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Metabolic and Hematological Biomarkers Alterations during the Transition Period in Healthy Farm Animals: A Review

Mohamed Tharwat[1,2], Saleh Alkhedhairi[3,*], Islam M Saadeldin[4,5] and Naglaa Gomaa[6,7]

[1]Department of Clinical Sciences, College of Veterinary Medicine, Qassim University, P.O. Box 6622, Buraidah, 51452, Saudi Arabia
[2]Department of Animal Medicine, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt
[3]Department of Medical Biosciences, College of Veterinary Medicine, Qassim University, P.O. Box 6622, Buraidah, 51452, Saudi Arabia
[4]College of Veterinary Medicine, Chungnam National University, Daejeon, South Korea
[5]Department of Physiology, Faculty of Veterinary Medicine, Zagazig University, 44519, Zagazig, Egypt
[6]Department of Clinical Sciences, College of Veterinary Medicine, King Faisal University, Al-Ahsa 31982, Saudi Arabia
[7]Department of Animal Medicine, Faculty of Veterinary Medicine, Kafrelsheikh University, Kafrelsheikh, 33516, Egypt
***Corresponding author:** s.alkhedhairi@qu.edu.sa

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ABSTRACT

In the dairy animals, a critical stage particularly 3 weeks before and 3 weeks after parturition is named as the transition phase or period (TP), which is one of the most crucial physiological periods as almost all of the metabolic as well as infectious diseases happen during this stage. For addressing nutritional requirements and fulfill managemental strategic approaches to overcome these physiological and metabolic changes occurring at this period, a lot of research had been carried out for the better understanding of the biology of the animals during transition stage. Although these attempts, the dairy animal persist to show higher rates of metabolic diseases that are harmful to the welfare of animals and also for its productivity with following a significant financial impact on the stockholders. Several production diseases were encountered during TP; these disorders may include lameness, mastitis, rumen acidosis, ketosis, milk fever, left-displaced abomasum, fatty liver, hypophosphatemia, post-parturient hemoglobinuria, subacute ruminal acidosis, retained placenta and metritis. This review article emphasizes the significance changes during the TP in farm animals including cattle, buffaloes, sheep, goats and camels. This review will discuss alterations that occur physiologically during TP either in the hematological or biochemical parameters. In addition, hepatic fat contents, acute phase proteins, bone biomarkers, apoptosis of leukocytes and hepatocytes and nutrient metabolism biomarkers, oxidative stress and biomarkers of inflammation changes during TP.

Key words: Animals, Diagnosis, Diseases, Physiology, Transition period

INTRODUCTION

In the dairy animal, the transition or periparturient phase is three weeks before and after parturition (±3 weeks) in which significant physiological changes occur. The transition period (TP) is associated with the progressive development of the fetus, readiness for calving and initiation of milk production. Several periparturient diseases were recorded during this phase (Tharwat et al. 2015a,b; Tharwat et al. 2024). During TP, the animal expresses a state of negative energy balance. Smooth transition during TP will save huge economic losses and it will increase the survival rate of the neonates as well as the following convalescence of the dam (Lean et al. 2013).

For addressing nutritional requirements and ensure managemental strategies to overcome the physiological and metabolic differences that happen during the TP, lots of research had been carried out better to try to realize the biology of the transition animal (Daros et al. 2022). But, in spite of this, animals at the TP keep to show high incidence of metabolic abnormalities that are important to the animal managemental welfare issues as well as for its productivity and of course it will affect the financial sides of the stockholders (Redfern et al. 2021).

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The TP is also a very critical time that affects the dairy animal productivity and can also influence the health status and its metabolism as well as their reproductive efficiency and milk yield performance in the following lactation cycle (Roche et al. 2015). A drop in dry matter intake periparturient may lead to a negative energy balance (NEB) during the early lactation, which is probably one of the principal problems with the status of metabolic homeostasis. Excessive lipolysis and increased levels of non-esterified fatty acids (NEFA) during the state of NEB are often linked with the elevation of triglycerides (TG) in hepatic cells thus disturbing liver function and resulting in an increased ketone body formation (Esposito et al. 2014). In addition, elevated blood NEFA levels could have a negative impact on oocyte formation and reproductive efficiency (Walsh et al. 2007). It was reported that a severe elevation in the blood NEFA pre-partum may be considered an influencing role affecting inflammatory responses of the transition dairy animals (Sordillo and Raphael 2013). Elevated blood NEFA concentrations might also be related to an increased risk of metritis and retained placenta (Ospina et al. 2010a), mastitis (Suriyasathaporn et al. 2000), displaced abomasum (Chapinal et al. 2011) and lower milk yield (Ospina et al. 2010b), while it may also result in culling during early-lactation phase (Roberts et al. 2012).

Several production diseases were encountered during TP in dairy cows. These disorders may include lameness, mastitis, rumen acidosis, ketosis, milk fever, left-displaced abomasum, fatty liver, hypophosphatemia, post-parturient hemoglobinuria, subacute ruminal acidosis, retained placenta and metritis (Tharwat et al. 2004a, b; Sundrum 2015). Many researches had reported and emphasized the diagnostic and prognostic indicators of several biomarkers in animal´s species (Tharwat 2012, 2020a, b, c, d, e; 2023; Tharwat et al. 2012a, 2013a, b, c, d, e, 2014a, b; 2021; 2024; Tharwat and Al-Sobayil 2014a, b, 2015a; 2018a, b; 2020, 2022a, b; Al-Sobayil and Tharwat 2021; Tharwat and El-Deeb 2021; Almundarij and Tharwat 2023).

Since long time ago, researchers have reported that fundamental physiological abnormalities occur in several parameters before and after parturition. However, these differences are not surely indicating disease status of the animal, but it points to physiological diversities. This review article was designed to emphasize the significance of these changes during the TP in farm animals including cattle, sheep, goats and camels. In order, this review will discuss alterations that occur physiologically during the TP either in the hematological or biochemical parameters. In addition, acute phase proteins, bone biomarkers, apoptosis of leukocytes and hepatocytes and nutrient metabolism biomarkers, oxidative stress and inflammation biomarkers changes during the TP will also be summarized.

Hematological alterations

In dairy cows, the hematological biomarkers during the TP show significant changes. This is because of the physiological settlements necessary as a response to the metabolic needs during the final stage of pregnancy and in the initiation of lactation phase. This of course guarantees the nutritional demands in energy and oxygen transportation via the blood (Coelho de Oliveira et al. 2019). Neutrophilia constitutes the most significant hematological alterations after parturition in the female dromedaries (Tharwat et al. 2015a). Similar findings are found in cattle during the TP that occur as a result of stress associated with parturition and milk yield (El-Ghoul et al. 2000). Complete blood count (CBC) did not change in a significant way among the pre-partum, at parturition and post-partum phases (Coelho de Oliveira et al. 2019). However, in buffaloes, a non-significant difference in RBC numbers and Hb content were found during the 1st and 2nd weeks after parturition while total leukocytes especially neutrophil count showed significant increases during post-permutation TP (Gomaa et al. 2021).

The picture of CBC in periparturient goats shows increased neutrophils a week post-parturition and decreased monocytes at 2nd and 3rd weeks of parturition. A drop in the red blood cells (RBCs) count is observed at weeks prepartum. In a similar manner, a decline in the hematocrit (HCT) percent is found 14 days before parturition and just at parturition. Other hematological abnormalities involve a reduced mean corpuscular volume 3 weeks after parturition. Lymphocytes, eosinophil, basophil, hemoglobin, mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) did not differ significantly before and after parturition (Tharwat et al. 2015b). The most important hematological changes in the goats during the TP are the neutrophilia, monocytopenia and decreased RBCs count. These changes are also reported in cattle and buffalo during TP. The decrease of RBCs count was attributed to nutritional condition of animals during this period that affected erythropoiesis (Delfino et al. 2018). While the increases of WBCs were attributed to decrease of glucocorticoid receptor expressions in neutrophils and an elevation of cortisol level, inducing neutrophilic leukocytosis as the influence of the stress that accompany parturition and yielding of milk (El-Ghoul et al. 2000).

In female camels, the total leukocytic count (WBCs) show a non-significant change at all tested time points before, at, and after parturition. Lymphopenia is observed at week before and at parturition and neutrophilia at 1- and 2-weeks post-partum. However, monocyte and eosinophils did not differ significantly during the TP. The RBCs, hemoglobin, HCT, platelets and mean corpuscular volume did not differ significantly. On the other side, the MCHC and MCH elevate in a significant manner 2nd week after parturition (Tharwat et al. 2015a).

From the above-mentioned studies, it is evident that all hematological changes that occur during the TP in healthy farm animals are physiological, however, in farm animals during the dry period and at the first stages of lactation these abnormalities could be due to the metabolic changes. Therefore, elevations in the hemogram during the TP did not reveal infection. Hence, in the future interpretation of hematological results during the TP should be supported by a critical physical examination accompanied with full previous and immediate history of the examined farm animal.

Biochemical alterations

In periparturient animals, the activity of aspartate aminotransferase (AST) significantly increases at parturition and the levels of the non-esterified fatty acids (NEFA) significantly increase during all phases of TP. The concentrations of β–hydroxy butyric acid (BHBA) is also elevated at parturition and at the 3rd week post-parturition. Other variables consisting of albumin, globulin, total protein, glucose, phosphorus, calcium and total cholesterol did not change significantly before and after parturition. The TG is markedly elevated at parturition and at 3 weeks after partition compared with values 3 weeks before parturition. Similarly, the glycogen concentration is high at parturition and at 3 weeks after parturition compared with values 3 weeks pre-calving (Fig. 1) (Tharwat et al. 2012b).

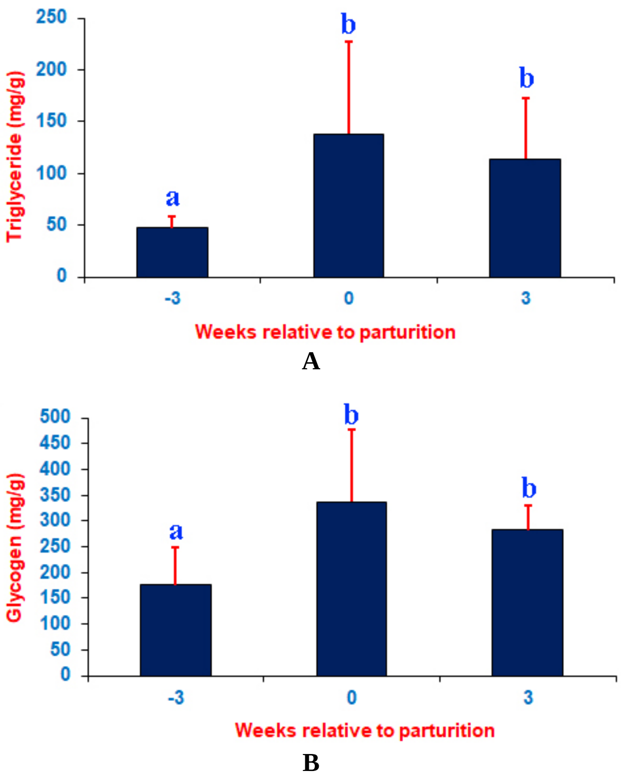

Fig. 1: Hepatic triglycerides (**A**) and glycogen (**B**) (mg/g wet tissue) in dairy cows 3 weeks before expected parturition (**-3**), at parturition (**0**) and 3 weeks after parturition (**3**). Different superscripts show significant differences (P<0.001) (Tharwat et al. 2012b).

In the periparturient female goat, total protein increases dramatically from a week before parturition until 3 weeks after parturition. Globulin increases also from week 2 before until 3 weeks after parturition. Albumin concentration however decreases, but not significantly, during 2 weeks before until 3 weeks post-parturition (Tharwat et al. 2012b). Calcium concentration also decreases a week before, at parturition and at the 2nd week after parturition in goats, but returns to pre-partum level 3 weeks after parturition. Similarly, magnesium concentration decreases, but not significantly, from 2nd week before until 3rd week post-parturition. Conversely, phosphorus concentration increases significantly 2 weeks before and 2 weeks after parturition but decreases at parturition and at a week after parturition (Tharwat et al. 2015b). Marked elevation are found in the AST and γ-glutamyl transferase (GGT) in goats during the TP because of the TG hepatic accumulation, as also found in cows (Tharwat et al. 2012b). The high alkaline phosphatase (ALP) activity pre-partum in goats may be the result of increased production of this enzyme by placenta, as also detected in cattle (Tharwat et al. 2015b). The TG concentration did not differ significantly in the goats during TP. However, the concentration of total cholesterol decreases significantly from a week before until at parturition, while the concentration of low-density lipoproteins (LDL), high-density lipoproteins (HDL) and very low-density lipoproteins (VLDL) did not differ significantly during TP in goats (Tharwat et al. 2015b).

In female goats, progesterone decreases markedly until 3 weeks after parturition and even thereafter decreases; this is a physiological change (Khan and Ludri 2002b; Alwan et al. 2010). However, estrogen increases markedly at parturition and decreases after that (Tharwat et al. 2015b). This is also a physiological that is required for myometrial contraction at parturition phase (Alwan et al. 2010; Tharwat et al. 2015b). Hyperglycemia occurs at 2nd week before and at the 3 weeks after parturition. The serum activity of creatine kinase (CK) declines at 2nd week before parturition but returns to normal during remaining times of TP (Tharwat et al. 2015b). Hypoglycemia encountered at parturition may be due to glucose utilization by the developing fetuses and also due to stress at this phase (Khan and Ludri 2002a).

At final period pregnancy, adrenocorticotropic hormone secretion increases that originates from the pituitary gland of the fetus, stimulating the speedy development of the fetal adrenal gland, and finally rising in the cortisol concentration. This cortisol gets in the maternal blood circulation and finally it induces parturition through activating the formation of prostaglandin F2α (Suganya and Gomathy 2009; Tharwat et al. 2015b). Therefore, serum cortisol reaches to its maximum level at time of parturition (Tharwat et al. 2015b). Different biochemical changes were recorded during TP in female camels (Tharwat et al. 2015a). The albumin and total protein concentrations did not change markedly during TP. However, globulin concentration increases significantly at 3rd week after parturition (Tharwat et al. 2015a). Similar results have been found in dairy cows (Tharwat et al. 2012b). During TP, calcium concentrations did not differ significantly in female camels. However, the phosphorus and magnesium concentrations increase significantly at 2nd week before and 3rd week after parturition, respectively (Tharwat et al. 2015a).

Glucose concentration increases significantly at parturition and at 1st week post-partum. On the contrary, CK did not elevate markedly pre- and post-partum (Tharwat et al. 2015a). BUN concentrations did not elevate significantly before- and after parturition. However, creatinine concentrations decrease significantly at 1st week post-partum (Tharwat et al. 2015a). Cortisol concentration increases significantly in female camels at parturition. Estrogen concentration increases significantly at from 2nd week before until parturition, but decreases significantly from 1st week until 3rd week after parturition. Progesterone concentration increases significantly at 2nd week before and decreases from parturition until 3rd weeks later (Khan and Ludri 2002a; Alwan et al. 2010).

From the above-mentioned reports, it is found that some metabolites such as AST, NEFA, BHBA, TG, glycogen, GGT, ALP, CK, HDL, LDL, VLDL, albumin, globulin, total protein, glucose, phosphorus, calcium, magnesium, estrogen, progesterone, differ during the TP in the healthy farm animals. The variations of these metabolites either by the increase or decrease are also physiological and did not reveal systematic abnormalities as found in the hematological variables. Therefore, as pointed above concerning changes in the hemogram, future interpretation of biochemical profile during the TP should also be supported by a thorough clinical examination as well as full previous and immediate history of the examined farm animal.

Inflammatory response and acute phase proteins

Biomarkers of inflammation or acute-phase proteins (APPs) are a group of proteins that elevate or drop following infection, trauma or inflammation (Murata et al. 2004). This phenomenon is named either acute-phase reaction or acute-phase response (APR). As a result of injury, inflammatory cells excrete a number of cytokines and the liver reacts by manufacturing a massive amounts of APPs (Tharwat et al. 2014b). Examples of APPs are C-reactive protein, haptoglobin (Hp), ceruloplasmin, fibrinogen, serum amyloid A (SAA) and α 1-acid glycoprotein (Eckersall and Bell 2010).

Compared to mean values at the 3rd week before parturition, Hp, SAA and fibrinogen in female goats increases significantly at parturition then decreases significantly 3 weeks after parturition (Tharwat and Al-Sobayil 2015a). As reported in female camels during the TP, an APR occurs in goats at parturition. This is clearly shown by marked increases in SAA, Hp and fibrinogen. These elevations differentiate physiological restraint to parturition from other pathologies conditions at the TP (Tharwat and Al-Sobayil 2015a).

An APR is reported in female camels during the TP. It is clarified by significant values of serum SAA and Hp and that occurred at parturition versus at 3rd week just before and post-parturition. The elevated SAA and Hp levels are not evidenced to pathological situations, as evidenced by unchanged WBCs among the tested time points during the TP but could be due to hormone and cortisol productions and to stress related to the phase of parturition (Tharwat and Al-Sobayil 2015b). The SAA concentration at 3 weeks after parturition decreases significantly compared to values at 3rd week pre-partum and at parturition (Tharwat and Al-Sobayil 2015b). It is reported that the concentration of APPs (C-reactive protein, SAA, Hp) increases with severity of fatty infiltration in liver in dairy cows, and therefore it can be used as a promising biomarker for prediction and early diagnosis of hepatic lipidosis along with ultrasonography and, liver enzymes and NEFA and BHBA (Singh et al. 2021).

Critical analysis of the studies above shows that the biomarkers of inflammation including HP, SAA, fibrinogen and C-reactive protein change significantly during the TP in the healthy farm animals. These reports also suggested that the variations in APPs can differentiate between physiological and pathological states and can also be used as sensitive biomarkers for predicting diseases during the TP. Therefore, it is strongly recommended in the future to implement analysis of APPs in farm animals during the TP.

Biomarkers of bone metabolism

Usage of markers of bone metabolism seems to be beneficial for assessing the bone remodeling in mares and cows during the TP (Filipovic et al. 2008, 2010; Sato et al. 2011). These markers commonly include bone-specific alkaline phosphatase (b-ALP) and osteocalcin (OC) and amino and carboxy propeptides of collagen type I as bone formation biomarkers. However, deoxypyridinoline enzyme tartrate resistant acid phosphatase, pyridinoline cross-links (PYD) and amino and carboxy telopeptides of collagen type I as biomarkers for bone resorption (Filipovic et al. 2008, 2010; Sato et al. 2011; Tharwat and Al-Sobayil 2020).

In female goats, b-ALP and OC values during the TP did not show any significant differences. However, compared to a value at the 3rd week pre-partum, PYD decreases markedly at parturition, but the PYD concentration differed significantly at the 3rd week post-partum (Tharwat 2020a, c). The serum concentrations of b-ALP and OC in female camels reveal no significance. In contrast, PYD decreases markedly at parturition. At the 3rd week post-partum, the PYD concentration differs significantly (Tharwat and Al-Sobayil 2015b). Liesegang et al. (2006) indicated that the efficacy of the osteoblasts is lowered in ewes during late pregnancy. The PYD decreases markedly at parturition versus to 3rd week pre-partum. However, at third week after parturition, the PYD serum values increases dramatically versus levels at parturition (Tharwat and Al-Sobayil 2015b). In the camels, the increases in the PYD concentration at 3rd week pre- and post-parturition versus levels at parturition is in accordance with that increases in markers of bone resorption that was found at the imitation of milking in ewes, goats and dairy cows (Holtenius and Ekelund 2005; Liesegang et al. 2006, 2007; Filipovic et al. 2008). The biomarkers of bone formation did not change greatly during the TP of the female camels (Tharwat and Al-Sobayil 2015b); a result parallel to that in dairy cows, where significant levels of b-ALP were not detected either in late pregnancy or at early lactation (Filipovic et al. 2008). The activity of b-ALP in mares is declined in final stages of pregnancy versus early periods of lactation (Filipovic et al. 2010).

Analyzing the reports mentioned above shows that the bone biomarkers b-ALP, OC and PYD change during the TP in the healthy farm animals. However, except for the bone resorption biomarker PYD, the significance of the bone formation biomarkers b-ALP and OC is of less importance. Therefore, future analysis of b-ALP and OC during the TP in healthy farm animals may be neglected but estimation of PYD is recommended.

Apoptosis of leukocytes and hepatocytes

During the transition phase, the animal shows immunosuppression and often has to manage with sudden onset of dietary changes that leads to digestive troubles. In addition to the endocrine, immune system and metabolic disorders sophisticated by transition animal, they are also having environmental stress factors coming from the normal group changes that are linked with farm managemental polices of either dry or lactating animal (Mulligan and Doherty 2008).

Single cell gel electrophoresis (SCGE) test or the comet assay is a method used for discovery of DNA breakdown in interphase cells. This assay is particularly sensible in evaluating DNA single-strand breaks in body cells. Versus other traditional ways of discovery of DNA deterioration, SCGE has the benefits of displaying DNA damage. It is also a straightforward, sensible, rapid, powerful and simple method applied in toxicological trials. The obvious benefits of the comet assay beyond other methods that detect strand breaks of DNA is its capability to determine heterogeneity within the compound populations. The alkaline version of the comet assay initially measures breaks of DNA. It is generally known that SCGE carried out under alkaline conditions initially detects single-strand breaks of DNA and alkali-labile areas in DNA (Tharwat et al. 2012c; 2012e).

In dairy cattle, mean values of polymorphonuclear neutrophils leukocytes (PMN) tail moment did not differ significantly during the TP. On the other hand, peripheral blood mononuclear cells (PBMC) tail moment values differ greatly versus values post-parturition (Tharwat et al. 2012d). The intact DNA will stay within the center; however, the damaged DNA migrates from the core and directs towards the anode, forming a tail of a comet. In normal cells, the DNA is firmly pressed and preserved the round shape of the normal nucleus (Fig. 2) (Tharwat et al. 2012e). A statistically significant difference of comet moment of PBMC is detected at partition and 3 weeks after parturition compared with comet values measured 3 weeks before parturition. The measured high apoptotic activities of PBMC, especially 3 weeks after parturition, could be attributed, at least in part, to different stressors applied to the transition cows mainly in the high lactating dairy cows. In addition, it is reported that apoptosis of PMN is not statistically different between the three periods examined during the TP (Fig. 3) (Tharwat et al. 2012e).

It is also reported that apoptosis occurs in the hepatic cells of the transition cow and depends on the hepatic TG accumulation. Monitoring apoptosis in the liver of the transition cow in general requires careful pre-evaluation of suitable detecting methods for identification and following up of apoptosis based on the different biochemical mechanisms. The comet assay and immunohistochemical staining of caspase-3 and ssDNA and examination of ultrastructure of hepatocytes by transmission electron microscopy (TEM) are truly reflecting apoptosis even in its earlier stages and can thus be recommended as reference methods for studying apoptosis in the periparturient dairy cow (Tharwat et al. 2012c). Compared to values 3 weeks before parturition, there are dramatic increases in the mean tail moment values of hepatic cells at partition and at 3 weeks after parturition (Fig. 4) (Tharwat et al. 2012c). No significant alterations are observed by TEM in hepatocytes 3 weeks before parturition. On the contrary, condensation of nuclear chromatin, typical sign of apoptosis, is observed 3 weeks after parturition (Fig. 5) (Tharwat et al. 2012c).

Critical analysis of reports documenting apoptosis of leukocytes during the TP showed that high apoptotic activity was measured in the PBMC but not PMN. Concerning apoptosis of hepatocytes during the TP, analysis of the studies mentioned above stressed that apoptosis was found in hepatic cells depending on the amount of stored TG. In addition, staining of caspase-3 and ssDNA and examination of hepatocytes by TEM can detect apoptosis even in its earlier stages and can thus be recommended as reference methods for studying apoptosis in the hepatocytes during the TP.

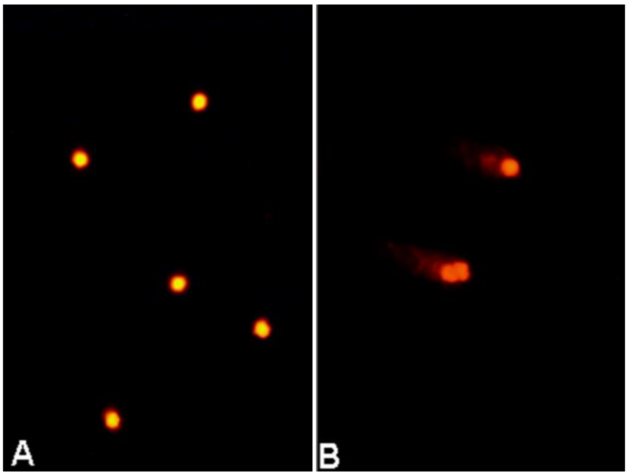

Fig. 2: Comet images of peripheral blood mononuclear cells; **A**: In undamaged cells, the DNA is tightly compressed and maintains the circular disposition of the normal nucleus (week 3 before parturition). **B**: The damaged DNA migrates from the core toward the anode, forming the tail of a comet (week 3 after parturition) (Tharwat et al. 2012e).

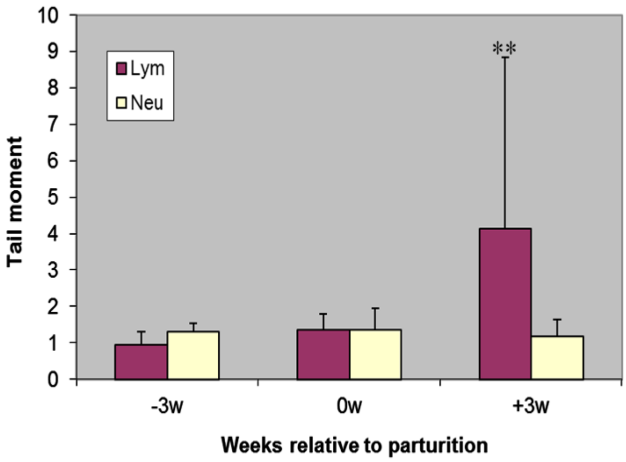

Fig. 3: Tail momentum of lymphocytes (Lym) and neutrophils (Neu) in dairy cows during the transition period 3 weeks before parturition (−3w), at parturition (0w) and 3 weeks post-calving (+3w). $^{**}P < 0.01$ (Tharwat et al. 2012e).

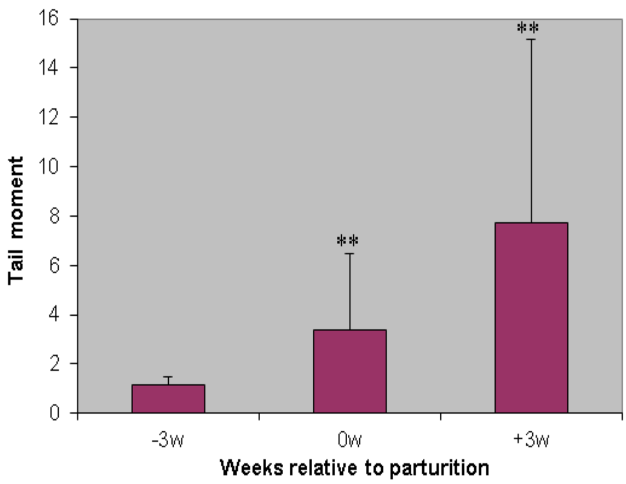

Fig. 4: Tail momentum of hepatic cells in dairy cattle 3 weeks before parturition (-3w), during parturition (0w), and 3 weeks after parturition (+3w). P=0.05 (Tharwat et al. 2012c).

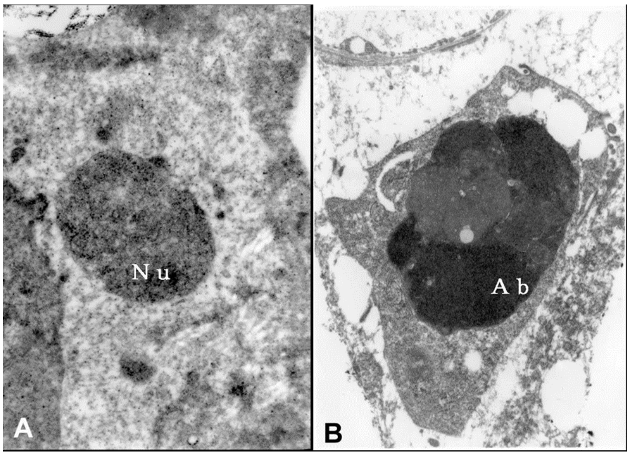

Fig. 5: Transmission electron microscope images of hepatocytes, 3 weeks before parturition (**A**) and 3 weeks after parturition (**B**). No significant alterations are observed in hepatocytes 3 weeks before parturition. On the contrary, condensation of nuclear chromatin, typical sign of apoptosis, is observed 3 weeks after parturition (Tharwat et al. 2012c).

Biomarkers of nutrient metabolism, inflammation and oxidative stress

The transition from late period in gestation to the first phases of lactation exploits a rapid metabolic adaptation for the dairy cow, subjecting them to health defects that affect their overall fulfillment and affect the financial impact of the farms. Oxidative stress has a principal role in the occurrence of these disorders and has been linked as a bridge between inflammation and nutrient metabolism during this stage (Sordillo and Mavangira 2014). Thus, adjusting these circumstances through perfect antioxidant activity could presently progress the animals' health performance. Therefore, calibration of oxidative status valuation in dairy cows is crucial, as an initial way for foundation of critical levels that could aid in realizing perfect sheltering nutritional strategic methods on the fundamentals of antioxidant addition (Abuelo et al. 2015).

Constantinescu et al. (2015) found low levels of superoxide dismutase and glutathione-peroxidase in early lactating dairy cows. It is important to improve control actions in order to batter the influence of oxidative stress detected after parturition, and one solution is to implement the antioxidants a month before parturition till 2^{nd} month post-parturition (Constantinescu et al. 2015).

In conclusion, periparturient or TP is very crucial phase for the dairy animals. Smooth transition during this period will protect dams from several diseases. It also will assist in helping the neonatal animals to pass this period safely. Various alterations occur physiologically during the TP either in the hematological or biochemical parameters. Hepatic fat contents also change during this period. In addition, acute phase proteins and bone biomarkers alter during TP. Finally, apoptosis of leukocytes and hepatocytes, biomarkers of nutrient metabolism, inflammation, and oxidative stress change dramatically during the TP.

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

Author contributions

MT: concept and design the proposal. MT, SA, IS, and NG: collected and analyzed the published data. MT: wrote the manuscript draft. All authors revised and approved the final manuscript.

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