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Differential adaptation of metabolic inflammation between primiparous and multiparous Zebu cows during transition period

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ABSTRACT

This study aimed to estimate the changes in the milk yield, milk fat, energy indicators [NEFA, BHBA, Dry Matter Intake (DMI) and Body Condition Score (BCS)] and concentration of innate immune molecules (Haptoglobin: Hp, Serum Amyloid A: SAA, TLR-4, TNF-α, IL-1β, IL-6, and IL-8), during the transition period in primiparous and multiparous dual-purpose zebu (Deoni) cows. The blood sample was collected at weekly intervals during pre-partum (-21±2, -14±1, -7±1, d), date of calving (day 0), and postpartum period (3±1, 7±1, 14±1, 21±2 d) for estimation of the above plasma variables using commercially available bovine specific ELISA kits. DMI and BCS during the corresponding period were also recorded. Data were analyzed using a linear mixed model considering group, time and their interaction as fixed effects. Group, time and their interaction had significant effect on DMI where primiparous cows consumed higher DMI during early postpartum period as compared to multiparous cows. Group alone had significant effect on milk yield, milk fat per cent and BHBA level while time alone influenced BCS. The interaction of group and time had significant effects on plasma TLR-4 and IL-8 concentration. Group also had significant effect on Hp and TNF-α levels. It was concluded that parity had significant effect on metabolic and immune indicators where higher DMI during transition period resulted in more milk yield in primiparous than multiparous indigenous (Deoni) cows.

Keywords: Deoni cows, Inflammatory indicators, Metabolic indicators, Milk yield, Parity, Transition period

The transition period, from three weeks prepartum to three weeks postpartum, is an important stage that determines postpartum milk yield. Transition cows undergo physiological, nutritional, behavioural, metabolic, and immunological changes (Wankhade *et al*. 2017) and these changes occur with intention of physiological adaptation towards non-lactating, pregnant state to lactating, non-pregnant condition (Trevisi *et al*. 2016). Among the various challenges, metabolic and immunological changes (i.e. metabolic inflammation) start several weeks before parturition but, plays a key role in deciding subsequent health and production performances during later postpartum period (Leblanc 2010, Kerhli 2015). Acute-phase proteins (APPs) are important non-specific innate immune molecules and considered as a marker of inflammation (Eckersall and Bell 2010). Haptoglobin (Hp) and Serum Amyloid A (SAA) are the major bovine APPs and play an important role in animal reproduction (Manimaran *et al*. 2016). Inflammatory cytokines are believed to be a central integrator of metabolic and immune function (Sordillo *et al*. 1995). Several researchers reported the relationship of metabolic and immune indicators such as IL-1β, TNF-α, and IL-6 with metabolic diseases during peri-partum period in *Bos taurus* (Zhang *et al*. 2016, Dervishi *et al*. 2016) or zebu (Boro *et al*. 2015, Kumari *et al*. 2016) cows and limited information is available about overt metabolic inflammatory changes without any pathological conditions during transition period (Bionaz *et al*. 2007, Bradford *et al*. 2015). Previously, we reported active functioning of the immune system, more dry matter intake, and efficient metabolic adaptation during transition period enabled to synthesize more milk and conceive early during postpartum period in apparently healthy multiparous, Deoni cows (Wankhade *et al*. 2018, Wankhade *et al*. 2019).

Several researchers observed that parity is a well-known risk factor for postpartum complications (Kimura *et al*. 2006, Seifi *et al*. 2011). Ruprechter *et al*. (2018) also observed influence of parity on metabolic profiles in healthy and sick cows during the transition period. Ospina *et al*. (2010) reported that degree of fat mobilization and its consequent efficiency of utilization for milk synthesis are altered by parity. These studies in high yielding *Bos taurus* breeds suggested that energy balance regulations are different across parity and thus the management of

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peri-parturient period should be different. Neave *et al*. (2017) reported that feeding behaviour of primiparous and multiparous cows are different during transition period and thus they require different management practices. An existence of such similar conditions in low yielding *Bos indicus* (zebu) cows such as Deoni is not clear. Conversely, we assume that understanding the influence of parity, in Deoni cows will be useful to formulate the preventive measures to avoid metabolic diseases, which is reported as 5% proportional rate in this important dual-purpose indigenous cattle breed of southern and western India (Kuralkar *et al*. 2014, Sharma 2021). Although dual-purpose breeds are low yielding compared to milch breeds of Indian dairy cattle, Deoni cattle is more preferred than other breeds by the small farmers in tropical drought-prone native tract areas, due to their better disease resistance and heat tolerance ability (Soumya *et al*. 2017). The average milk yield of Deoni cows was reported as 780 kg in a lactation (Das *et al*. 2011) and the peak yield is reached only after 4 to 5 lactations. We hypothesized that metabolic inflammation is differentially altered between primiparous and multiparous Deoni cows during transition period. Accordingly, we aimed to evaluate the influence of parity on milk yield and other indicators of metabolic-inflammation during transition period in apparently healthy Deoni cows.

MATERIALS AND METHODS

Experiment animals and management: The study was conducted at LRC, SRS, ICAR-NDRI, Bengaluru, Karnataka (India), which is located in southern Plateau and Hill agro-climatic region (12º 97`N latitude and 77º 56`E longitude). The experimental procedures were duly approved by Institute Animal Ethical Committee (CPCSEA/IAEC/LA/SRS-ICAR-NDRI-2017-07). Pregnant heifers (n=6) and multiparous cows (n=6) were enrolled a month before the expected date of calving and followed up to 45 days after calving. All animals were apparently healthy and free from any diseases while enrollment. The experimental cows were maintained under individual tie-barn housing system. The shed used for this experiment were open from all side, concrete paved with tiled roof. The housing space for cows was as per (BIS). All the cows were fed according to NRC (2001) recommendation using institute grown seasonal green fodders like maize, jowar, hybrid napier, paragrass, guinea grass, and cowpea along with dry fodder (ragi straw) and commercially available concentrates (Nandini gold-cow feed; M/s Karnataka Milk Federation, Bengaluru) containing 16-18% crude protein, 70-72% TDN, 2.5-3.5% fat, 5.5-6% crude fibre, 1-1.5% acid insoluble ash and 10-11% moisture. The cows were fed 15-20 kg green fodder, 2-3 kg ragi straw and 1.5-2.5 kg concentrates during prepartum transition period. After calving, the animals were offered 18-22 kg green fodder, 2-3 kg ragi straw, and 2.5-3 kg concentrate divided in equal proportion fed at the time of milking during morning and evening hours based on milk production of individual cow. The animals were provided with clean drinking water four times a day.

Milk yield and grouping of animals: The milk yield was recorded after five days of the colostrum period until the dry-off period. We considered the minimum lactation length of 11 weeks for multiparous and primiparous Deoni cows for statistical analysis. The milk fat was measured at weekly interval. The average bodyweight (kg) of multiparous and primiparous cows during one month before calving was 360 kg and 277 kg and the bodyweight during one month after calving was 307 kg and 263 kg, respectively. The average age at first calving was 3.33 and 3.68 years in primiparous and multiparous cows, respectively. The average age and parity of multiparous cows during inclusion of study were 6.74 years and 3.4 (range 3-4), respectively.

Blood sampling and biochemical analysis: Blood samples were collected in transition Deoni cows from jugular vein using vacutainer tubes with heparin as anti-coagulant on -21±2, -14±1, -7±1, 0, 3±1, 7±1, 14±1, and 21±2 days relative to calving before feeding in morning hours. The blood samples were centrifuged within 30 min after collection, at 3000 rpm for 10 min and plasma was stored at -20ºC until further analysis. Blood plasma variables were analyzed using commercially available bovine specific ELISA kits and microplate reader (Multiskan GO, M/s Thermo scientific, USA). The ELISA kits used for Haptoglobin (Hp) was based on a solid phase ELISA and obtained from M/s Life Diagnostics, Inc., West Chester, PA (USA). The sandwich ELISA based kits for estimation of Serum Amyloid A (SAA), Tumor Necrosis Factor-α (TNF-α), Interleukin 1β (IL-1β), Interleukin 6 (IL-6), Interleukin 8 (IL-8), Toll-like Receptor-4 (TLR-4) and β-hydroxy Butyric Acid (BHBA) were obtained from M/s Clound-Clone Corporation, Houston, TX (USA) and competitive ELISA based kit for NEFA estimation was obtained from M/s MyBiosource, Southern California, San Diego (USA).

Estimation of dry matter intake (DMI) and Body condition score (BCS) of individual cows: The DMI and BCS were also assessed on similar day of blood collection. DMI was calculated by the amount of feed offered and amount of residue obtained on next day (i.e. 24 h) and then DMI was estimated per 100 kg body weight. All the cows were assessed for BCS on a five-point scale as per Kellogg (2010).

Statistical analysis: Linear mixed model was used to test the significant difference in level of APPs, cytokines, energy indicators, milk yield and fat per cent between primiparous and multiparous cows considering group, time and their interaction as fixed effect. The data is presented as Mean±SEM. The differences between groups were considered significant when $P \leq 0.05$. The statistical analysis was performed using SPSS version 22 software package (SPSS for windows, V22.0; M/s SPPS Inc., Chicago, IL, USA).

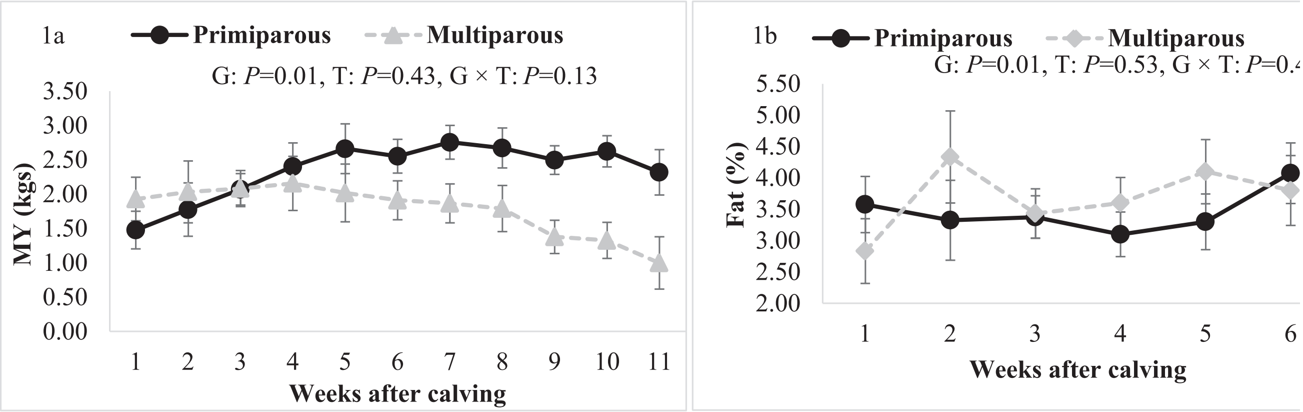

Fig. 1. Weekly average Milk yield (1a) and Milk fat per cent (1b) in primiparous (*n*=6) and multiparous (*n*=6) Deoni cows. First week observation was considered after colostrum period of 5 days. P≤0.05 for group (G), sampling day (T) and their interaction (G × T) was considered as statistically significant.

RESULTS AND DISCUSSION

Milk yield, DMI, BCS, and energy metabolites levels during transition period in primiparous and multiparous Deoni cows: We observed significant (*P*=0.01) influence of group on milk yield (Fig. 1a) and milk fat per cent (Fig. 1b), but time and its interaction with group had no effects on milk yield and fat per cent. Overall, higher milk yield in primiparous cows as compared to multiparous cows (average of 2.35 vs 1.77 kg) was observed particularly during 9th, 10th, and 11th week of postpartum period.

Group, time and their interaction had significant (*P*=0.001) effect on DMI where, higher DMI of primiparous cows was observed during early postpartum period as compared to multiparous cows (Fig. 2a). Although BCS was reduced significantly (time: *P*=0.001) from pre-partum

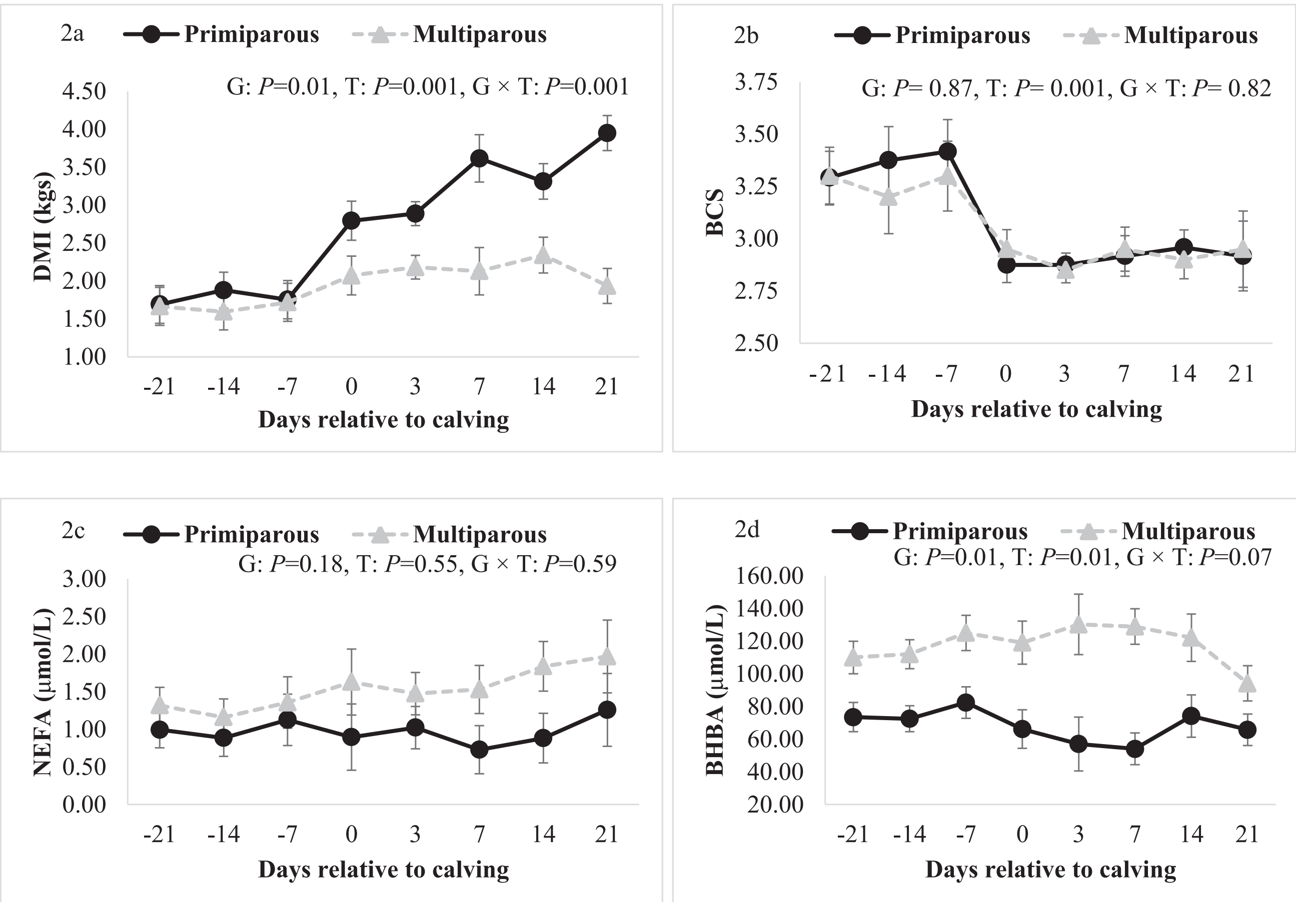

Fig. 2. (2a) Dry Matter Intake (DMI/100 Kg BW), (2b) body condition score (BCS), (2c) Plasma concentration of NEFA and (2d) BHBA during transition period in primiparous (*n*=6) and multiparous (*n*=6) Deoni cows. P≤0.05 for group (G), sampling day (T) and their interaction (G × T) was considered as statistically significant.

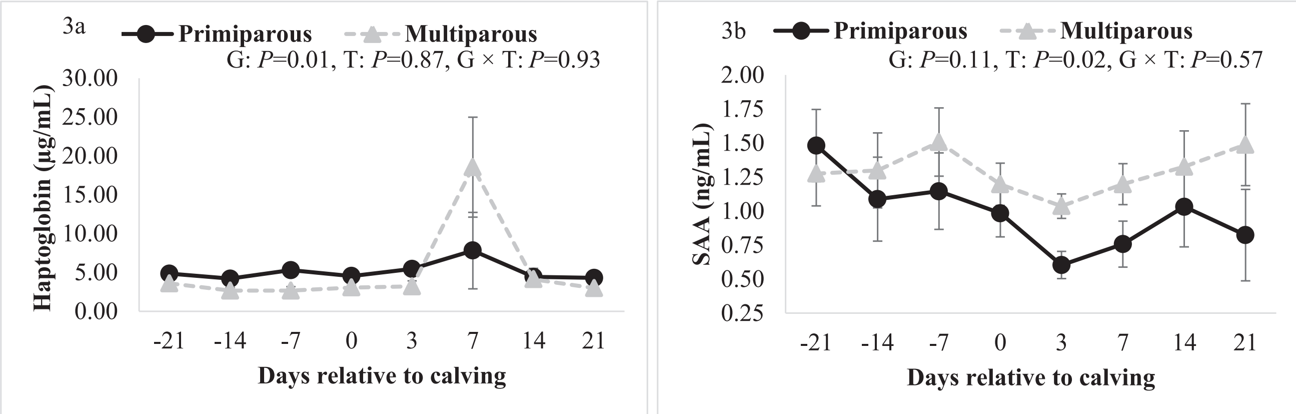

Fig. 3. Plasma concentrations of Haptoglobin (3a) and Serum Amyloid A (3b) during transition period in primiparous (*n*=6) and multiparous (*n*=6) Deoni cows. P≤0.05 for group (G), sampling day (T) and their interaction (G × T) was considered as statistically significant.

period to calving day in both the groups (0.3 in multiparous, 0.1 in primiparous), interaction of group and time had no significant (*P*=0.82) effect on BCS during transition period (Fig. 2b). Similar to BCS, about 50 kg bodyweight was reduced from one-month prepartum to one-month postpartum period in multiparous cows, while primiparous cows lost only 14 kg during same period. Group alone had significant (*P*=0.01) effect on plasma BHBA level. Fixed factors alone or their interactive effect had no significant influence on plasma NEFA (Fig. 2c) and BHBA (Fig. 2d) concentrations.

Primiparous cows experience different metabolic state as they require nutrients for their continued growth as well as for their developing calf and milk yield. To our knowledge, the influence of parity on metabolic and inflammatory indicators was mostly focussed on high-yielding multiparous cows in relation to disease outcome and little is known in healthy primiparous Zebu cows. It is commonly accepted that milk production gradually increases after calving and reaches a peak at approximately

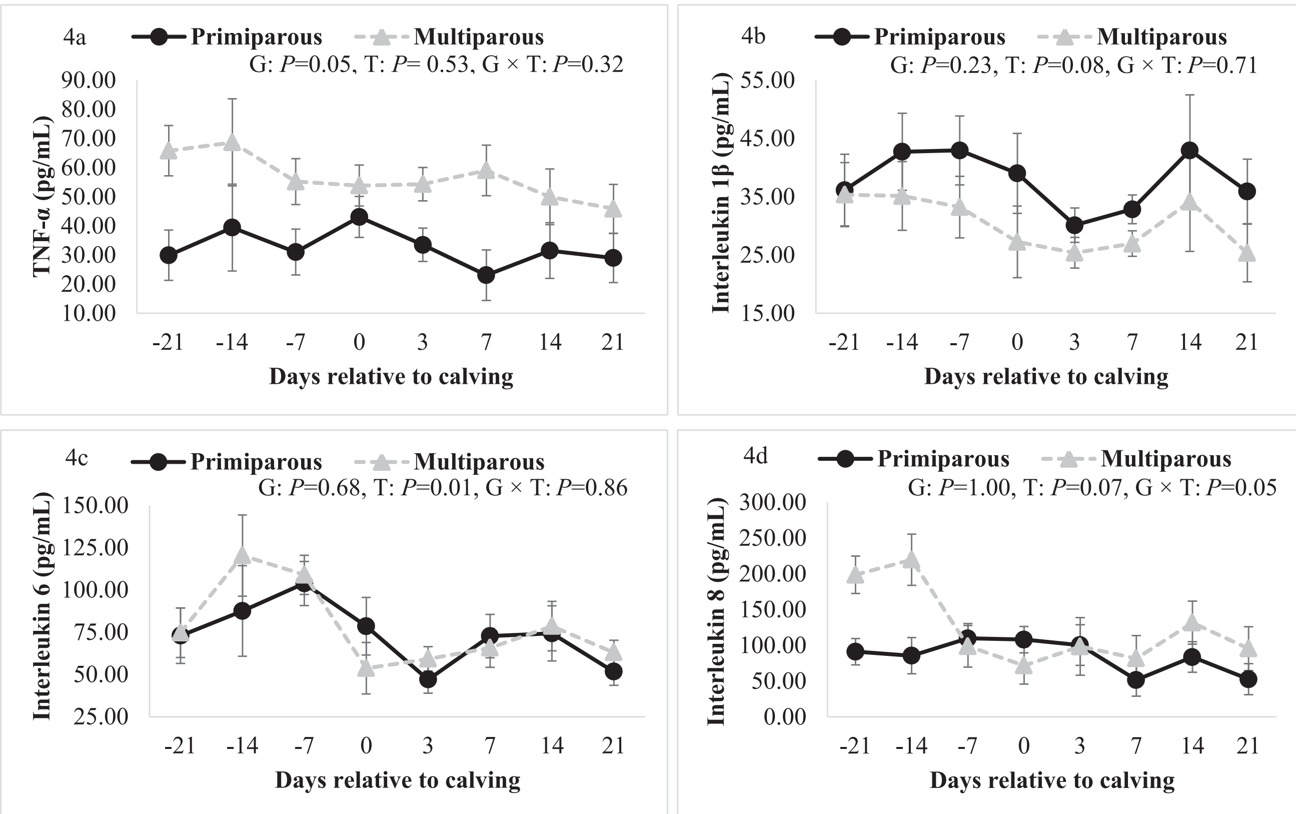

Fig. 4. Plasma concentration of TNF-α (4a), IL-1β (4b), IL-6 (4c) and IL-8 (4d) during transition period in primiparous (*n*=6) and multiparous (*n*=6) Deoni cows. P≤0.05 for group (G), sampling day (T) and their interaction (G × T) was considered as statistically significant.

4 weeks postpartum (Wang *et al*. 2019). Similar trend of increasing milk yield after 4 weeks of calving and maintenance up to 11 weeks was observed in primiparous cows. However, the multiparous cows showed declining trends of milk production after 4 weeks of calving. Average daily milk yield was also higher in primiparous than multiparous Deoni cows. Earlier studies in Deoni cows revealed that majority of the multiparous cows produced more milk yield (i.e. 3-6 kg/d), but a group of multiparous cows were very less efficient and produced very less milk (i.e. 1.77 kg; range 1.0-2.2 kg; Wankhade *et al*. 2018). On the contrary, observed more yield in primiparous than multiparous Deoni cows indicates their higher efficiency in terms of feed conversion. When the lactating cows meet their energy demands from DMI, the tissue mobilization will be minimized (Roche *et al*. 2009), and thus mobilization of body fat and milk production are closely related (Pryce *et al*. 2002). The higher DMI by primiparous cows with no changes in NEFA concentration supports this phenomenon. In fact, the recovery of postpartum DMI is an important strategy for avoiding a negative energy balance and improving milk yield (Grummer 1995, Herdt 2000), and improved DMI during early lactation period potentially decreases the risk of metabolic disorders (Kuhla 2020). The lack of any significant interactive effects of group and time on NEFA and BHBA levels, which were observed within the physiological limits in transition Deoni cows further substantiate the absence of any negative energy balance in these cows and thus increased milk yield in primiparous cows might solely be due to higher DMI. Adequate availability of glucose to meet the demand of milk yield through higher DMI in primiparous cows might have prevented the excessive lipolysis and thus kept the NEFA and BHBA concentrations at normal levels (Zebeli *et al*. 2015). More proliferation of milk-secreting alveolar cells in post-calving primiparous cows than multiparous could also be a reason for higher yield in these cows (Miller *et al*. 2006). Any significant changes in BCS were not found (on a five-point scale) between different parity groups, though multiparous was showed higher trend of loss in BCS and bodyweight from pre-partum period to the day of calving. The observed higher level of BHBA (*P*=0.01) may corroborate well with more loss of BCS or bodyweight in multiparous cows. Several researchers reported lack of relationship between BCS and milk yield in high yielding *Bos taurus* (Aeberhard *et al*. 2001, Theurer *et al*. 2003) or dual-purpose zebu cows (Jilek *et al*. 2008). Reshalaitihan *et al.* (2020) also reported no significant difference of BCS between different parity animals during transition period. Collectively, it indicated that an enhanced DMI during early postpartum could be the reason for more milk yield in primiparous cows. The role of metabolic hormones in differential regulation of energy balance between the primiparous and multiparous cows cannot be ruled out as they play very important role. For instance, Wathes *et al*. (2007) reported different endocrine patterns of insulin-like growth factor-I and leptin concentrations during peripartum period in primiparous cows than in multiparous cows.

Relationship of inflammatory indicators during transition period with parity in Deoni cows: No significant interactive effect of group and time were found on plasma concentration of acute-phase proteins such as Hp (Fig. 3a) and SAA (Fig. 3b) and inflammatory cytokines such as TNF-α (Fig. 4a), IL-1β (Fig. 4b), and IL-6 (Fig. 4c). Group alone had significant effect on Hp and TNF-α level while time alone had significant effect on SAA and IL-6 levels. The interaction of fixed factors had significant (*P*=0.05) effects on plasma IL-8 (Fig. 4d) and TLR-4 (Fig. 5) concentrations.

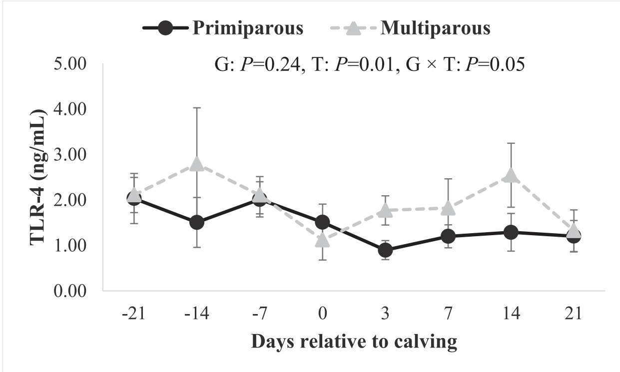

Fig. 5. Plasma concentration of TLR-4 during transition period in primiparous (*n*=6) and multiparous (*n*=6) Deoni cows. $P \leq 0.05$ for group (G), sampling day (T) and their interaction (G × T) was considered as statistically significant.

In general, innate immune response is initiated by pathogen recognition receptors (e.g. TLRs) and release of mediators such as pro-inflammatory cytokines e.g. IL-1β, TNF-α and IL-6) or chemokines (IL-8) which subsequently stimulate the synthesis of acute phase proteins (Hp and SAA) in liver or at site of infection (Manimaran *et al*. 2016). In this study, the concentrations of TLR-4, TNF-α, IL-8 and Hp were higher in multiparous cows during transition period. Studies from same animals revealed that TLR-4 is an important innate immune molecule to regulate postpartum performance during transition period (Manimaran *et al*. 2021). TLR-4 mediated synthesis of pro-inflammatory cytokines such as TNF-α, IL-β and IL-6 is an important innate immune regulation mechanism (Bronzo *et al*. 2020, Budikhina *et al*. 2021) and same could be the reason for higher levels of cytokines and Hp in multiparous cows. IL-8 is an important inflammatory cytokine and primary chemoattractant for immune cells at the site of infections. IL-8 is also believed to affect blood-milk barrier functions and affects milk synthesis and secretion (Watanabe *et al*. 2008) as observed in this study. But several existing studies on the effect of parity on disease risk are differential (Barca *et al*. 2021). Ohtsuka *et al*. (2010) reported differential regulation of systemic and udder immunity among primiparous and multiparous cows. They also observed no significant differences in the cytokine mRNA levels between primiparous and multiparous cows. Zarei *et al*. (2017) reported no impact of parity on colostrum IgG and IgM concentrations in HF cows. Large variation in cytokines concentration between individual cows and the relatively small sample size of the groups may also be reason for observed effect. Therefore, further studies are required with suitable sample size to understand the energy balance and immunity in different parity of Deoni (Zebu) cows. Altogether, it is concluded that parity had significant effect on metabolic and immune indicators, where higher DMI during transition period resulted in more milk yield in primiparous than multiparous Deoni cows.

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