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PERIPARTUM METABOLITES AND HORMONAL IMBALANCE THAT CAN INFLUENCE COW FERTILITY - A REVIEW

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Abstract

During the last decades breeding dairy cows has severely affected the fertility of this species because this is a multi-factorial objective that can involve genetic, environmental and managerial factors. The main purpose of this review is to describe the modification of different metabolites and hormones that are involved in cow's fertility after calving. High milk yield during the fresh period predispose dairy cows to enter in negative energy balance (NEB). This happens because of fat tissue is mobilised faster than the liver is able to metabolize it. For a normal metabolize, the liver needs glucose. Non-esterified fatty acids (NEFA) offers an alternate source of energy but in the same time it can lead to liver accumulation of ketone bodies (acetone, acetoacetate and β-hydroxybutyrate). A small quantity of ketone production is normal for dairy cows but high amounts can lead to clinical and subclinical ketosis. Such diseases can predispose to a decrease milk production, a low fertility, and even culling.

Key words*: dairy cows, non-esterified fatty acids, β-hydroxybutyrate, milk production, negative energy balance.*

INTRODUCTION

After the transition period, which is defined as the last 3 weeks before calving and the first 3 weeks after calving, there is a high increase in dry matter intake (DMI) and milk yield (Barletta et al., 2017); also during this period of time, the health condition of the cow is particularly at risk because of cellular and humoral response of the immune system which is highly active as the cow is predisposed to uterine and mammary infections (Constantin and Bîrțoiu, 2014).

All dairy farmers want to accomplish the old challenge: "one calf per year from each cow". For this, biologists, nutritionists and geneticists are working on understanding the biological mechanism of dairy cows that lead to impaired fertility and, also on strategies to avoid this aspect (Walsh et al., 2011).

The main factor which influences the postpartum health of the cow is the high milk yield production. The milk production is correlated with the energy consumption that is linked with blood volume that pass through portal vain into the liver. Because progesterone and estradiol are first metabolized in the liver tissue, the increasing blood flow leads to a decrease concentration of these hormones. Because of this, heat detection is harder as heats tend to be silent and fertility is impaired. (Farraretto et al., 2014).

Reproduction efficiency represents the number one priority for all breeding systems in dairy cows. Because of this, during the last seven decades the genetical changes have focused on increasing the yield milk production. For example, at the beginning of last century dairy cows had milk productions of 2000 kg/year; one century later these productions have multiplied by four (Miglior et al., 2017). According to Miglior et al. (2017), between 1917-2017 milk production was the most wanted aspect by amelioration (more than 65%) where the milk quantity, protein and fat percents were followed. Body aspect was the second fact (around 25%), then the longevity, easy calving, and work performance. Fertility was considered last (less than 5%).

BODY CONDITION SCORE AND NEGATIVE ENERGY BALANCE

High milk production dairy cows need a high energy level to supplement the increasing milk production especially between 4^{th} and 8^{th} weeks postpartum. This high energy consumption is hard to achieve because of limiting appetite and a low dry matter intake. Low dry matter intake will predispose cows to entering a negative energy balance (NEB) and a high body reserve mobilization. The consequences of NEB are represented by increasing metabolic diseases that occur mainly in the first month of lactation, by immune function reduction and by decreasing fertility (Carvalho et al., 2014).

The evaluation of body condition score (BCS) is made by inspection and palpation, and the transitory modifications are used to check the nutritional estate and the health level of high yield milk production cows.

BCS loss is correlated with low reproductive performances. The females with low BCS at calving or those that suffer high looses of BCS early after calving, will have high chances to not ovulate, will show low rates of estrus appearance, will have low conception rate at first insemination, and they will also have high embryo mortality and prolonged calving intervals (Walsh et al., 2011). For cows with moderate milk production a BCS between 2.5 and 3 (scale between 1 to 5) is recommended. Cows that achieve this at the beginning of the transition period will have reduced body reserve mobilization and low NEFA and β-hydroxybutyrate acid (BHBA) concentrations (Barletta et al., 2017). A low BCS (between 1.5 and 2.5) is correlated with low fecundity of oocytes. In contrast, obese cows (BCS over 3.5) also have low fertility because of decreased DMI before calving in direct association with high fat mobilization after severe NEB postpartum (Walsh et al., 2011). NEB also reduces the growth of dominant follicles and estradiol production because of low insulin, low IGF-1 concentration and LH pulses alteration (Barletta 2017).

High temperatures can exacerbate the effects of NEB. During high temperature stress, lactating cows have a low appetite and a low BCS during the puerperal period. Also, the concentrations of glucose, insulin growth factor 1 (IGF-1) and cholesterol are reduced, compared to NEFA and blood urea nitrogen concentrations that are increasing in dairy cows that suffer of high temperature stress (Walsh et al., 2011).

Kafi and Mirzaei (2010) observed a delayed ovulation in cows that looses more than 1 BCS point in first 49 days in milk. Also, the risk of delayed ovulation increased by 16.5 times for females that loosed 0.75 of BCS during the same period of time.

METABOLIC DISEASES IMPLICATED IN INFERTILITY

During the transition period, cows cross through calving stress, lactation debut and a high amount of energy and protein needs for milk production. Because these cows have inadequate energy stores they will enter a NEB characterized by physiological, metabolic and endocrine imbalances. Cows that are immunosuppressed have a high risk to develop metabolite diseases as acidosis, retained fetal membranes and abomasal displacement. Cows that suffer metabolic imbalance and low dry matter intake before calving are more at chance to develop metritis, laminitis and endometritis, all of these ultimately leading to low reproductive parameters (Wathes et al., 2013).

At the start of lactation the liver and adipose tissue increase the release of growth hormone (GH).

Because of NEB, insulin concentrations remain low leading to a low liver GH and IGF-1 receptors expression. These two processes will alter the hipotalamo-hypophyses axis because insulin and IGF-1 are not capable to accelerate the action of gonadoreline (GnRH) on ovarian cells, preventing ovulation and retarding the estrous cyclicity (Carvalho et al., 2014).

LIPIDIC METABOLISM THAT IS IMPLICATED IN REPRODUCTION

Lipids are represented by cholesterol, phospholipids and triglycerides. These, among theirs derivates, offer energy support, are part of all cells membranes and are important elements involved in a large variety of endocrine mechanisms. The adipose tissue represent the main source of lipids, even if they are also stored in other tissues like muscles and liver. The majority (more than 95%) of fat tissue is composed by triglycerides stored as lipid droplets. The adipose tissue secretes some adipokins like: leptin, resistin, tumoral necrosis factor alpha (TNF-α) and interleukin 6 (IL-6). These adipokins send signals to hypothalamus and other tissues that are involved in energy homeostasis (Wathes et al., 2013).

The liver plays a major role in lipid metabolism. When the liver capacity for lipids export is over-passed, the triglycerides accumulation into hepatic cells leads to fatty liver syndrome. This is true for almost all dairy cows, with highest incidence during the second week of lactation. Beyond the hepatic cell disorder, triglycerides induce apoptosis of endoplasmic reticulum, stress and derangement of mitochondrial' membranes (Wathes et al., 2013). Mitochondria represents the critical point for energy storage and controls the energy balance metabolism of cells and is also the main intracellular oxygen consumer.

In vitro maturation of oocytes offer high amounts of mature oocytes that are capable to support embryo development (Prates et al., 2014). Also, *in vitro* studies showed that oocytes and embryos accumulate fatty acids into their cytoplasm. Marei et al. (2012) showed that bovine oocyte maturity in the presence of linoleic acid influences mitochondria distribution into cellular cytoplasm and increases the level of reactive oxygen species. Moreover, Van Hoeck et al. (2011) obtained reduced oocyte quality because of different NEFA exposure. Similar effects were obtained for bovine embryos cultivated in blood serum of heifers fed with rich diets in lipids and palm oil. All of these show that an abrupt NEB after parturition will be followed by increase concentrations of NEFA and oocyte quality alteration (Wathes et al., 2013).

In contrast, Sinclair (2010) obtained better results using alpha linoleic acid into oocytes growing medium and a better enhance of post fertilization of oocytes. The mechanisms associated with this positive response showed an increase concentration of prostaglandin E_2 at the level of *cumulus ooforus*-oocyte complex.

A cow can't breed short after calving because the genital tract takes time to regenerate and to be capable for a new pregnancy. Probably the main cause for high embryo mortality is represented by unsuitable uterine environment that is seen in dairy cows with repeat breeding syndrome. At this moment the uterus can be contaminated by different pathogens because the immune status is off during this period, cows developing endometritis. Because of this, a local insulin resistance effect is present. The healing process of endometrial tissue will be arduous because IGF-1, an important restorer element, is low.

INSULIN, LEPTIN AND IGF-1 IN RELATION TO COWS FERTILITY

Insulin is a peptide hormone IGF like and is liberated by the pancreas as a response to high level of glucose. Insulin induced by glucose stimulates glycogen formation, enhances glucose absorption by almost all tissues (except muscles and liver), inhibits lipolysis, gluconeogenesis and stimulates lipid storing in the liver (Veerkamp et al., 2003). Fat accumulation into non adipose tissues (like muscles and liver) is linked with peripheral insulin resistance. In humans fatty accumulation at organ level leads to metabolic syndrome and a combination of medical disorders as cardiac hypertension and diabetes type 2 (Sinclair, 2010).

Negative energy balance is defined by a increase mobilization of all body resources, by a decrease concentrations of insulin, IGF-1 and glucose, and by an increase concentrations of NEFA and BHBA. It seems that high GH and NEFA concentrations antagonize insulin action, leading to peripheral insulin resistance in fresh cows (Thatcher et al., 2011). Insulin concentration during dry-off period decrease dramatically (60 days before calving the insulin concentration is around 0.63 ng/ml, and 5 days before parturition is less than 0.26 ng/ml) (Baruselli et al., 2016).

Even if insulin has an important role in cells metabolism, an excess of it can interfere with reproductive and metabolic processes (Baruselli et al., 2016). The highest insulin limit in cows is considered to be over 37 mIU/ml.

It seems that IGF-1 is the most important mediator of GH from milk because it regulates milk secretion by mammary gland (Knop et Cernescu, 2009).

IGF-1 concentrations reflects low amount release of GH by the liver. It seems that IGF-1 has a longer anabolic action comparing to acute insulin action. For example, IGF-1 enhances protein synthesis and theca and granulosa cell proliferation, increases steroidogenesis, and releases luteinizing hormone (LH) (Veerkamp et al., 2003).

During NEB, IGF-1 - GH axis is down regulated because of GH receptors deficiency of liver, in direct link to reduced IGF-1 concentration and with increased GH concentration. All these, along with low insulin level, offer an endocrine environment that sustains the direct action of GH for lipolysis and for gluconeogenesis at the start of lactation (Knop et Cernescu, 2009).

Leptin is a cytokine like hormone released by fat tissue and acts on the central nervous system, controlling the LH pulses. Most probable, leptin acts together with insulin for ovulation relapse (Rodney et al., 2018).

NEFA AND BHBA EVALUATION FOR A BETTER REPRODUCTION

Dairy cows with high milk yield production cross a tremendous period of glucose, amino acids and fatty acids shortage that starts soon before calving.

At the start of lactation, all adipose resources are mobilized as NEFA for energy support. Through increased blood flow these acids are transported to the liver where they are metabolized into triglycerides and very low density lipoproteins by oxidation and re esterification (Barletta et al., 2017).

The liver metabolizes by oxidation around 15-20% of NEFA and produce ketone bodies (acetone, acetoacetate acid and BHBA) (McArt et al., 2013). Blood BHBA concentration can indicate the grade of fatty acids oxidation. It seems that more than 50% of dairy cows cross a short period of subclinical ketosis during the first month of lactation. This fact is an adaptative strategy for glucose maintenance (Knop and Cernescu, 2009) because BHBA acts as energy source for the brain and heart (McArt et al., 2013).

Circulating NEFA concentrations are inversely with DMI. For example, cows with BCS higher than 4 at calving will present increased concentrations of NEFA in the first 7 weeks of lactation.

A number of studies reported a negative relationship between NEFA and reproductive activity. Ospina et al. (2010a) showed that NEFA concentrations during transition period were associated with low pregnancy rate after 70 days in milk, and Ospina et al. (2010b) signaled the same result for the first 21 days in milk.

Females with severe NEB are more susceptible to develop different diseases. For example, subclinical hypocalcemia, increased level of NEFA, metritis, respiratory and digestive problems predispose the cow to a delayed estrous cycle over 50 days of lactation, negatively affects embryo quality, decreases the number of pregnant cows per service and increases embryo loss. High level of NEFA is corelated to a low pregnancy rate per service, and high concentration of NEFA and BHBA are associated with different clinical disorders (Barletta et al., 2017).

Ospina et al. (2010) proposed to measure NEFA and BHBA variations during the transition period for a better diagnosis of ketosis and NEB. Hence, antepartum cows with NEFA $\geq$ 0.27 mEq/L and with postpartum NEFA $\geq$ 0.72 mEq/L and BHB $\geq$ 10 mg/dL presented low chances to remain pregnant after 70 days of voluntary waiting period. The milk production was lower for cows that have antepartum NEFA $\geq$ 0.33 mEq/L. For cows in first lactation a decrease milk production was registered when NEFA and BHBA values were 0.72 mEq/L and 10 mg/dL, respectively (Ospina et al., 2010). For NEFA measurement, blood must be collected 14 to 3 days before calving because in the last 3 days before labour an increase in NEFA concentration is naturally present (McArt et al., 2013). With a level of 1.4 mmol/L of BHBA, Raboisson et al. (2014) certified that fresh cows are in a clinical ketosis state even though clinical signs appear over 3.0 mmol/L (McArt et al., 2013). Kafi and Mirzaei (2010) showed that cows with delay ovulation have high BHBA concentrations in the first 42 days in milk.

ESTROUS CYCLE RELAPSE

For dairy cows, normal puerperal period is defined as complete uterine involution, relapsing of follicular growth, ovulation of dominant follicle soon after calving, and continuous estrous cycles at 21 days intervals. A number of factors are involved in the delay of first ovulation after calving. Heifers need more days to ovulate after parturition (31.8 $\pm$ 8.3 days) comparing to multiparous (17.3 $\pm$ 6.3 days). Moreover, primiparous cows need higher amounts of energy for body growth and for lactation, and this predisposes them to a faster NEB than multiparous cows. Other risk factors are postpartum disorders, seasonal calving, mastitis, lameness, and severe decrease of BCS. For diagnosed with mastitis and lameness, ovulation relapses with a delay of 7 to 17 days. Comparing to healthy cows, animals that suffer of endometritis have 4.5 times chances for a delay ovulation, and 4.4 times chances to have a longer luteal phase. Because of bacteria environment, endometrial cells secretion of prostaglandin $F_{2\alpha}$ is shifted to prostaglandin E2 (Walsh et al., 2011).

CONCLUSIONS

Even though in the last decades the dairy industry has been focusing on continuously improving milk production through genetic selection in detriment of fertility, this review shows that high milk yield production and NEB represent strong reasons for a change in this strategy on long-term. Also, farmers and veterinarians should focus on using cow side tests for NEFA and BHBA concentrations for a correct monitoring of dairy cows during the peripartum period.

REFERENCES

Barletta R.V., Maturana Filho M., Carvalho P.D., Del Valle T.A., Netto A.S., Renno F.P., Mingoti R.D., Gandra J.R., Mourao G.B., Fricke P.M., Sartori R., Madureira E.H., Wiltbank M.C. (2017). Association of changes among body condition score during the transition period with NEFA and BHBA concetrations, milk production, fertility, and health of Holstein cows. *Theriogenology*, 104(1), 30-34.

Baruselli P.S., Vieira L.M., Sa Gilho M.F., Mingoti R.D., Ferreira R.M., Chiaratti M.R., Oliveira L.H., Sales J.N., Sartori R. (2016). Associations of insulin resistance later in lactation on fertility of dairy cows. *Theriogenology*, 86(1), 263-9.

Carvalho P.D., Souza A.H., Amundson M.C., Hackbart K.S., Fuenzalida M.J., Herlihy M.M. (2014). Relationships between fertility and postpartum changes in body condition and body wight in lactating dairy cows. *Journal of dairy science*, 97(1), 3666-83.

Constantin N.T. and Bîrțoiu I.A. (2014). Immunological status of the puerperial uterus in cow. *Scientific Works. Series C. Veterinary Medicine*, 60(1), 18-26.

Kafi M., Mirzaei A. (2010). Effects of first postpartum progesterone rise, metabolites, milk yield, and body condition score on the subsequent ovarian activity and fertility in lactating Holstein dairy cows. *Tropical Animal Health and Production*, 42(1), 761-767.

Knop R., Cernescu H. (2009). Effects of negative energy balance on reproduction in dairy cows. *Lucrări științifice Medicină Veterinară*, 42(2), 198-205.

McArt J.A.A., NyDam D.V., Oetzel G.R., Overton T.R. (2013). Elevated non-esterified fatty acids and β-hydroxybutyrate and their association with transition dairy cow performance. *The Veterinary Journal*, 198(3), 560-70.

Miglior F., Fleming A., Malchiodi F., Brito L., Martin P., Baes C.F. (2017). A 100-year review: Identification of genetic selection of economically important traits in dairy cattle. *Journal of Dairy Science*, 100(12), 10251 – 10271.

Ospina P.A., Nydam D.V., Stokol T., Overton T.R. (2010). Associations of elevated nonsterified fatty acids and β-hydroxybutyrate concentrations with early lactation reproductive performance and milk production in transition dairy cattle in the northeastern Unaited States. *Journal of Dairy Science*, 93(1596-1603), a.

Ospina P.A., Nydam D.V., Stokol T., Overton T.R. (2010). Association between the production of sampled transition cows with increased nonesterified fatty acids and β-hydroxybuttyrate and disease incidence, pregnancy rate, and milk production at the herd level. *Journal of Dairy Science*, 93(3595-601), b.

Prates E.G., Nunes J.T., Pereira R.M. (2014). Role of lipid metabolism during cumulus-oocyte complex maturation: impact of lipid modulators to improve embryo production. *Mediators of inflammation*, 2014(2), 692067.

Raboisson D., Mounie M., Maigne E. (2014) Diseases, reproduction performance, and changes in milk production associated with suclinical ketosis in dairy cows: A meta-analysis and review. *Journal of Dairy Science*, 97(1), 7547-7563.

Rodney R.M., Celi P., Scott W., Breinhild K., Santos J.E.P., Lean I.J. (2018). Effects on nutriton on the fertility of lactating dairy cattle. *Journal of Dairy Science*, 101(1), 5115-5133.

Sinclair K.D. (2010). Declinig fertility, insulin resitance and fatty acid metabolsim in dairy cows: Developmental consequences for the oocyte and pre-implantation embryo. *Acta Scientiae Veterinariae*, 38(2), s545-s557.

Thatcher W., Santos J.E.P., Staples C.R. (2011). Dietary manipulation to improve embryonic survical in cattle. *Theriogenology*, 76(1), 1619-31.

van Knegsel A.T.M., van der Drift S.G.A., Cermakova J., Kemp B. (2013). Effects of shorting the dry period of dairy cows on milk production, energy balance, health, and fertility: A systematic review. *The Veterinary Journal*, 198(3), 707-713.

Walsh S.W., Williams E.J., Evans A.C.O. (2011). A review of causes of poor fertility in high milk producing dairy cows. *Animal Reproduction Science*, 123(1), 127-138.

Wathes D.C., Clempson A.M., Pollott G.E. (2013). Associations between lipidic metabolism and fertility in the dairy cow. *Reproduction, Fertility and Development,* 25(1), 48-61.