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Inflammatory Mediators and Hormonal Changes in Subclinical and Clinically Affected Mastitis Cows

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A B S T R A C T

To investigate the changes that occur in inflammatory mediators and reproductive hormones levels in mastitis crossbred cows, the crossbred cows were screened for SCM incidence (24) by mCMT, SCC, electric conductivity of milk and abnormal milk. Based on this, the cows were divided as group I (n=8) - no clinical symptom of mastitis (healthy), group II (n=8) - showing chronic sub-clinical mastitis (SCM), group III (n=8) - showing clinical mastitis symptoms (CM). Blood samples were collected from group I and II the cows at weekly intervals from day 54 to 138 of lactation. A single blood sample was collected from group III before giving antibiotic treatment. Plasma Nitric Oxide (NO), Interleukin-8 (IL-8), Tumor Necrosis Factor- α (TNF-α), cortisol and prostaglandin (PGFM) levels were higher (P<0.001) in clinical mastitis cows followed by low levels in subclinical mastitis cows. Plasma levels of their parameters were lowest (p<0.001) in healthy cows. Plasma progesterone levels were significantly higher (P<0.001) in healthy cows in comparison to group II and III cows. Plasma TNF-α, PGFM and progesterone levels showed significant (P<0.001) variations between days and between groups I and group II cows whereas NO, IL-8 and cortisol levels did not change.

Introduction

Dairy animals encounter mastitis as one of the most important disease causing hindrance in the development of dairy sector. Selective breeding of dairy cattle has led to a dramatic increase in milk yield over recent decades giving India an honour to become the highest milk producer country in the world but simultaneous increase in high incidence of mastitis and huge economic losses have been reported (Heald *et al.*, 2000; Seegers *et al.*, 2003; Oltenacu and Algers, 2005). Researchers agree that the economic impact of subclinical forms of mastitis is larger than clinical mastitis (Singh *et al.*, 2016). The overall prevalence of sub-clinical mastitis has been reported to be 59.43% with quarter level prevalence of 34.78% (Bhat *et al.*, 2016). The annual economic losses due to mastitis have been calculated to be Rs.7165.51 crores both cows and buffaloes almost with rupees 3649.56 and 3515.95 crores, respectively (PDAMAS, 2011). Subclinicacl mastitis alone causes economic losses of rupees 4151.16 crores (Bogni *et al.*, 2011). This could be minimized by using certain makers in milk and plasma of mastitis animals. It has been found that nitric oxide (NO), interleukins (IL) and tumor necrosis factor (TNF-α) could play a vital role in the pathophysiology of this (Kushibiki *et al.*, 2003; Hansen *et al.*, 2004).

Mastitis not only influence milk production and composition but adversely influence reproductive performance of dairy cows (Schrick *et al.,* 2001; Santos *et al.,* 2004; Hansen *et. al.,* 2004) as homeostatic alterations in hormone viz., prostaglandin, progesterone and estrogen affects oocyte maturation, follicular development, luteal life span, resulting the embryonic losses, increased service period and more number of AI per conception and days open. Enhanced cortisol depressed LH and thereby affects ovulation process (Li *et al.,* 1983; Padmanabhan *et al.,* 1983). Considering the economic losses due to mastitis, the present investigation was undertaken to find out plasma inflammatory mediators of infection and hormone levels in mastitis crossbred cows.

Materials and Methods

Selection of Animals and management

The experiment was conducted after getting necessary approval from the Institute's Animal Ethics Committee. 32 Karan Fries cows immediately after parturition were selected from the experimental herd of the Institute. These were divided into three groups of eight each as healthy, SCM and CM animals. The cows were grouped based on screening by California Mastitis Test (mCMT) and milk SCC. Healthy cows during the experiment served as control while cows suffering from sub clinical mastitis were in SCM group. Eight cows suffering from clinical mastitis were also selected on the basis of clinical symptoms from which milk samples were taken only once.

The animals were managed in loose housing with brick floor and asbestos roof shed over the feeding manger. Cows were fed ad lib green fodder (berseem, maize and jowar fodder) and wheat straw and the concentrate mixture was offered based on milk yield. The feed and water was available ad lib all the time to these cows. Blood samples were collected in heparinized vacutainer tubes from healthy and SCM cows at weekly intervals from 54^{th} day to 138 days of lactation. A single blood sample was also collected from clinical mastitis cows before treatment of cows with antibiotic.

Plasma nitric oxide (NO) was determined by method of Shoker *et al.,* (1997). Plasma tumor necrosis factor- α (TNF- α), interleukin-8 (IL-8), progesterone, cortisol and PGFM (prostaglandin F_2 -α) were estimated by commercially available analytical ELISA kits.

The data was analyzed statistically by a SYSTAT software package. Mean ± SE was found and the significance was tested by employing two way ANOVA.

Results and Discussion

Inflammatory mediators

Plasma NO level was higher in CM cows in comparison to SCM and healthy group cows (Table 1 and 2). Significantly higher plasma NO level has been reported earlier Bastan *et al.,* (2011) in cows with mastitis. The concentration tended to increase massively during bacterial infections. The research experiment carried out in vitro and in vivo also suggests that NO concentrations increase during clinical infections being induced with E. coli endotoxin and Staphylococcus spp. (Blum *et al.,* 2000; Boulanger *et al.,* 2001; Blum *et al.,* 2003; Komine *et al.,* 2004). Further bovine PMN have also been considered the source of NO production by (Boulanger *et al.,* 2001; Komine *et al.,* 2004).

Mean plasma TNF-α level was more ($p<0.001$) in healthy and SCM groups of

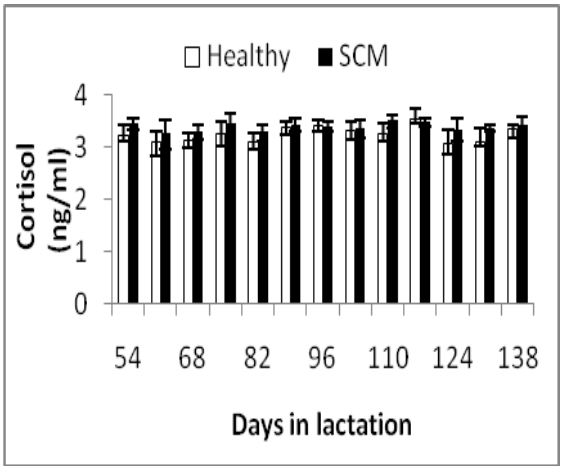
cows. Plasma TNF-α levels varied (P<0.001) between the groups. TNF- α is released locally in mammary gland of mastitis cows and its absorption into the circulation elevates plasma concentration (Hoeben *et al.*, 2000). These cytokine induced and mediated neural and endocrine changes play key roles in the induction of systemic symptoms of mastitis, e.g. fever, lethargy, loss of appetite (anorexia) and many catabolic changes in energy (lipid, carbohydrate), protein and mineral metabolism (Huszenicza *et al.*, 2004). Plasma TNF-α concentrations increase within hours after i.v. administration of LPS, in *E. coli*-induced mastitis and in natural cases of coliform mastitis, in cattle (Hirvonen *et al.*, 1999; Kinsbergen *et al.*, 1994), and TNF- α production initiates immunological and metabolic reactions which could be detrimental locally (Hirvonen *et al.*, 1999). Further large quantities of LPS must be produced continuously to induce and elevated TNF-α concentrations in blood because i.v. administration of LPS causes a transient rise of TNF-α in cattle (Kinsbergen *et al.*, 1994: Kahl *et al.*, 1997). Severe cases of coliform mastitis are accompanied by the highest increase in blood plasma concentrations of both TNF-α and NO (Kahl *et al.*, 1997; Hirvonen *et al.*, 1999; Blum *et al.*, 2000; Komine *et al.*, 2004). Elevated TNF α in blood of mastitis animals (Blum *et al.*, 2000, Hoeben *et al.*, 2000; Ohtuska *et al.*, 2001) can increase $PGF_2\alpha$ synthesis (Starzynski *et al.*, 2000) and suppress LH surge leading to inhibition of fertilization and development of embryos (Hansen *et al.*,2004).

Plasma IL-8 levels varied (p<0.001) between groups. The levels were significantly (P<0.001) higher in CM cows as Compared to the SCM and healthy cows (Table 2). Kim *et al.*, (2011) concluded that significant (P<0.001) IL-8 expression in the serum was not evident for any infected groups of Holstein cows 14 days post infection. Therefore it can be concluded that increased secretion of IL-8 is an important maker of inflammatory processes. Interleukin 8 (IL-8) is a chemokine produced by macrophages and other cell types such as epithelial cells and neutrophils. Several studies have confirmed higher IL-8 level in *E. coli* infected mastitis cows as compared with healthy glands (Riollet *et al.*, 2000; Lee *et al.*, 2003b; Bannerman *et al.*, 2004c; Vangroenweghe *et al.*, 2004, 2005).

Plasma cortisol levels varied non-significant between the group of cows and between days.

Fig.1 Mean plasma cortisol levels in healthy and subclinical mastitis cows during lactation

Fig.2 Overall mean cortisol levels in different groups of lactating Cows



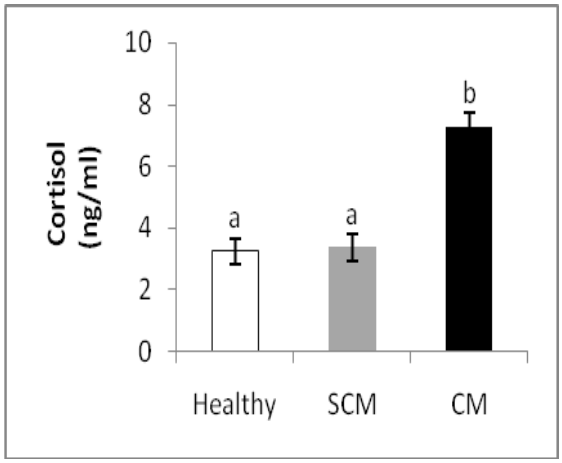
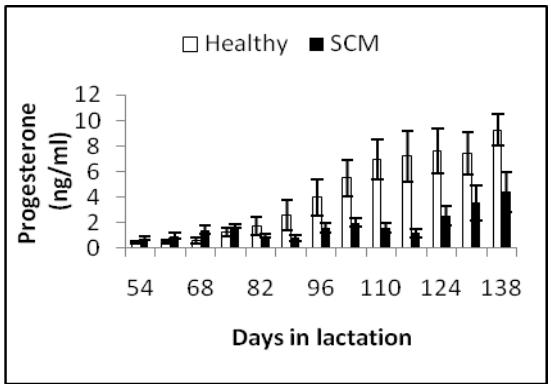


Fig.3 Mean plasma progesterone levels in healthy and subclinical mastitis cows during lactation, **Fig.4** Overall mean progesterone levels in different groups of lactating cows



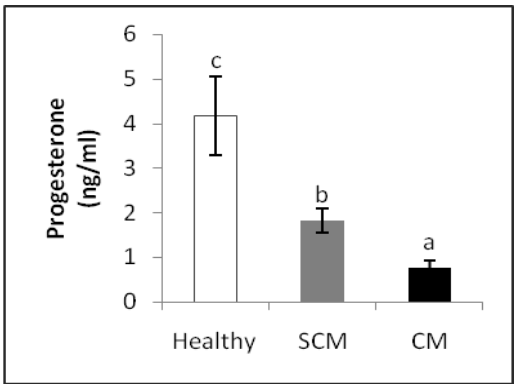
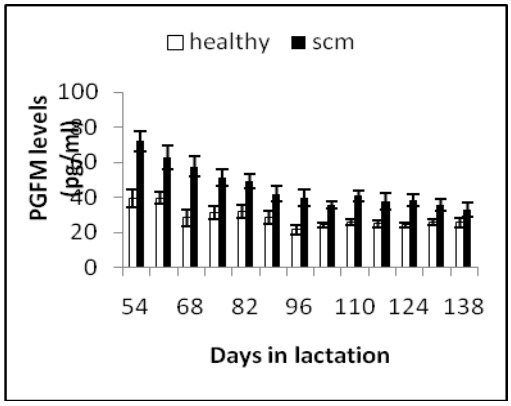


Fig.5 Mean plasma prostaglandin F_2-α levels in healthy and subclinical mastitis cows during lactation, **Fig.6** Overall mean prostaglandin F_2-α levels in different groups of lactating cows



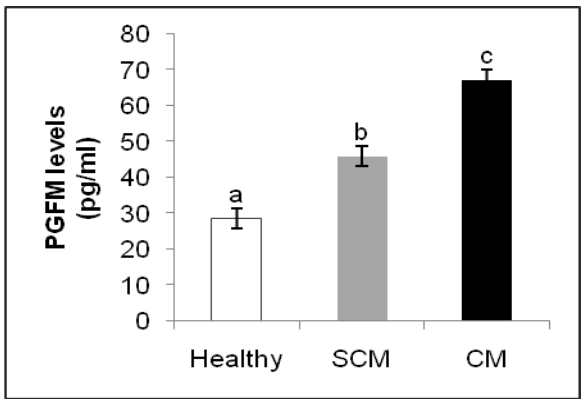


Table.1 Mean plasma NO (µmol/L), TNF-α (pg/ml) and IL-8 (pg/ml) levels in healthy and subclinical mastitis cows during lactation

Mediators / Postpartum Days	Nitric Oxide (NO)		Tumor Necrosis Factor- α (TNF-α)		Interleukin-8 (IL-8)	
	Healthy	**SCM**	**Healthy**	**SCM**	**Healthy**	**SCM**
54	$35.75^{a}\pm1.06$	$38.03^{a}\pm1.6$	$48.74^{Aa}\pm4.33$	$197.69^{Ab}\pm6.58$	$7.43^{a}\pm0.36$	$7.97^{a}\pm0.43$
61	$35.17^{a}\pm1.08$	$37.3^{a}\pm1.25$	$50.5^{Aa}\pm 3.51$	$197.01^{Ab}\pm7.27$	$7.64^{a}\pm0.39$	$8.17^{a}\pm0.46$
68	$35.62^{a}\pm1.03$	$37.59^{a}\pm1.35$	$51.54^{Aa}\pm3.95$	$197.47^{Ab}\pm4.40$	$7.97^{a}\pm0.36$	$8.36^{a}\pm0.43$
75	$35.36^{a}\pm1.24$	$37.31^{a}\pm1.24$	$50.40^{Aa}\pm3.66$	$196.04^{Ab}\pm11.59$	$7.49^{a}\pm0.37$	$8.16^{a}\pm0.45$
82	$34.69^{a}\pm1.24$	$36.56^{a}\pm1.05$	$54.30^{Aa}\pm2.94$	$185.19^{Ab}\pm4.46$	$7.06^{a}\pm0.48$	$7.76^{a}\pm0.30$
89	$35.47^{a}\pm0.95$	$37.14^{a}\pm0.90$	$57.04^{Aa}\pm2.39$	$179.87^{Ab}\pm4.39$	$6.92^{a}\pm0.88$	$8.08^{a}\pm0.46$
96	$35.18^{a}\pm1.34$	$37.38^{a}\pm1.31$	$58.22^{Aa}\pm2.42$	$177.88^{Ab}\pm3.96$	$7.21^{a}\pm0.37$	$8.00^{a}\pm0.46$
103	$35.21^{a}\pm1.66$	$37.00^{a}\pm1.23$	$54.28^{Aa}\pm2.41$	$163.92^{Ab}\pm7.20$	$7.29^{a}\pm0.71$	$7.94^{a}\pm0.43$
110	$34.24^{a}\pm0.95$	$36.21^{a}\pm1.17$	$57.17^{Aa}\pm2.10$	$159.87^{Ab}\pm7.03$	$7.21^{a}\pm0.59$	$7.81^{a}\pm0.45$
117	$33.83^{a}\pm1.15$	$36.08^{a}\pm1.20$	$57.23^{Aa}\pm2.16$	$157.03^{Ab}\pm 6.37$	$7.34^{a}\pm0.34$	$7.85^{a}\pm0.37$
124	$33.5^{a}\pm0.61$	$35.5^{a}\pm1.51$	$56.40^{Aa}\pm2.81$	$145.01^{BEFb}\pm7.58$	$7.63^{a}\pm0.46$	$8.12^{a}\pm0.38$
131	$33.29^{a}\pm1.01$	$34.46^{a}\pm0.93$	$56.25^{Aa}\pm1.57$	$145.70^{CEFb}\pm6.29$	$7.24^{a}\pm0.31$	$7.82^{a}\pm0.36$
138	$33.51^{a}\pm0.83$	$34.31^{a}\pm1.29$	$58.08^{Aa}\pm2.16$	$135.78^{DFb}\pm11.5$	$7.20^{a}\pm0.24$	$7.55^{a}\pm0.50$
Over all mean± SEM	**$34.68^{a}\pm0.24$**	**$36.75^{a}\pm0.359$**	**$54.63^{a}\pm0.90$**	**$171.80^{b}\pm 6.32$**	**$7.35^{a}\pm0.12$**	**$7.96^{a}\pm 0.14$**

Values with different superscripts ^{ab} and ^{ABCDEF} differ ($p<0.05$) in a row and column respectively

Table.2 Mean plasma NO, TNF-α and IL-8 levels in different group of cows

Groups / Mediators	Healthy	SCM	CM
NO(µmol/L)	**34.68^{a}±0.24**	**36.75^{a}±0.359**	**59.96^{b}±2.53**
TNF-α(pg/ml)	**54.63^{a} ±0.90**	**171.80^{b}± 6.32**	**695.50^{c}±43.98**
IL-8(pg/ml)	**7.35^{a} ±0.12**	**7.96^{a}± 0.14**	**24.35^{b}±1.19**

Values with different superscripts ^{abc} differ ($p<0.05$) in row

However, plasma cortisol level was significantly ($P<0.001$) higher in clinical mastitis cows than the healthy and subclinical mastitis cows (Figure 2). Kuldeep, (2011) observed three times higher plasma cortisol levels in clinical mastitis cows. Cortisol act as powerful immunosuppressive agent and facilitates the invasion of environmental pathogens leading to increased incidence of mastitis (Goff and Horst, 1997; Kehrli *et al.*, 1991). Higher cortisol level also suppresses the lymphogenic response to mitogens and certain aspects of neutrophil function (Jacob *et al.*, 2001). This could be the reaction of higher cortisol levels in clinical mastitis cows found in this study (Fig. 1).

Endotoxin challenges also cause higher cortisol level (Soliman *et al.*, 2002; Waldron *et al.*, 2003; Lehtolainen *et al.*, 2003).

The PGFM levels varied significantly ($P<0.001$) between healthy, SCM and CM group cows (Figures 3 and 4). Elevated $PGF_2\alpha$ levels in subclinical and clinical mastitis cows in to comparison to healthy cows, resulted in low progesterone concentration resulting the impaired embryonic development and increased number of services per conception service period and higher oxytocin concentration (Hockett *et al.*, 2000).

Plasma progesterone levels was significantly different ($p<0.001$) between healthy, SCM and CM group cows (Figures 5 and 6). Higher levels of progesterone after 75 days of lactation in healthy cows indicated pregnancy status. However, SCM cows rise in progesterone levels was less and occur after 124 days. The confirmed pregnancy percent in healthy and SCM cows was 87.5% and 75% respectively. The delay in pregnancy varied significantly ($P<0.001$) between the groups.

Based on the results of hormonal and biochemical parameters it was concluded that monitoring of inflammatory markers could be used as a biomarker to identify the cows at high-risk of infection. This will facilitate prompt treatment and pro-active management practices in reducing disease incidence and the dairy farms are likely to improve overall productivity of the animal.

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