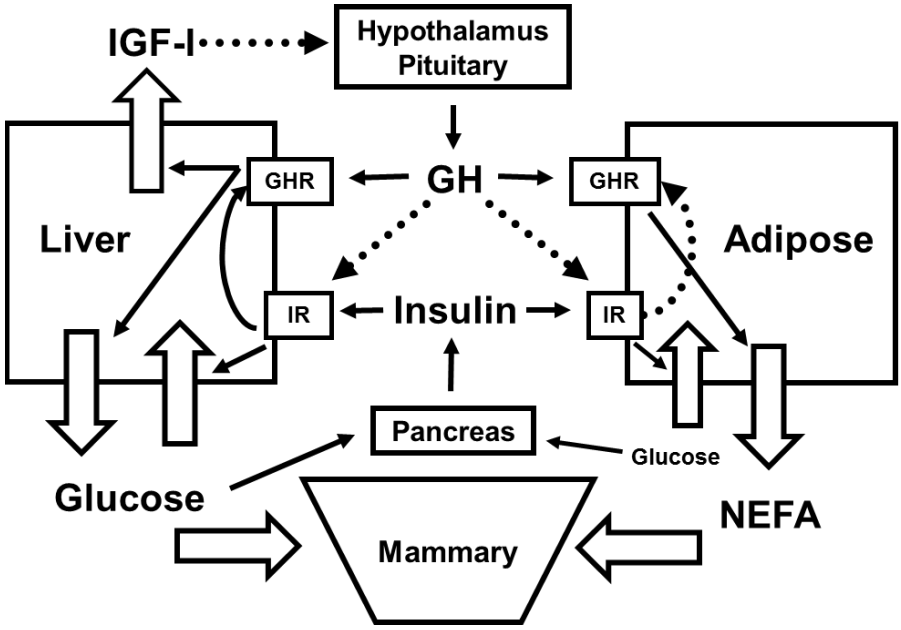

Figure 1. Model for the interaction of growth hormone (GH) and insulin in postpartum dairy cows (Lucy, 2008). Solid lines infer stimulatory actions. Broken lines infer negative feedback or inhibitory actions. Growth hormone signals in liver and adipose through its receptor (GHR) and inhibits the activity of the insulin receptor (IR). Early postpartum and high producing dairy cows have high GH, low insulin, and peripheral insulin resistance. The condition promotes glucose and NEFA availability for milk synthesis. Later lactation and low producing cows have lower GH, higher insulin, and greater insulin sensitivity. The later condition reduces NEFA mobilization and shunts glucose to peripheral tissues (including adipose). See text for specific details and the endocrine sequence of events in postpartum cows.

Despite these physiological mechanisms, the cow becomes hypoglycaemic after calving because glucose demand drives blood glucose concentrations downward (Lucy et al., 2014). The hypoglycaemia keeps blood insulin concentrations low. Low blood insulin maintains the state of low liver GH receptor expression and low circulating IGF1. The low circulating IGF1 keeps GH secretion high because there is no negative feedback on GH. The low concentrations of glucose have an additional consequence; specifically, inadequate glucose supply contributes to the incomplete oxidation of NEFA, which creates elevated BHB postpartum (White, 2015).

The Shift from a Catabolic to an Anabolic State Postpartum

The preceding section describes the catabolic state of early lactation. The endocrine state of early lactation (high GH, low IGF1, low insulin, low glucose, and high NEFA and BHB) remains in place until the cow progresses toward a positive energy balance (anabolic state). A key regulatory molecule is glucose (Lucy et al., 2014). In time, the cow's ability to generate glucose through the expansion of digestive capacity postpartum, a greater capacity to consume and digest nutrients, and greater gluconeogenesis leads to an increase in glucose supply. The cow also passes peak lactation so that the demand for glucose is less. The increase in glucose supply relative to demand increases available glucose and stimulates insulin secretion. Greater insulin secretion causes an increase in GH receptor expression (Butler et al., 2003). The increase in GH receptor expression causes an increase in IGF1. The increase in IGF1 feeds back negatively on GH. The reduction in GH postpartum relieves the insulin resistance so that excess glucose can now flow into other tissues. This shift in glucose flow is equivalent to the shift from a catabolic state to an anabolic state postpartum. A cow that is catabolic can begin to restore glycogen in liver and muscle and also gain adipose tissue mass.

The shift from a catabolic to an anabolic state is important relative to the body condition score (BCS) of the postpartum cow. The exact mechanisms are unclear but cows that maintain greater BCS postpartum are generally better with respect to reproduction (Kawashima et al., 2012).

▪ Linking Metabolism to Reproduction Postpartum

Scientific thinking about the link between metabolism and postpartum reproduction has progressed far beyond the traditional notions of negative energy balance and interval to first ovulation. It is clear that there is a complex interplay between the endocrine systems controlling metabolism, the endocrine systems controlling the ovary, the endocrine system within the ovary itself, and the immune system of the cow.

Postpartum Reproduction Starts with a Healthy Liver

Perhaps the most-important first step toward maintaining good reproduction on a dairy is to maintain a healthy liver in transition dairy cows. Maintaining a healthy liver is best achieved through appropriate dry cow and transition cow management to maintain an appropriate BCS at calving and prevent excessive BCS loss after calving. Appropriate dry cow nutritional management is essential (Drackley and Cardoso, 2014). An appropriate BCS at calving cannot be underemphasized. Cows with excessive BCS at calving and excessive BCS loss after calving develop fatty liver postpartum. The sequence of deleterious events associated with fatty liver are depicted in Figure 2. Cows that have excessive BCS at calving typically develop fatty liver because of poor intake postpartum. The poor intake postpartum can be explained by insufficient appetite perhaps caused by the excessive BCS. Failure to consume adequate feed leads to excessive adipose tissue loss and elevated NEFA in blood. The NEFA enter the liver but cannot be fully metabolized so fat builds up in liver tissue. Fat causes inflammation in 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., 2015). The problems that begin with inadequate intake, inflammation and poor liver health, therefore, eventually affect the entire metabolic make-up of the cow.

Linking Liver Health to Reproduction

There are a number of consequences to fatty liver that go beyond the immediate damage of the liver tissue. The abnormal metabolic and hormonal environment created by the inflamed and damaged liver can affect not only the capacity for the cow to consume feed and make milk but also the capacity of the cow's immune system to combat disease (Zerbe et al., 2000) as well as the capacity of her reproductive axis to function normally (Clarke, 2014).

Postpartum Immunology

The current theory is that the metabolic environment in postpartum cows suppresses the innate immune system through effects on the function of polymorphonuclear neutrophils (PMN; Graugnard et al., 2012; LeBlanc, 2012). Changes in circulating concentrations of nutrients and metabolites that occur normally in the postpartum cow are exactly opposite to those that would benefit the function of PMN. In extreme cases, like those seen for fatty liver or ketotic cows, the shifts in hormones and metabolites are greater and there is the potential to compromise immune function further. For example, glucose is the primary metabolic fuel for PMN (Moyes, 2015). 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

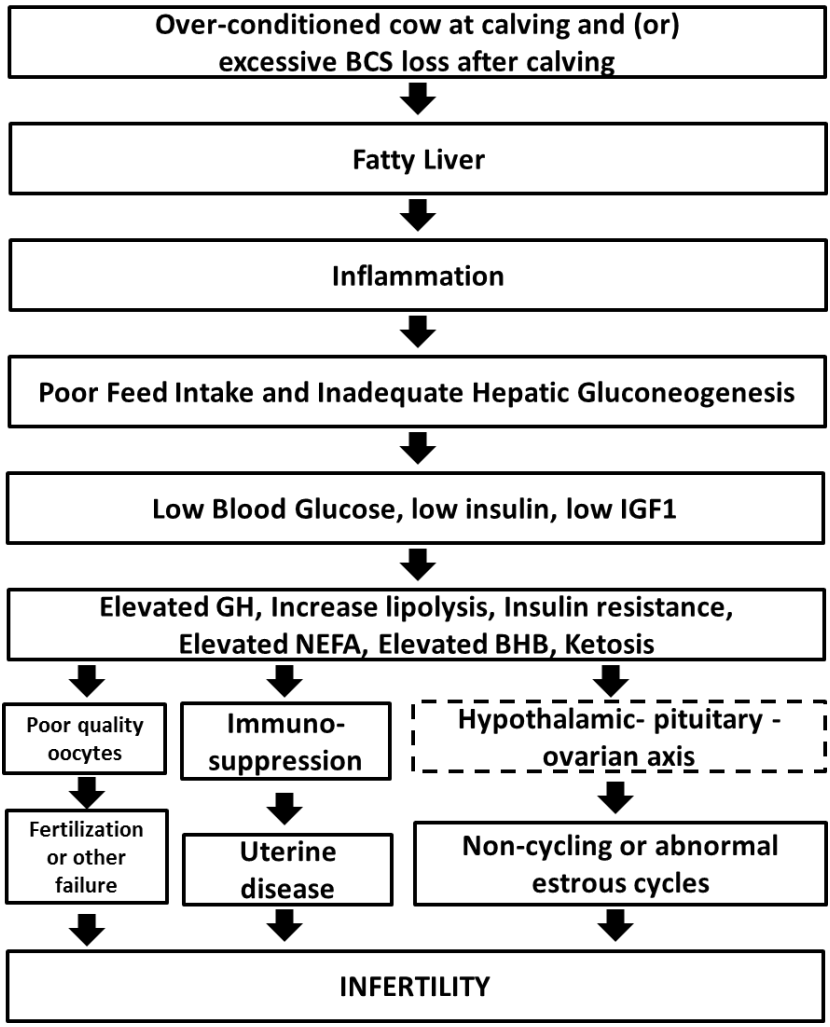

Figure 2. Sequence of events that link excessive body condition score (BCS) at calving and (or) excessive BCS loss after calving to infertility later postpartum. The dashed line around the box for "hypothalamus-pituitary-ovarian axis" indicates in inhibitory effect of the metabolic profile. See text for specific details and the sequence of events in postpartum cows.

predisposes the cow to uterine disease during the early postpartum period and infertility later postpartum (Chapinal et al., 2012; Esposito et al., 2014; Wathes, 2012). A plausible hypothesis is that the abnormal metabolic profile of the postpartum cow creates immunosuppression. This immunosuppression

leads to a poor response to uterine infection. The poor response to uterine infection can lead to metritis in the short term and subclinical endometritis in the long term. Subclinical endometritis leaves a permanent “scar” on uterine tissue that remains after the disease state is seemingly resolved (LeBlanc, 2012). The nature of scar left by subclinical endometritis is unknown but clearly creates the risk for infertility and early embryonic loss later postpartum.

The cells that respond to uterine infection (predominantly PMN) are the same cells that combat the organisms that cause mastitis and pneumonia (2 additional common diseases of the postpartum cow). These diseases do not directly affect reproductive tissues but secondary responses of the cow to the disease can disrupt the estrous cycle and cause embryonic loss. In a recent study, Fuenzalida et al. (2015) found that a mastitis event during the breeding period was associated with lower fertility. Cytokines and other hormones released by the inflamed mammary tissue can circulate throughout the cow and block ovulation or cause premature regression of the corpus luteum (Sheldon, 2015).

Cows that fail in the fresh cow pen may do so because their compromised immune system fails to overcome the initial challenge from pathogens. There is perhaps a “tipping point” beyond which a cow cannot recover from infection. With respect to immune system function early postpartum, an appropriate metabolic response to early lactation may maintain adequate immune cell functionality so that the tipping point is not reached.

Restoration of Ovarian Activity

The traditional focus for reproductive biologists studying dairy cows postpartum has been interval to first ovulation. This is because in traditional dairy systems the non-cycling cow was a major concern. The interval to first ovulation depends on the initiation of luteinizing hormone (LH) secretion from the pituitary. The secretion of LH depends on the release of gonadotropin-releasing hormone (GnRH) form the hypothalamus. LeRoy et al. (2008) concluded that glucose and insulin were the most likely molecules to exert an effect on GnRH secretion in the postpartum dairy cow. 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]. This strong synergism explains the well-established relationship between circulating concentrations of insulin and IGF1 and the interval to first postpartum ovulation (Kawashima et al., 2012; Lucy, 2011; Velazquez et al., 2008). In general, improved metabolic indicators are associated with an earlier interval to first ovulation.

Restoration of “normal” Ovarian Cycles

Recent studies have demonstrated that cows may not cycle “normally” after first ovulation (Remnant et al., 2015). Abnormal estrous cycles include short

cycles, long cycles with normal luteal phase progesterone concentrations, long cycles with subnormal luteal phase progesterone concentrations, and failure to ovulate with one week after luteolysis. The same hormones that control when the cow begins to cycle (insulin, IGF1, FSH, 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 (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. Common problems that are encountered in lactating cows, for example, poor estrus expression (presumably caused by inadequate estradiol production by the follicle; Woelders et al., 2014) and sub-optimal luteal phase progesterone (inadequate progesterone production by the corpus luteum; Wiltbank et al., 2011) could be explained by the fact that the cow has inadequate insulin and IGF1 to synergize with FSH and LH to maintain steroidogenesis by the ovary. The manifestation of this biology at the level of the cow may be a series of abnormal estrous cycles that largely go undetected by the producer because they are difficult to track in cows with poor expression of estrus. Part of the success of ovulation synchronization programs that are used widely in some countries can be explained by effectively overcoming abnormal patterns of estrous cyclicity that typify postpartum dairy cows (Wiltbank and Pursley, 2014).

Oocyte Health

The ovary has 2 functions in the postpartum cow. The first is an endocrine function (as described above) to produce a variety of hormones that include progesterone and estradiol. The second is to produce the female gamete (oocyte). The oocyte rests in a quiescent state within the ovary until approximately 2 months before ovulation. At that time, it initiates growth along with the surrounding granulosa cells. There is good evidence from several sources that the metabolic environment within which the oocyte develops can affect its capacity for fertilization and further development (Berlinguer et al., 2012; LeRoy et al., 2008; LeRoy et al., 2011). One theory is that the long development program of the oocyte before ovulation enables an irreversible imprinting of the metabolome on the oocyte itself. If this imprint is negative then this may explain why cows with metabolic disease early postpartum have infertility several months later.

▪ Solutions

As stated above, avoiding metabolic and other disease in transition cows should theoretically improve reproduction later postpartum. There is very strong evidence to support this point (Drackley and Cardoso, 2014). Avoiding problems in transition cows begins with appropriate management and feeding

of dry cows and continues through the management in calving pens, fresh cow pens and early lactation pens.

Ultimately, the genetics of modern dairy cows needs to be improved so that the cow possesses the underlying biological to sustain health and productivity in an extremely metabolic condition. The greater emphasis that is now placed on health, reproduction and longevity in most genetic indices should enable this genetic change to occur (Berry et al., 2015). The implementation of genomic technologies will shorten the time required to achieve the desired genetic change.

▪ Conclusions

The reproductive and immune systems of the cow must function within the highly metabolic environment required to produce large volumes of milk in early lactation. Unfortunately, years of genetic selection for milk production without consideration of other traits led to problems in health, reproduction, and longevity in modern dairy cows. One of the underlying reasons for the genetic problem was that the hormones and metabolites that control the highly metabolic environment were at odds with the endocrine axes controlling reproduction. The highly metabolic environment also leads to immunosuppression after calving and this immunological state predisposes the cow to common diseases such as metritis and endometritis that can negatively affect reproduction. Genetic selection for high-producing healthy cows should reverse current trends and create a future cow that can transition well and reproduce successfully in a highly metabolic environment. The implementation of genomic technologies will shorten the time required to achieve the desired genetic change.

▪ References

Bauman, D.E. and W.B. Currie. 1980. Partitioning of nutrients during pregnancy and lactation: a review of mechanisms involving homeostasis and homeorhesis. J. Dairy Sci. 63:1514-1529.

Bell, A.W. 1995. Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation. J. Anim. Sci. 73:2804-2819.

Berlinguer, F., A. Gonzalez-Bulnes, I. Contreras-Solis, A. Spezzigu, L. Torres-Rovira, S. Succu, S. Naitana, and G.G. Leoni. 2012. Glucogenic supply increases oocyte developmental competence in sheep. Reprod. Fertil. Devel. 24:1055-1062.

Berry, D.P., N.C. Friggens, M. Lucy, and J.R. Roche. 2015. Milk production and fertility in cattle. Annu. Rev. Anim. Biosci. (In press).

Butler, S.T., A.L. Bork, S.H. Pelton, R.P. Radcliff, M.C. Lucy, and W.R. Butler. 2003. Insulin restores hepatic growth hormone (GH) responsiveness during lactation-induced negative energy balance in dairy cattle: effects on expression of insulin-like growth factor-I and GH receptor 1A. J. Endocrinol. 176:205-217.

Chapinal, N., S.J. Leblanc, M.E. Carson, K.E. Leslie, S. Godden, M. Capel, J.E. Santos, M.W. Overton, and T.F. Duffield. 2012. Herd-level association of serum metabolites in the transition period with disease, milk production, and early lactation reproductive performance. J. Dairy Sci. 95:5676-5682.

Clarke, I.J. 2014. Interface between metabolic balance and reproduction in ruminants: focus on the hypothalamus and pituitary. Horm. Behav. 66:15-40.

Drackley, J. and F. Cardoso. 2014. Prepartum and postpartum nutritional management to optimize fertility in high-yielding dairy cows in confined TMR systems. Animal 8:5-14.

Esposito, G., P.C. Irons, E.C. Webb, and A. Chapwanya. 2014. Interactions between negative energy balance, metabolic diseases, uterine health and immune response in transition dairy cows. Anim. Reprod. Sci. 144:60-71.

Fuenzalida, M.J., P.M. Fricke, and P.L. Ruegg. 2015. The association between occurrence and severity of subclinical and clinical mastitis on pregnancies per artificial insemination at first service of Holstein cows. J. Dairy Sci. 98:3791-3805.

Garcia, M., B.J. Bequette, and K.M. Moyes.2015. Hepatic metabolic response of Holstein cows in early and mid-lactation is altered by nutrient supply and lipopolysaccharide in vitro. J. Dairy Sci. 98:7102-7114.

Graugnard, D.E., M. Bionaz, E. Trevisi, K.M. Moyes, J.L. Salak-Johnson, R.L. Wallace, J.K. Drackley, G. Bertoni, and J.J. Loor. 2012. Blood immunometabolic indices and polymorphonuclear neutrophil function in peripartum dairy cows are altered by level of dietary energy prepartum. J. Dairy Sci. 95:1749-1758.

Kawashima, C., M. Matsui, T. Shimizu, K. Kida, and A. Miyamoto. 2012. Nutritional factors that regulate ovulation of the dominant follicle during the first follicular wave postpartum in high-producing dairy cows. J. Reprod. Devel. 58:10-16.

LeBlanc, S.J. 2012. Interactions of metabolism, inflammation, and reproductive tract health in the postpartum period in dairy cattle. Reprod. Domest. Anim. 47 Suppl 5:18-30.

Leroy, J.L., D. Rizos, R. Sturmey, P. Bossaert, A. Gutierrez-Adan, V. Van Hoeck, S. Valckx, and P.E. Bols. 2011. Intrafollicular conditions as a major link between maternal metabolism and oocyte quality: a focus on dairy cow fertility. Reprod. Fertil. Devel. 24:1-12.

Leroy, J.L., T. Vanholder, A.T. Van Knegsel, I. Garcia-Ispierto, and P.E. Bols. 2008. Nutrient prioritization in dairy cows early postpartum: mismatch between metabolism and fertility? Reprod. Domest. Anim. 43 Suppl 2:96-103.

Lucy, M.C. 2008. Functional differences in the growth hormone and insulin-like growth factor axis in cattle and pigs: implications for post-partum nutrition and reproduction. Reprod. Domest. Anim. 43:31-39.

Lucy, M.C. 2011. Growth hormone regulation of follicular growth. Reprod. Fertil. Devel. 24:19-28.

Lucy, M., S. Butler, and H. Garverick. 2014. Endocrine and metabolic mechanisms linking postpartum glucose with early embryonic and foetal development in dairy cows. Animal 8:82-90.

McCarthy, M.M., M.S. Piepenbrink, and T.R. Overton. 2015. Associations between hepatic metabolism of propionate and palmitate in liver slices from transition dairy cows. J. Dairy Sci. 98:7015-7024.

Moyes, K. 2015. Triennial Lactation Symposium: Nutrient partitioning during intramammary inflammation: A key to severity of mastitis and risk of subsequent diseases? J. of Anim. Sci. 93:5586.

Remnant, J.G., M.J. Green, J.N. Huxley, and C.D. Hudson. 2015. Variation in the interservice intervals of dairy cows in the United Kingdom. J. Dairy Sci. 98:889-897.

Sheldon, I.M. 2015. Milk somatic cell counts and pregnancy rates in dairy cattle. Vet Rec. 176:409-410.

VanRaden, P.M. 2004. Invited review: selection on net merit to improve lifetime profit. J. Dairy Sci. 87:3125-3131.

Velazquez, M.A., L.J. Spicer, and D.C. Wathes. 2008. The role of endocrine insulin-like growth factor-I (IGF-I) in female bovine reproduction. Domest. Anim. Endocrinol. 35:325-342.

Wathes, D.C. 2012. Mechanisms linking metabolic status and disease with reproductive outcome in the dairy cow. Reprod. Domest. Anim. 47 Suppl 4:304-312.

White, H. 2015. The role of TCA cycle anaplerosis in ketosis and fatty liver in periparturient dairy cows. Animals 5:793-802.

Wiltbank, M.C., and J.R. Pursley. 2014. The cow as an induced ovulator: timed AI after synchronization of ovulation. Theriogenology 81:170-185.

Wiltbank, M.C., A.H. Souza, P.D. Carvalho, R.W. Bender, and A.B. Nascimento. 2011. Improving fertility to timed artificial insemination by manipulation of circulating progesterone concentrations in lactating dairy cattle. Reprod. Fertil. Devel. 24:238-243.

Woelders, H., T. van der Lende, A. Kommadath, M.F. te Pas, M.A. Smits, and L.M. Kaal. 2014. Central genomic regulation of the expression of oestrous behaviour in dairy cows:a review. Animal 8:754-764.

Zerbe, H., N. Schneider, W. Leibold, T. Wensing, T.A. Kruip, and H.J. Schuberth. 2000. Altered functional and immunophenotypical properties of neutrophilic granulocytes in postpartum cows associated with fatty liver. Theriogenology 54:771-786.