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Metabolic Alterations during Peripartum Period and its Effect on Fertility in Bovines

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ABSTRACT

The peripartum period in bovines, spanning from the final weeks of gestation through the early stages of lactation, is a critical phase marked by substantial metabolic and physiological changes that profoundly influence reproductive performance. During the transition period, cows undergo a substantial increase in nutrient needs to support the growth of the fetus and the onset of lactation. However, this demand is often not met due to a concurrent decline in dry matter intake, resulting in a state of negative energy balance (NEBAL). This imbalance triggers a cascade of metabolic adaptations, including elevated concentrations of non-esterified fatty acids (NEFA) and beta-hydroxybutyric acid (BHBA), along with reductions in blood glucose and insulin levels. These metabolic disturbances can adversely affect ovarian function delaying the resumption of normal estrous cycles postpartum. As a result, conception rates decline, leading to extended calving intervals and reduced reproductive efficiency. Moreover, the metabolic stress experienced during this period increases the cow's susceptibility to a range of postpartum disorders, such as ketosis, fatty liver disease, metritis, and retained placenta. These conditions further compound reproductive challenges and compromise overall productivity. Understanding the complex interplay between metabolic status and reproductive physiology during the peripartum period is essential for formulating targeted nutritional and management interventions. Such strategies aim to optimize energy balance, support immune function, and enhance reproductive outcomes. This review provides a comprehensive overview of the key metabolic alterations occurring during the peripartum period and explores their implications on fertility in bovines

KEYWORDS: Peripartum, NEBAL, NEFA, BHBA, ketosis, fatty liver, metritis

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1. INTRODUCTION

Reproductive inefficiency in dairy cattle remains a significant source of frustration for dairy producers (Call and Stevenson, 1985). Even under ideal conditions, achieving optimal reproductive outcomes is challenging due to the many factors involved in producing a live calf. Effectively managing the complexities of the estrous cycle and the overall annual reproductive cycle requires a deep understanding of numerous interrelated physiological processes. Additionally, reproductive efficiency is not solely dependent on animal management-it also relies heavily on the effective coordination and performance of the personnel responsible for milking, feeding, housing, inseminating, and caring for the cows (Stevenson, 2001).

A particularly critical phase in the reproductive and productive lifecycle of a dairy cow is the transition period, defined as the three weeks before and three weeks after calving (Van Saun, 2016). Closely tied to this is the peripartum period, encompassing the days immediately before, during, and after parturition. During this time, the cow experiences a remarkable transformation as her body shifts from a pregnant, non-lactating state to a high-performing, milk-producing state. This phase is marked by intense physiological and biochemical changes, setting the stage for successful lactation and overall productivity. The common physiological and metabolic changes, or transitions occurring in the dry and early lactation periods include; cessation of milking at dry-off, changes in environment and ration composition, rapid fetal growth, decline in dry matter intake just before calving, initiation of colostrum production, hormonal changes including declining progesterone and rising estrogen blood levels, the process of giving birth and rapid increase in milk production (McClary et al., 2015). These changes are responsible for the stress in animals and increase their susceptibility to infectious and metabolic diseases, which leads to huge economic losses to the farmers. The transition cows experience negative energy balance (NEBAL) and micronutrient deficits as a result of their decreased feed intake and increased energy and nutritional requirements for the synthesis of colostrum and milk (Toledo-Alvarado et al., 2017; Perez-Baez et al., 2019; Song et al., 2021). The NEBAL further accelerates the mobilization of body fat reserves, leading to a higher release of non-esterified fatty acids (NEFA) into the bloodstream. As the liver processes these fatty acids, it leads to the accumulation of beta-hydroxybutyric acid (BHBA), a key indicator of metabolic stress during the transition period (Wankhade et al., 2017). During this time, dairy cows typically exhibit hypoglycemia, hypoinsulinemia, and increased concentrations of ketone bodies and NEFAs in the bloodstream (Gross and Bruckmaier, 2019; Bach, 2019; Sundrum, 2015). The degree (depth) and duration of the negative balance are the main factors to consider since they will determine how quickly the cow can adjust and achieve a positive balance. Immune suppression during this period is multifactorial and can be related to hypocalcemia, elevated blood glucocorticoids levels, hypoglycemia, elevated ketones, and elevated blood NEFA levels (Rodrígue et al., 2017; Bradford et al., 2015; Wankhade et al., 2017). The combined effects of negative energy and protein balance, along with weakened immune function, significantly increase the risk of various metabolic and infectious diseases (Abdelli et al., 2017). Common conditions that may arise include retained fetal membranes, ketosis, metritis, displaced abomasum, and mastitis, among other health issues frequently encountered during the transition period. The growth and dominance of follicles on the ovaries and the subsequent ovulation are influenced by nutritional metabolic changes that occur during the post-parturient period (Sammad et al., 2020; Caixeta et al., 2017), while reproductive tract diseases can have a direct impact on fertilization, embryo/fetal development, implantation, and placental development (Ribeiro et al., 2016; Furukawa et al., 2021). The management of energy balance and maintenance of immunological function throughout the transition from pregnancy to nursing are critical for better reproductive performance and successful lactations. The cow is prepared for a smooth transition before start of the following lactation, during the dry phase. Adequate nutrition, a clean environment, and strategic immunization are key components in restoring normal immune function and disease resistance in the periparturient period.

2. METABOLIC CHANGES DURING PERIPARTUM PERIOD

2.1. Reduction in dry matter intake

In the weeks preceding calving, dry matter intake typically declines, hitting its lowest level at parturition. Around 32% of this reduction occurs during the last three weeks of gestation, with approximately 89% of the decrease happening within five to seven days before calving (Hayirli et al., 2002). Following calving, there is a steady increase in dry matter intake. Nevertheless, the post parturient rise in DMI often remains inadequate to meet the elevated nutritional and energetic requirements associated with early lactation. While peak milk production generally occurs between the fourth and sixth week postpartum, the maximum DMI is usually not reached until 8 to 10 weeks after calving. Consequently, dairy cows are frequently subjected to a state of NEBAL for a minimum of 50 days following parturition (Perez-Baez et al., 2019). Prepartum measurements of dry matter intake as a percentage of body weight and energy balance were found to be significantly associated with postpartum indigestion and other digestive disorders, indicating their potential as predictors of postpartum digestive disturbances (Perez-Baez et al., 2021). Several theories and concepts have been proposed to explain the reduction in DMI during the periparturient period. The decline in DMI during the final trimester of pregnancy is largely due to the physical pressure from the expanding fetus on the rumen, which can reduce rumen capacity and trigger negative signals to the satiety center of hypothalamus, ultimately suppressing the voluntary feed intake (Reddy et al., 2016). Reduced plasma estradiol concentration and the existence of clinical or subclinical illnesses may potentially be contributing factors to the reduction in feed intake near the end of pregnancy (Grummer, 1995). Apart from these, Allen and Bradford (2009) proposed "Hepatic oxidation theory" which explains the relationship between the feeding centre in the brain and concentration of ATP in the liver. According to this theory, when there is more production of ATP by oxidation of fuel due to lipid mobilization during the peripartum period, there will be less firing on satiety center, while lesser amount of ATP due to insufficient fuel oxidation results in more firing or stimulation of feed intake. However, the exact mechanism behind the regulation of feed intake by ATP-mediated neuron firing rate is not fully understood. The lower plasma insulin concentration and its sensitivity during the transition period leads to excess mobilization of fat in the form of NEFA, it is likely to suppress the feed intake during this period by inhibiting the satiety center.

However, the underlying cause of reduced DMI during the prepartum period and its connection to postpartum health challenges remains unclear and continues to be a topic of investigation. Bertoni et al., 2009 reported that a transient reduction in feed consumption during the final two weeks before calving, has been linked to systemic inflammation as shown by elevated blood haptoglobin concentrations. This prepartum systemic inflammation has been associated with a higher concentration of pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- α. A 4-day feed restriction model was presented by Pascottini et al. (2019) to replicate the typical observations made in the final two weeks prior to calving. As per this study, fat mobilization as indicated by >2-fold greater NEFA concentration; however, fat mobilization failed to generate systemic inflammation (based on haptoglobin and albumin concentrations). Thus, the authors concluded that their feed restriction model failed to trigger systemic inflammation because it did not exactly replicate the pattern and duration of naturally occurring reduction in DMI in the prepartum period. Consequently, the cause of the decreased feed intake during the prepartum phase was still unknown.

2.2. Periparturient immunosuppression

Immunosuppression is defined as decreased immunological response. Impaired immune responses are a result of endocrine alterations and physiological stressors during transition; however, not all stress-related neuroendocrine responses are immunosuppressive. The precise physiological mechanisms underlying immunosuppression during the periparturient period and the consequent elevated risk of clinical diseases have not yet been fully elucidated. Most cases of clinical mastitis in dairy cows occur during the early stages of lactation, and it has been found that opportunistic infections are the primary cause (Hill, 1981). As a result, cows in this stage have their immune system suppressed. This finding prompted further investigation into immunosuppression during the periparturient period. The immunity of cattle against infectious diseases is mediated by various interrelated cellular and humoral processes. Neutrophils are one of the most significant cell types within the natural defense mechanisms due to their ability to respond quickly and destroy microbes without prior exposure to a disease. Neutrophils can also release cytokines, which may trigger further signals for neutrophil recruitment (Kerhli, 2015). Macrophages are the primary source of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF, which are found in various organs, including the liver, brain, and adipose tissue. It is believed that the decrease in DMI and consequent fat mobilization during the prepartum period are responsible for the release of these cytokines into the bloodstream. In the liver, these cytokines activate the production of positive acute-phase proteins such as haptoglobin while reducing the synthesis of negative acute-phase proteins like albumin (Pascottini et al., 2020; Mezzetti et al., 2020). According to Trevisi et al. (2015), an elevated inflammatory status characterized by increased levels of IL-1β prior to calving is associated with a diminished liver functionality index during early lactation. This reduction is evidenced by changes in critical liver biomarkers, including albumin, cholesterol, and bilirubin. The concentration of IL-1 β is linked to a low liver functionality index in the final month of the dry period, which appears to be related to the likelihood of clinical diseases occurring in the subsequent early lactation.

During the periparturient period, cows undergo many neuroendocrine changes. Hormone fluxes such as elevated levels of estrogens and progesterone in the final stages of gestation may adversely affect immune cell function. Supraphysiologic concentrations of estradiol have been reported to suppress neutrophil function (Comline et al., 1974). Additionally, the progesterone binding capacity of human lymphocytes is increased during pregnancy, which results in reduced lymphocyte functions and the production of antibodies and cytokines by lymphocytes is significantly reduced leading to neutrophil dysfunction and a higher risk of periparturient disorders. Additionally, the breakdown of body fat reserves produces ketone bodies that weaken the immune system even further. It is vital to take proactive measures to protect cow health during this critical period and mitigate the risk of infections. The take home message is that a dairy cow's immune system begins to deteriorate several weeks before she actually delivers birth, and even before the rise in endogenous cortisol that takes place between 36 hours before and 36 hours after calving. This phenomenon is known as periparturient immunosuppression. Regardless of its causation, the immunosuppressive state experienced by periparturient dairy cows make them extremely vulnerable to the development of new infections, especially in the mammary gland, and the subsequent progression of these new subclinical infections into clinical disease, including metritis, mastitis, and postpartum outbreaks of intestinal diseases like salmonellosis, to mention a few. This is not to say that one disease or issue causes another, but rather that there are often associations that exist such that when one condition is observed, there is a higher likelihood of seeing other related conditions. Cows exhibiting greater immune suppression during the periparturient period are at an increased risk of retained fetal membranes, metritis, and mastitis, while those suffering from more severe negative energy balance are more susceptible to ketosis, displaced abomasum, and ovarian dysfunction.

2.3. Negative energy balance

Glucose, the primary product of carbohydrate digestion in the rumen, undergoes rapid fermentation into volatile fatty acids (VFAs) and is subsequently resynthesized in the liver through gluconeogenesis. In postpartum dairy cows, a substantial portion of this glucose is utilized for the synthesis of lactose, the principal sugar in milk, with approximately 72 grams of glucose required for each kilogram of milk produced (Bell, 1995). As previously discussed, the decline in DMI during the peri-parturient period, coupled with the increased energy demands of lactation, are key contributors to the onset of NEBAL. A marked reduction in DMI typically occurs during the final ten days preceding parturition, followed by a gradual increase thereafter. However, this rise in intake is generally insufficient to meet the heightened energy and nutrient demands associated with early lactation. Peak lactation is typically achieved within 4 to 6 weeks postpartum, whereas the peak in DMI often does not occur until 8 to 10 weeks postpartum. Consequently, dairy cows commonly experience NEBAL for at least the first 50 days following parturition (Perez-Baez et al., 2019). During this period, several physiological adaptations take place, including enhanced hepatic gluconeogenesis, reduced glucose utilization by peripheral tissues, increased mobilization of NEFAs from adipose tissue, and elevated NEFA uptake by peripheral tissues. Dairy cows undergoing NEBAL typically present a metabolic profile characterized by hypoglycemia, hypoinsulinemia, and elevated circulating levels of ketone bodies and NEFAs (Gross and Bruckmaier, 2019; Bach, 2019; Sundrum, 2015). The presence of NEBAL is associated with an elevated incidence of nutritional metabolic disorders (Abdelli et al., 2017). According to current literature, postpartum nutritional and metabolic imbalances are major contributing factors to reproductive disorders in dairy cows following parturition (Cardoso et al., 2020).

3. EFFECT OF EARLY POSTPARTUM GLUCOSE ON REPRODUCTIVE PERFORMANCE

3.1. Effect on restoration of ovarian cyclicity postpartum

Glucose and insulin are considered key regulators of hypothalamic gonadotropin-releasing hormone (GnRH) secretion in postpartum dairy cows. Alongside gonadotropins such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), both insulin and insulin-like growth factor 1 (IGF-1) play essential roles in supporting follicular cell proliferation and survival. Reduced glucose availability during early lactation results in decreased circulating levels of insulin and IGF-1, contributing to a catabolic state in which the cow mobilizes body tissues to meet energy demands. As lactation progresses and milk production declines, insulin and IGF-1 levels increase, facilitating a shift toward an anabolic state (Leroy et al., 2008). In this phase, glucose is redirected to peripheral tissues such as muscle and adipose tissue, and the reproductive axis is reactivated. A study by Green et al. (2012) reported that cows failing to conceive after the first artificial insemination (AI) at approximately 60 days postpartum exhibited lower plasma glucose concentrations during the initial 30 days postpartum compared to those that became pregnant. Post partum negative energy balance and the subsequent accumulation of NEFA in follicular fluid disrupt the metabolic environment, impair energy production in granulosa cells, and ultimately lead to their death, potentially affecting follicle development and fertility (Aardema et al., 2019). Elevated levels of NEFA and β-hydroxybutyrate (BHBA) in the bloodstream of diseased cows reduce and impair the function of insulin-like growth factor 1 (IGF-1). Since IGF-1 plays a key role in regulating GnRH and LH activity, its suppression leads to decreased estradiol (E2) production. As a result, follicular dominance is disrupted, ovulation fails to occur, and the onset of first ovulation is delayed (Piechotta et al., 2015).

3.2. Effect on uterine health and immune function

Postpartum negative energy balance and elevated concentrations of NEFAs have been associated with increased inflammatory responses, as evidenced by the upregulation of proinflammatory cytokines and Toll like receptor (TLR) expression, which contribute to compromised uterine function (Zhang et al., 2018). Additionally, NEFAs exert cytotoxic effects at the cellular level and are implicated in immunosuppression (Bradford et al., 2015; Wankhade et al., 2017). In the liver, NEFAs are oxidized to meet energy demands; however, excessive mobilization can lead to ketosis and hepatic accumulation of triglycerides (TGs), ultimately resulting in fatty liver development. Galvao et al. (2010) reported that cows with reduced glycogen concentrations in their polymorphonuclear leukocytes (PMNs), which diminishes their oxidative burst capacity, are more susceptible to uterine infections. This finding highlights the essential role of glucose as a key energy substrate for optimal immune cell function and uterine health.

3.3. Effect on estrous cyclicity during the breeding period

A variety of essential metabolic processes in the oocyte is compromised by the low glucose, insulin, and IGF1 and it also found that the 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 (Walsh et al., 2012). The reduced synthesis of estradiol from the preovulatory follicle and greater steroid metabolism in lactating compared with non-lactating cows can lead to abnormal patterns of follicular growth, anovulatory conditions, multiple ovulations, reduced estrous expression and a poor-quality oocyte that may not develop after fertilization (Wiltbank et al., 2011).

3.4. Effect on luteal function and development of embryo and fetus

Low blood glucose levels may impair several critical metabolic processes within ovarian cells, including those of the oocyte, which relies on glucose as a primary energy source (Berlinguer et al., 2012). The corpus luteum formed from a compromised follicle produce less progesterone and this can lead to embryonic loss as it is needed for the uterine histotroph secretion. Most probably the pregnancy is lost because the mother fails to recognize the pregnancy due to the inadequate interferon-tau (IFNT) production by the slowly developing foetus and undergoes luteal regression as if she is not pregnant (Robinson et al., 2008). The metabolic profile of post partum cow affects the growth of fetus and placenta. Low glucose concentrations can lead to pregnancy loss, compromising the fetus as placenta may not have adequate substrate for the creation of new cells. The mammary gland's ability to extract glucose from the circulation is crucial. Ketosis, which arises as a sequela of NEBAL, is a metabolic disorder commonly observed in high-producing postpartum dairy cows. During ketosis, increased concentrations of NEFA in systemic circulation, ovarian follicles, and the uterine milieu can interfere with key metabolic processes, particularly those involving fatty acid oxidation and energy production. This metabolic disruption may impair the elongation, cellular differentiation, and overall survival of preimplantation embryos, potentially reducing reproductive success (Ribeiro et al., 2016; Furukawa et al., 2021). Ketosis in cows can suppress the immune system, making them more vulnerable to bacterial infections, such as uterine inflammation and endometritis. This immune suppression, along with altered endometrial fatty acid metabolism, can negatively impact early embryo implantation, ultimately reducing fertility in postpartum cows (Aleri et al., 2016; Lacasse et al., 2018).

4. PERIPARTURIENT DISEASE COMPLEXES AND THE ROLE OF IMMUNE SUPPRESSION, ENERGY IMBALANCE, AND CALCIUM

During the periparturient period, dairy cows are particularly vulnerable to a range of metabolic and infectious diseases due to significant physiological stress, nutritional imbalances, and immune suppression. Common conditions linked to impaired immune function include retained fetal membranes (RFM), metritis, and mastitis. On the other hand, disorders primarily associated with excessive NEBAL include displaced abomasum, ketosis, and ovarian dysfunction, such as cystic ovarian disease or prolonged anestrus (Duffield et al., 2009; Huzzey et al., 2007). Calcium homeostasis plays a significant role in both categories of periparturient disease. Around 50% of multiparous cows experience hypocalcemia after calving (Neves et al., 2017). Cows suffering from clinical or subclinical hypocalcemia often experience compromised muscle function, gastrointestinal motility disorders (gastrointestinal stasis), and reduced feed intake. These factors significantly elevate the risk of developing metabolic diseases. Low blood calcium levels, along with fatty acid profiles, can help predict the risk of displaced abomasum (Chapinal et al., 2011). Moreover, calcium is essential for proper immune system function. Intracellular calcium (Ca^{2+}) acts as a vital secondary messenger during the early activation stages of immune cells such as monocytes and neutrophils (Kimura et al., 2002). When blood calcium levels drop during the periparturient period, intracellular calcium availability in immune cells is also reduced, leading to impaired immune responses and a heightened risk of infectious diseases, particularly mastitis. Hypocalcemia has also been shown to prolong the interval to first conception postpartum, increase the risk of culling (Venjakob et al., 2017), and is significantly associated with a higher incidence of metritis within 24 hours after calving (Rodrígue et al., 2017). Moreover, hypocalcemia hinders ovarian recovery and lowers pregnancy rates after the voluntary waiting period and first service (Caixeta et al., 2017).

In addition to its role in metabolic and immune function, hypocalcemia can induce a physiological stress response. At parturition, circulating plasma cortisol, a key stress hormone, naturally increases approximately three to four times above baseline levels. However, in cows experiencing subclinical hypocalcemia, plasma cortisol levels may increase five to seven times above normal, while in cases of clinical hypocalcemia, they can rise as much as ten to fifteen times beyond baseline levels (Horst and Jorgensen, 1982). This exaggerated stress response further exacerbates immune suppression and contributes to metabolic instability. Importantly, periparturient disease conditions are often interconnected, creating a cascade of complications. For example, diseases driven by NEBAL can increase the likelihood of developing immune-related disorders, and vice versa. This interplay illustrates the complex and multifactorial nature of health challenges faced by dairy cows during the transition period. Effective management of energy balance, calcium metabolism, and immune function is essential for reducing the incidence and severity of periparturient diseases and ensuring optimal productivity and reproductive performance.

5. CONCLUSION

The peripartum period in dairy cows is characterized by substantial metabolic changes, particularly negative energy balance, which can adversely affect fertility by delaying the resumption of ovarian activity and increasing the risk of reproductive disorders. Effective nutritional management and vigilant health monitoring during this critical phase are essential to reduce metabolic stress and support reproductive efficiency. Ensuring a smooth transition from pregnancy to lactation is vital for achieving optimal reproductive and productive performance in the postpartum period, ultimately enhancing overall herd productivity.

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7. REFERENCES

Aardema, H., van Tol, H.T., Vos, P.L., 2019. An overview on how cumulus cells interact with the oocyte in a condition with elevated NEFA levels in dairy cows. Animal Reproduction Science 207, 131–137.

Abdelli, A., Raboisson, D., Kaidi, R., Ibrahim, B., Kalem, A., Iguer-Ouada, M., 2017. Elevated non-esterified fatty acid and β-hydroxybutyrate in transition dairy cows and their association with reproductive performance and disorders: A meta-analysis. Theriogenology 93, 99–104.

Aleri, J.W., Hine, B.C., Pyman, M.F., Mansell, P.D., Wales, W.J., Mallard, B., Fisher, A.D., 2016. Periparturient immunosuppression and strategies to improve dairy cow health during the periparturient period. Research in Veterinary Science 108, 8–17.

Allen, M.S., Bradford, B.J., 2009. Control of eating by hepatic oxidation of fatty acids. A note of caution. Appetite 53(2), 272–273.

Bach, A., 2019. Effects of nutrition and genetics on fertility in dairy cows. Reproduction, Fertility and Development 31(1), 40–54.

Bell, A.W., 1995. Regulation of organic nutrient metabolism during transition from late pregnancy to early lactation. Journal of Animal Science 73(9), 2804–2819.

Berlinguer, F., Gonzalez-Bulnes, A., Contreras-Solis, I., Spezzigu, A., Torres-Rovira, L., Succu, S., Leoni, G.G., 2012. Glucogenic supply increases oocyte developmental competence in sheep. Reproduction, Fertility and Development 24(8), 1055–1062.

Bertoni, G., Trevisi, E., Lombardelli, R., 2009. Some new aspects of nutrition, health conditions and fertility of intensively reared dairy cows. Italian Journal of Animal Science 8(4), 491–518.

Bradford, B.J., Yuan, K., Farney, J.K., Mamedova, L.K., Carpenter, A.J., 2015. Invited review: Inflammation during the transition to lactation: New adventures with an old flame. Journal of Dairy Science 98(10), 6631–6650.

Caixeta, L.S., Ospina, P.A., Capel, M.B., Nydam, D.V., 2017. Association between subclinical hypocalcemia in the first 3 days of lactation and reproductive performance of dairy cows. Theriogenology 94, 1–7.

Call, E.P., Stevenson, J.S., 1985. Current challenges in reproductive management. Journal of Dairy Science 68(10), 2799–2805.

Cardoso, F.C., Kalscheur, K.F., Drackley, J.K., 2020. Symposium review: Nutrition strategies for improved health, production, and fertility during the transition period. Journal of Dairy Science 103(6), 5684–5693.

Chapinal, N., Carson, M., Duffield, T.F., Capel, M., Godden, S., Overton, M., LeBlanc, S.J., 2011. The association of serum metabolites with clinical disease during the transition period. Journal of Dairy Science 94(10), 4897–4903.

Comline, R.S., Hall, L.W., Lavelle, R.B., Nathanielsz, P.W., Silver, M., 1974. Parturition in the cow: endocrine changes in animals with chronically implanted catheters in the foetal and maternal circulations. Journal of Endocrinology 63(3), 451–472.

Duffield, T.F., Lissemore, K.D., McBride, B.W., Leslie, K.E., 2009. Impact of hyperketonemia in early lactation dairy cows on health and production. Journal of Dairy Science 92(2), 571–580.

Furukawa, E., Chen, Z., Ueshiba, H., Wu, Y., Chiba, H., Yanagawa, Y., Hui, S.P., 2021. Postpartum cows showed high oocyte triacylglycerols concurrently with high plasma free fatty acids. Theriogenology 176, 174–182.

Galvão, K.N., Flaminio, M.J.B.F., Brittin, S.B., Sper, R., Fraga, M., Caixeta, L., Gilbert, R.O., 2010. Association between uterine disease and indicators of neutrophil and systemic energy status in lactating Holstein cows. Journal of Dairy Science 93(7), 2926–2937.

Green, J.C., Meyer, J.P., Williams, A.M., Newsom, E.M., Keisler, D.H., Lucy, M.C., 2012. Pregnancy development from day 28 to 42 of gestation in postpartum Holstein cows that were either milked (lactating) or not milked (not lactating) after calving. Reproduction 143(5), 699.

Gross, J.J., Bruckmaier, R.M., 2019. Metabolic challenges in lactating dairy cows and their assessment via established and novel indicators in milk. Animal 13(S1), s75-s81.

Grummer, R.R., 1995. Impact of changes in organic nutrient metabolism on feeding the transition dairy cow. Journal of Animal Science 73(9), 2820–2833.

Hayirli, A., Grummer, R.R., Nordheim, E.V., Crump, P.M., 2002. Animal and dietary factors affecting feed intake during the prefresh transition period in Holsteins. Journal of Dairy Science 85(12), 3430–3443.

Hill, A.W., 1981. Factors influencing the outcome of Escherichia coli mastitis in the dairy cow. Research in Veterinary Science 31(1), 107–112.

Horst, R.L., Jorgensen, N.A., 1982. Elevated plasma cortisol during induced and spontaneous hypocalcemia in ruminants. Journal of Dairy Science 65(12), 2332–2337.

Huzzey, J.M., Veira, D.M., Weary, D.M., Von Keyserlingk, M.A.G., 2007. Prepartum behavior and dry matter intake identify dairy cows at risk for metritis. Journal of Dairy Science 90(7), 3220–3233.

Kerhli, M.E., 2015. Immunological dysfunction in periparturient cows: evidence, causes and ramifications. In Florida Ruminant Nutrition Symposium, 14–29.

Kimura, K., Goff, J.P., Kehrli Jr, M.E., Reinhardt, T.A., 2002. Decreased neutrophil function as a cause of retained placenta in dairy cattle. Journal of Dairy Science 85(3), 544–550.

Lacasse, P., Vanacker, N., Ollier, S., Ster, C., 2018. Innovative dairy cow management to improve resistance to metabolic and infectious diseases during the transition period. Research in Veterinary Science 116, 40–46.

Leroy, J.L.M.R., Vanholder, T., Van Knegsel, A.T.M., Garcia-Ispierto, I., Bols, P.E.J., 2008. Nutrient prioritization in dairy cows early postpartum: mismatch between metabolism and fertility? Reproduction in Domestic Animals 43, 96–103.

McClary, D., Rapnicki, P., Overton, M., 2015. The vital 90 TM days and why it's important to a successful lactation. In 2015 Florida Ruminant Nutrition Symposium, 1.

Mezzetti, M., Bionaz, M., Trevisi, E., 2020. Interaction between inflammation and metabolism in periparturient dairy cows. Journal of Animal Science 98(Supplement_1), S155–S174.

Neves, R.C., Leno, B.M., Stokol, T., Overton, T.R., McArt, J.A.A., 2017. Risk factors associated with postpartum subclinical hypocalcemia in dairy cows. Journal of Dairy Science 100(5), 3796–3804.

Pascottini, O.B., Carvalho, M.R., Van Schyndel, S.J., Ticiani, E., Spricigo, J.W., Mamedova, L.K., LeBlanc, S.J., 2019. Feed restriction to induce and meloxicam to mitigate potential systemic inflammation in dairy cows before calving. Journal of Dairy Science 102(10), 9285–9297.

Pascottini, O. B., Leroy, J.L., Opsomer, G., 2020. Metabolic stress in the transition period of dairy cows: Focusing on the prepartum period. Animals 10(8), 1419.

Pérez-Báez, J., Risco, C.A., Chebel, R.C., Gomes, G.C., Greco, L.F., Tao, S., Galvao, K.N., 2019. Association of dry matter intake and energy balance prepartum and postpartum with health disorders postpartum: Part II. Ketosis and clinical mastitis. Journal of Dairy Science 102(10), 9151–9164.

Pérez-Báez, J., Risco, C.A., Chebel, R.C., Gomes, G.C., Greco, L.F., Tao, S., Galvao, K.N., 2019. Association of dry matter intake and energy balance prepartum and postpartum with health disorders postpartum: Part I. Calving disorders and metritis. Journal of Dairy Science 102(10), 9138–9150.

Pérez-Báez, J., Risco, C.A., Chebel, R.C., Gomes, G.C., Greco, L.F., Tao, S., Galvao, K.N., 2021. Investigating the use of dry matter intake and energy balance prepartum as predictors of digestive disorders postpartum. Frontiers in Veterinary Science 8, 645252.

Piechotta, M., Mysegades, W., Ligges, U., Lilienthal, J., Hoeflich, A., Miyamoto, A., Bollwein, H., 2015. Antepartal insulin-like growth factor 1 and insulin-like growth factor binding protein 2 concentrations are indicative of ketosis in dairy cows. Journal of Dairy Science 98(5), 3100–3109.

Reddy, P.R.K., Raju, J.K., Reddy, A.N., Reddy, P.P.R., Hyder, I., 2016. Transition period and its successful management in dairy cows. Indian Journal of Natural Sciences 7(38), 11691–11699.

Ribeiro, E.S., Gomes, G., Greco, L.F., Cerri, R.L.A., Vieira-Neto, A., Monteiro Jr, P.L.J., Santos, J.E.P., 2016. Carryover effect of postpartum inflammatory diseases on developmental biology and fertility in lactating dairy cows. Journal of Dairy Science 99(3), 2201–2220.

Robinson, R.S., Hammond, A.J., Wathes, D.C., Hunter, M.G., Mann, G.E., 2008. Corpus luteum–endometrium–embryo interactions in the dairy cow: underlying mechanisms and clinical relevance. Reproduction in Domestic Animals 43, 104–112.

Rodríguez, E.M., Arís, A., Bach, A., 2017. Associations between subclinical hypocalcemia and postparturient diseases in dairy cows. Journal of Dairy Science 100(9), 7427–7434.

Sammad, A., Umer, S., Shi, R., Zhu, H., Zhao, X., Wang, Y., 2020. Dairy cow reproduction under the influence of heat stress. Journal of Animal Physiology and Animal Nutrition 104(4), 978–986.

Song, Y., Wang, Z., Zhao, C., Bai, Y., Xia, C., Xu, C., 2021. Effect of negative energy balance on plasma metabolites, minerals, hormones, cytokines and ovarian follicular growth rate in Holstein dairy cows. Journal of Veterinary Research 65(3), 361.

Stevenson, J.S., 2001. Reproductive management of dairy cows in high milk-producing herds. Journal of Dairy Science 84, E128-E143.

Sundrum, A., 2015. Metabolic disorders in the transition period indicate that the dairy cows' ability to adapt is overstressed. Animals 5(4), 978–1020.

Toledo-Alvarado, H., Cecchinato, A., Bittante, G., 2017. Fertility traits of holstein, brown swiss, simmental, and alpine grey cows are differently affected by herd productivity and milk yield of individual cows. Journal of Dairy Science 100(10), 8220–8231.

Trevisi, E., Jahan, N., Bertoni, G., Ferrari, A., Minuti, A., 2015. Pro-inflammatory cytokine profile in dairy cows: consequences for new lactation. Italian Journal of Animal Science 14(3), 3862.

Van Saun, R.J., 2016. Indicators of dairy cow transition risks: Metabolic profiling revisited. Tierarzt. Prax. Ausg. G. Grosstiere Nutztiere 44(2), 118–126.

Venjakob, P.L., Borchardt, S., Heuwieser, W., 2017. Hypocalcemia-Cow-level prevalence and preventive strategies in German dairy herds. Journal of Dairy Science 100(11), 9258–9266.

Walsh, S.W., Mehta, J.P., McGettigan, P.A., Browne, J.A., Forde, N., Alibrahim, R.M., Evans, A.C., 2012. Effect of the metabolic environment at key stages of follicle development in cattle: focus on steroid biosynthesis. Physiological Genomics 44(9), 504–517.

Wankhade, P.R., Manimaran, A., Kumaresan, A., Jeyakumar, S., Ramesha, K.P., Sejian, V., Varghese, M.R., 2017. Metabolic and immunological changes in transition dairy cows: a review. Veterinary World 10(11), 1367.

Wiltbank, M.C., Souza, A.H., Carvalho, P.D., Bender, R.W., Nascimento, A.B., 2011. Improving fertility to timed artificial insemination by manipulation of circulating progesterone concentrations in lactating dairy cattle. Reproduction, Fertility and Development 24(1), 238–243.

Zhang, Y., Li, X., Zhang, H., Zhao, Z., Peng, Z., Wang, Z., Li, X., 2018. Non-esterified fatty acids over-activate the TLR2/4-NF-κb signaling pathway to increase inflammatory cytokine synthesis in neutrophils from ketotic cows. Cellular Physiology and Biochemistry 48(2), 827–837.