Relationship of Negative Energy Balance and Reproduction in Dairy Cows

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Abstract

Reproductive efficiency is one of the most important factors influencing the profitability of the dairy cattle industry. Negative energy balance (NEB) is a common issue in high-yielding dairy cows, particularly during early lactation, as the energy requirements for milk production often exceed the available energy intake. This nutritional imbalance subsequently affects reproductive performance by changing metabolite levels in the metabolic, endocrine, and immune systems during the postpartum period. The low blood glucose levels in dairy cows trigger excessive lipid mobilization from adipose tissue, increasing circulating concentrations of non-esterified fatty acids (NEFA) and ketone bodies like β-hydroxybutyrate (BHBA). NEFA and BHBA are known to have a detrimental effect on follicular fluid and mitochondrial activity within the follicle, granulosa and cumulus cell apoptosis, oocyte maturation, and embryonic development. In addition to various metabolic diseases such as ketosis, fatty liver syndrome and hypocalcemia associated with NEB during early lactation, another consequence of NEB during early lactation is coupled with immune dysfunction during the postpartum period that leads to predisposing to infectious diseases including mastitis and endometritis which may have adverse effects on reproductive performances. This review summarizes the current knowledge on strategies to optimize the management of metabolic health during the transition period to improve the reproductive performance of dairy cows, focusing on the relationship between metabolic adaptation and reproductive parameters.

Keywords: Negative energy balance, Reproductive performance, Dairy cows

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Introduction

Reproductive efficiency and milk yield are crucial determinants of profitability in the dairy cattle industry (Pascottini et al., 2022). Fertility is a multifactorial trait influenced by the health status of the cows as well as nutrition, environment, stress, genetics, and management factors. These multiple factors can challenge and make it difficult to determine the underlying causes of declining fertility (Walsh et al., 2011; Leroy et al., 2018). Although genetic selection, improved nutrition, and enhanced herd management have significantly increased milk production in high-yielding dairy cows (Ruikar, 2024), these advancements have inadvertently compromised the reproductive performance of lactating cows (Ntallaris et al., 2017). For instance, cows experience longer times to return to estrus after calving, exhibit abnormal postpartum cyclicity, show poor estrus behavior, and have lower conception rates (Friggens et al., 2010). Additionally, there is an increase in the time to the first insemination and a decrease in the success rate of artificial inseminations (Thatcher et al., 2006; Lucy, 2019).

During the postpartum period, the alterations in the nutritional and health status of high-yielding dairy cows detrimentally affect the reproductive performance (Taylor et al., 2004) by modulating metabolites in the circulatory system, endocrine system, and immune system (Clemente-Suárez et al., 2023). Clinical or subclinical metabolic diseases manifest these system alterations (McArt et al., 2013). Consequently, the disease factor is considered a primary contributor to declining reproductive performance in dairy cows. In addition, several diseases (Yoo, 2010), especially ketosis, milk fever, and other metabolic diseases, contribute to reproductive performance decline (Miqueo et al., 2019). On the other hand, metabolic and hormonal changes linked to the cows' energy status directly affect reproductive organs. All these changes adversely impact follicular growth, fertilization, embryo and fetal development, implantation, and placentation directly or indirectly (Van Hoeck et al., 2014; Pascottini et al., 2022), thereby impairing cows' reproductive performance, causing economic losses, and decreasing profitability in the cattle industry (Lei & Simões, 2021).

This review explores energy imbalance-induced metabolic disorders in the postpartum period, their interplay, and their effects on reproduction. This includes research on cows' nutrition with respect to their body condition, metabolic status, and reproduction, as well as the effects nutrition has on metabolic hormones that regulate the reproductive endocrine system. Moreover, it discusses the direct impacts of metabolic metabolites on ovarian follicles, oocytes, and embryos.

2. Transition Period and Negative Energy Balance

Proper nutritional management is a key factor affecting reproductive efficiency and the health status of animals in livestock (Tufarelli et al., 2024). The period between late pregnancy and early lactation, commonly referred to as the "transition period," involves a complex interaction of various physiological pathways, including nutritional, metabolic, endocrine, inflammatory, immune, and reproductive changes.

These changes predispose cows to both clinical and subclinical diseases, with most of such diseases manifesting within the first five weeks post-partum in dairy cows (LeBlanc et al., 2006; Pascottini et al., 2020). In early lactation, elevated nutritional requirements for peak milk production combined with insufficient dry matter intake result in NEB in high-yielding cows (VandeHaar et al., 2016). The duration and depth of NEB vary depending on factors such as the cows' genetic characteristics, milk yield, body condition before parturition, feed intake, and diet (Wathes et al., 2007).

3. Hormonal and Metabolic Responses to Negative Energy Balance in Dairy Cows

3.1. Hormonal Disruptions Linked to Negative Energy Balance in Dairy Cows

NEB induces a cascade of hormonal changes in dairy cows, resulting in metabolic dysregulation and severely impairing reproductive performance. Disrupted endocrine signaling, extends calving intervals, delays the onset of first ovulation (Ion et al., 2022), increases the interval to first service, reduces conception rates (Ibtisham et al., 2018), decreases pregnancy rates per artificial insemination, and delays return of ovarian cyclicity (Vanholder, et al., 2006b) in a postpartum, which has been identified as a significant contributor to reproductive failure in dairy cows (Desta, 2024).

The hypothalamus is responsive to alterations in metabolic status and is crucial in mediating the impact of energy deficiency linked to the NEB on reproduction through the hypothalamic-pituitary-ovarian axis (Leroy et al., 2008; Matthews et al., 2017). Gonadotropin-releasing hormone (GnRH) is the primary reproductive hormone released by the hypothalamus that regulates follicular development and ovulation (Triwutanon & Rukkwamsuk, 2023) as well as incorporates numerous internal and external signals to modulate the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary gland (Hassanein et al., 2024). Inhibited GnRH secretion due to hypoglycemia disrupts LH pulsatility and amplitude (Walsh et al., 2011). As a result of impaired LH surge, resumption of ovarian activity is delayed (Castro et al., 2012; Desta, 2024), with intervals between calving and first ovulation being prolonged (Lucy, 2003; Webb et al., 2004). Besides, NEB diminishes ovarian response to LH stimulation (Shin et al., 2015). Proper LH pulsatility is crucial for optimal oocyte growth and maturation (Shimada & Richards, 2010; Dragotto et al., 2024), in addition to follicle cell luteinization, elevated follicular vascularity, and breakdown of the follicle wall that causing ovulation (Hessock et al., 2023). Furthermore, reduced LH suppress estradiol production from dominant follicles (Dobson et al., 2007), ultimately hampering estrus behavior (Roche, 2006), and follicular growth patterns (Vanholder et al., 2006b). Reduced follicular development and estradiol secretion delay the reinitiation of postpartum ovulation, compromise oocyte quality, and impede pregnancy in dairy cows (Bisinotto et al., 2018).

Metabolic changes in the serum and follicular fluid related to NEB are mediated by endocrine signaling, initiated by low insulin concomitant decreased insulin-like growth factor (IGF-I) and high growth hormone (GH) (Leroy et al., 2018). In addition to being responsible for antral follicle growth and function (Llewellyn et al., 2007), insulin has also shown a stimulatory effect on oocyte maturation and subsequent embryonic development (Gong et al., 2002). On the other hand, low plasma levels of IGF-1 correlate with an extended postpartum interval and delayed puberty (Desta, 2024). IGF-1 has a stimulatory effect on oocyte maturation and cumulus expansion (Araujo et al., 2020), subsequent embryonic development and quality of embryos (Sirisathien & Brackett, 2003), and can also inhibit apoptosis (Wasielak & Bogacki, 2007). During early lactation, plasma GH alterations are contrary to IGF-I and insulin (Butler et al., 2003). Circulating GH concentrations increase caused by declined negative feedback from low blood IGF-1 concentrations (Rhoads et al., 2008). Elevated GH and lesser IGF-1 in blood generate a catabolic state, reducing cows' body condition score and weight (Lucy et al., 2009). Moreover, GH has direct effects on cell growth and differentiation (Taylor et al., 2004).

3.2. Metabolic Changes Linked to Negative Energy Balance in Dairy Cows

Glucose is an essential molecule for the maintenance of the metabolic processes of most tissues. At the onset of lactation, the majority of glucose is supplied for milk production in the mammary gland (Roche et al., 2009). After parturition, the reduction of blood glucose concentration in dairy cows (Garverick et al., 2013) triggers excessive mobilization of triacylglycerols from adipose tissue, leading to an elevation in circulating glycerol and NEFA in the bloodstream (De Koster et al., 2018). Glycerol is used for gluconeogenesis, and NEFA is esterified in the liver. When the amount of NEFAs exceeds the oxidation ability of the liver, they are incompletely oxidized to ketone bodies such as BHBA, acetoacetic acid and acetone. Elevation of ketone bodies in the blood, urine, and milk is used to diagnose ketosis in dairy cows (Zhang & Ametaj, 2020). Furthermore, the blood concentration of BHBA is accepted as a gold standard method for determining ketosis. Because BHBA is the predominant ketone body in ruminants and is more stable than acetoacetate and acetone (Delić et al., 2020; Zhang et al., 2020).

An optimal intrafollicular environment is crucial since the metabolic environment of ovarian follicles significantly impacts the growth and maturation of oocytes and their subsequent development (Revelli et al., 2009). Due to NEB, metabolic changes in blood serum are which are strongly correlated with the biochemical composition of follicular fluid of the dominant follicle in dairy cows (Aardema et al., 2019), impacting follicle cell viability (Scaramuzzi et al., 2011), can thereby leading to the presence of developmentally incompetent oocyte at ovulation (Britt, 1991), coupled with diminished capacity for fertilization and further embryo survival (Leroy et al., 2012; Leroy et al., 2015). Furthermore, previous study has revealed that the presence of high concentrations of the three predominant NEFAs (palmitic, stearic, and oleic acid) in the final maturation stage results in blastocysts with a markedly lower cell number and an elevated apoptotic cell index and thereby causing a lower embryo quality and viability (Van Hoeck et al., 2011). On the other hand, accumulation of high NEFA in follicular fluid leads to accelerated apoptosis in granulosa and cumulus cells (Aardema et al., 2019).

4. Diseases Associated with Negative Energy Balance in Dairy Cows: Metabolic and Inflammatory Disorders

4.1. Metabolic Diseases

4.1.1. Hypocalcemia (Milk Fever)

Postpartum cows experience elevated mineral demands, particularly for calcium, to support the early lactation period (Zhang et al., 2020).

Lactation is the primary cause of hypocalcemia in cows' postpartum period, as the demand for calcium escalates rapidly, resulting in calcium consumption exceeding absorption. Hypocalcemia is classified as subclinical (1.4 to 2.0 mmol/L) or clinical (< 1.4 mmol/L), manifesting with symptoms such as mental restlessness, anorexia, and mild paralysis (Sammad et al., 2022). Hypocalcemia is a risk factor for displaced abomasum, ketosis, retained placenta, mastitis, and uterine prolapse, thus increasing the possibility of culling (Sammad et al., 2022). Recent studies reveal that hypocalcemia negatively impacts reproductive performance via a recovery of ovarian function, pregnancy rate, and higher risk of culling (Caixeta et al., 2017; Venjakob et al., 2017).

4.1.2. Fatty Liver

Fatty liver syndrome is a secondary metabolic disorder commonly observed in dairy cows, particularly during the postpartum period related to the NEB, defined by high triglyceride accumulation in the liver. Previous investigation has reported that during the first month after parturition, 5 to 10% of dairy cows exhibit severe fatty liver, while 30 to 40% present with moderate fatty liver, suggesting that up to 50% of dairy cows are at an elevated risk for illnesses and reproductive complications (Bobe et al., 2004). As a result of various prepartum events and NEB, massive NEFA mobilization is the primary cause of fatty liver, mainly due to decreased dry matter intake of lactating dairy cows (Ingvartsen, 2006). Fatty liver syndrome occurs when the liver's intake of NEFAs surpasses its capacity for oxidation and secretion, leading to the re-esterification of excess NEFAs into triglycerides and a decline in the liver's metabolic activities (Zhang & Ametaj, 2020). Fatty liver syndrome associated with NEB impairs liver function, which directly affects the reproductive system by reducing NEFA oxidation as an energy source and indirectly impacts reproductive performance by predisposing postpartum cows to ketosis and related problems (Sammad et al., 2022).

4.1.3. Ketosis

Ketosis is a prevalent metabolic disorder in high-yielding dairy cows during early lactation, marked by elevated levels of circulating ketone bodies, specifically β-hydroxybutyrate (BHBA), acetoacetic acid and acetone in blood, urine, and milk. This condition frequently adversely affects reproductive performance, leading to mortality or early culling (McArt et al., 2015; Mostert et al., 2018). Ketosis is classified into subclinical ketosis or clinical ketosis based on the presence or absence of clinical signs of disease and levels of BHBA in the blood. Subclinical ketosis is characterized by ≥1.4 mmol/L of blood BHBA and the absence of obvious clinical symptoms. Clinical ketosis is diagnosed by ≥3.0 mmol/L of blood BHBA with the presence of clinical symptoms (Delić et al., 2020; Zhang et al., 2020; Lei & Simões, 2021).

A study by Rutherford et al. (2016) indicate that cows with subclinical ketosis exhibit reduced pregnancy success at the first artificial insemination, a higher number of inseminations per pregnancy, diminished estrus duration, and an extended interval from calving to the onset of the first estrus compared to healthy cows. This proves that ketosis influences follicular development and decreases the proper synthesis of estradiol and progesterone in cows post-calving (Vanholder et al., 2006a). Elevating intrafollicular BHBA concentrations impairs the bovine follicular, oviductal and uterine microenvironment (Missio et al., 2022). Recent research demonstrates that BHBA significantly inhibits oocytes' maturation and developmental capacity. In addition, the cleavage and blastocyst rates were reduced in the presence of BHBA. Besides, the findings reveal that exposure to BHBA disrupts mitochondrial activity, induces oxidative stress, and initiates apoptosis in bovine oocytes (Zhang et al., 2023). Moreover, ketosis enhances oxidative stress, contributing to cellular damage in reproductive tissues (Song et al., 2021). An exact balance between inflammatory and anti-inflammatory responses in the uterus is essential for the attachment and implantation of the embryo, with an active immune system managing this complex balance (Sammad et al., 2022).

Ketosis has been shown to decrease immune responsiveness by compromising neutrophil and lymphocyte function and directly affecting reproductive performance (Lacetera et al., 2005; Lucy et al., 2014). This immune dysfunction further exacerbates reproductive challenges by predisposing susceptibility to postpartum inflammatory subclinical or clinical disease (LeBlanc, 2008).

4.2. Inflammatory Diseases

4.2.1. Endometritis/Metritis

Endometritis is one of the most common uterine disorders in dairy cows, characterized by inflammation of the endometrium, often leading to suboptimal reproductive efficiency (Várhidi et al., 2024). This results in delays in postpartum return of ovarian activity, prolonged intervals to first service, decreased pregnancy rates, increased number of services per conception, and higher culling rates (Sheldon et al., 2006).

Occurrence of subclinical endometritis being influenced by metabolic and immune alterations during the postpartum period. The onset of endometritis is closely associated with NEB, which frequently occurs in high-yielding dairy cows during early lactation. During NEB, increased mobilization of NEFAs and BHBA concentrations impair immune function and inflammatory responses (LeBlanc, 2008). Studies have shown that NEB-induced immunosuppression compromises neutrophil activity, reduces phagocytosis, and diminishes the expression of cytokines critical for immune defense (Hammon et al., 2006). These alterations impair the ability of the immune system to clear bacterial infections, increasing the risk of persistent uterine inflammation and delayed uterine involution (Gabler et al., 2010).

Endometritis profoundly compromises reproductive efficiency by disrupting uterine function, ovarian cyclicity, and embryo implantation. Persistent uterine inflammation impairs endometrial receptivity and embryo attachment, reducing fertility (Sheldon & Dobson, 2004). Increased concentrations of pro-inflammatory cytokines, including interleukin-1 and tumor necrosis factor-alpha, interfere with ovarian follicular development and steroidogenesis, resulting in poor oocyte quality and delayed resumption of cyclicity (Herath et al., 2009). Additionally, prolonged uterine inflammation elevates prostaglandin F2α levels, contributing to luteal insufficiency and early embryonic loss (Wathes et al., 2007). Systemic inflammation caused by endometritis exacerbates oxidative stress and apoptosis in ovarian and uterine tissues, which in turn adversely affects fertility outcomes (Sheldon et al., 2014).

4.2.2. Mastitis

Mastitis is an inflammatory response of the udder tissue in the mammary gland. It is a common disease among dairy cattle, resulting in

economic losses from reduced productivity and deterioration in milk quality (Cheng & Han, 2020). NEB, commonly observed in early lactation, is known to impair immune defenses and increase susceptibility to infections, putting cows at increased risk of mastitis. Invasion of bacteria to the mammary gland leads to mastitis and the production of lipopolysaccharides (LPS) and components of bacteria. This causes an immune response and inflammatory symptoms that lead to dysfunction of the reproductive organs, especially the ovary, corpus luteum, uterus, and embryo (Wang et al., 2021). The levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) elevate in the mammary epithelial cells of cows suffering from mastitis (Bannerman, 2009). Consequently, TNF-α enhances the nuclear lysis of blastocyst cells, decreased cell proliferation, fewer inner cell masses, decreased embryonic stem cell differentiability and reduced embryo survival rate (Soto et al., 2003).

The delay of estrus and hormonal abnormalities caused by inflammatory cytokines and the bacterial endotoxins in mastitis can affect fertility. Cytokines and other inflammatory mediators cause changes in state and activity in affected cells, such as apoptosis and hormonal production within the reproductive tracts (Wang et al., 2021). Mastitis causes a prolonged estrus interval and a reduced luteal phase in cows, which negatively impacts the pregnancy and embryonic development (Edelhoff et al., 2020). According to Boujenane et al. (2015), mastitis reduces reproductive efficiency in cows in several ways, causing damage to the ovarian follicles, disrupting oocyte development, and decreasing ovulation capacity.

Conclusion

In the dairy cow industry, the most important determining factor of profitability is achieving an equilibrium between reproductive efficiency and milk yield. Insufficient energy intake for high milk production during early lactation creates NEB in dairy cows, causing various metabolic and hormonal changes. Increased concentrations of NEFA and ketone bodies aggravate oxidative stress, promote apoptosis, and disrupt the function of the immune system, thus compromising the reproductive performance. Reduced secretion of GnRH and LH in the absence of normal ovarian cyclicity negatively affects oocyte maturation due to hormonal imbalance. In situations of metabolic disorders such as fatty liver syndrome and ketosis, these negative effects are enhanced by the unavailability of energy and systemic inflammation, increasing susceptibility to mastitis and endometritis. This leads to inflammation, which impairs uterine function and ovarian function, lowering fertility. This review underscores the synergistic effects of metabolic and reproductive factors, highlighting possible leverage points for NEB prevention through focused nutritional treatments, metabolic assessment, and disease prevention strategies. Therefore, future studies will be necessary to optimize nutritional options, decipher genetic predisposition, and these develop innovative management practices to minimize the negative effects of NEB. Addressing metabolic and hormonal abnormalities improves reproductive performance, reduces economic losses, and promotes sustainable production in dairy cattle.

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