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Case Study

RETENTION OF FETAL MEMBRANES IN DAIRY BOVINES: STILL A BOTTLENECK IN PARTURITION

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ABSTRACT

Retention of Fetal membranes (RFM) has a significant impact on the reproductive health and subsequent productivity of dairy cows and buffaloes. There are many risk factors which cause RFM and these include increased parity, abnormal calving and short gestation length *etc*. Amongst the several reproductive disorders, RFM is one of the most important risk factor for various uterine and udder infections, metabolic diseases like ketosis and displaced abomasum, reduced pregnancy rate and milk production. Besides, hormonal consequences, there is marked differences between cows with normal parturition and cows with retained foetal membranes in terms of fatty acid profile, some pro-inflammatory cytokines in blood plasma and utero-placental tissues and also with their expression in blood and tissue level. Moreover, there are many cellular mechanism involved in this reproductive problem. Since, different factors are involved in RFM, proper management, feeding and modulating the levels of these molecules like fatty acids especially SCFAs prior to parturition might help in reducing the incidence of RFM in cows.

KEYWORDS: RFM, bovine, reproductive, productivity, SCFAs, pro-inflammatory.

INTRODUCTION

Reproductive success in dairy animals is essential for the economic livelihood of producers. In many livestock production systems, poor fertility is the major factor that limits productivity. Reproductive success of an individual is determined by a sequence of events *viz.* the animal should attain sexual maturity at right time, mated with a fertile bull or insemination, conceive, carry the gestation to its full length, calve normally, resume cyclicity in early post-partum and conceive again. In this chain of events, calving associated problems and post-partum reproductive problems are the major determinants of reproductive efficiency. Because of RFM, productive and reproductive performance of the dairy animal is seriously affected leading to huge economic loss to farmers in terms of low milk production and veterinary expenses. Risk factors and metabolic indicators are involved in RFM. Fatty acids, especially SCFAs receptors, pro-inflammatory cytokines and various cell adhesion molecules are known to play an important role in expulsion of fetal membranes. So, strategies can be worked out to up-regulate the pro-inflammatory pathways, using SCFAs supplementation, to prevent occurrence of RFM in cows. The present review, is therefore done to study the various mechanism involved in RFM in dairy bovines.

What are bovine fetal membranes?

Fetal membranes (FM) are essential for prenatal transfer of nutrients and oxygen from the dam to the fetus and it normally drops within short time post partum (Hanafi *et al*., 2011; Filho *et al*., 2012). It is important for modulation of the maternal immune response to antigens of paternal and fetal origin and is a source of a great variety of hormones that ensure the maintenance of gestation (Filho *et al*., 2012). During further development of embryo, the allantois and the chorion fuse to form the chorioallantois, then with amnion it constitutes the extra-embryonic fetal membranes. As the extra embryonic fetal membranes grow and expand within the lumen of the uterus, the flat surface of the chorioallantois become irregular over the caruncles forming villous projections or cotyledons that interdigitate with recesses in the surface of the caruncle which enhances the contact surface with the advancement of gestation period, placentomes become domed ovoid shaped structures, which ranges from 10 to 12 cm long and 2–3 cm thick, approximately 100 caruncles are present and are evenly distributed throughout the bovine endometrium (Streyl *et al*., 2011).

Retention of Fetal Membranes (RFM)

Abnormal parturition leads to extended calving to conception interval, which in turn prolong the calving interval. After expulsion of the fetus, the fetal membranes are generally expelled within 8h of parturition. A failure in the separation of cotyledonary villi from the crypts of the maternal caruncles longer than 12 hrs results in a condition known as RFM (Roberts, 1971; Drillich *et al*., 2006; Hanafi *et al*., 2011). In dairy cattle, 4–11% of spontaneous

calvings have been reported to result in RFM (Hashem and Hussein, 2009).

FM are living organs that are oxygen-starved and nutrient-deprived, and during stress RFM produce and release chemicals that cause inflammation in the uterus, suppress the immune system, and lead to metritis and infertility (Stevens, 1997). RFM in cattle have adverse effects on fertility and production (Beagley, 2010). Hence, RFM is an important problem which causes great economic losses and leave the animal subfertile even after treatment and recovery. So, it is recommended to control the condition rather than to treat it (Hanafi *et al.*, 2011).

Factors affecting RFM

The main risk factors contributing to RFM are dystocia, milk fever, twin births, uterine inertia and impaired biochemical and immunological profiles (Kumaresan *et al.*, 2012). Besides, there are a number of risk factors associated with RFM, including induced parturition (Terblanche *et al.*, 1976), shortened gestation (Muller et al., 1974), abortion (Roberts *et al.*, 1986; Joosten., 1987), twinning (Muller *et al.*, 1974; Erb *et al.*, 1958), dystocia (Roberts *et al.*, 1986; Rajala *et al.*, 1998), fetotomy (Roberts *et al.*, 1986; Wehrend *et al.*, 2002), Cesarean section (Roberts *et al.*, 1986), nutritional deficiencies such as vitamin E, selenium, and carotene (Ronning *et al.*, 1953; Julien *et al.*, 1976) infectious agents such as bovine viral diarrhoea virus (Niskanen., 1995) and immune-suppression (Laven *et al.*, 1996).

Multiple etiologies like pre-partum illness, peri-partum events, maternal-fetal immunological compatibility, mineral deficiency *etc* have been proposed to be associated with the condition. Recently, the expression of MHC I (Davies *et al.*, 2004), oxidative stress, fatty acid composition of the placenta and defective neutrophil function have been implicated in the pathogenesis of RFM (Kimura *et al.*, 2002; Kumaresan *et al.*, 2012). Specifically, neutrophils from cows that went on to develop RFM had decreased chemotaxis from 1 week before to 1 week after parturition and decreased myeloperoxidase activity from 2 weeks before to 2 weeks after parturition (Kimura *et al.*, 2002). In addition, interleukin-8, an important chemotactic agent for neutrophils, was lower in cows with RFM than cows that expelled their placenta normally (Beagley *et al.*, 2010). Decreases in the antioxidant enzyme capacity of the placenta during pregnancy may also contribute to the etiology of RFM (Wischral *et al.*, 2001; Gupta *et al.*, 2005). Lower prepartum levels of placental superoxide dismutase and plasma estrogen were found in cows that subsequently developed RFM (Wischral *et al.*, 2001). In addition, trauma to the uterus can cause an increase in heparin release from mast cells at the site of injury (Gross *et al.*, 1985). Heparin inhibits collagenases (Au *et al.*, 1992) and can also delay uterine involution, whereby both could contribute to RFM (Eiler *et al.*, 2007). So, there are many risk factors (Kumari *et al.*, 2015a) and metabolic indicators (Kumari *et al.*, 2015b) that are involved in RFM. Fatty acids, especially SCFAs receptors, pro-inflammatory cytokines and various cell adhesion molecules are also known to play an important role in expulsion of fetal membranes in dairy bovines (Boro *et al.*, 2014 and Boro *et al.*, 2015).

Incidence of RFM:

The incidence of RFM has been reported by many researchers which vary considerably. Kumari *et al.*, 2015a reported the incidence of RFM in Zebu cows and its crosses, and in Murrah buffalo as 26, 16 and 13%, respectively.

TABLE 1: Incidence of RFM in different breeds of cows

Breeds	Incidence (%)	References
Jersey x Gir cross	13.90	Kaikini *et al.* (1981)
Cows and buffaloes	18.46 and 4.69	Dutta and Dugwekar (1983)
Crossbred cattle	7.82	Agarwal *et al.* (1984)
(HF, BS & Jersey) x Hariyana	17.48	Saini *et al.* (1988)
Karan Fries cattle	15.57	Mukherjee *et al.* (1993)
Sahiwal and its crossbred	5.00	Urade (2001)
Gir	8.79	Kulkarni *et al.* (2002)
Karan Fries cows	27.65	Satyapal (2003)
HF cows	18.30	Han and Kim (2005)
Karan Fries cows	27.34	Balasundaram (2008)
Holstein dairy cows	15.6	Melendez *et al.* (2009)
HF x Jersey cross	19.44	Lalrintluanga and Lalnuntluangi (2010)

Mechanism associated with RFM

Many cellular and molecular mechanisms are involved in RFM (Attupuram *et al.*, 2016). Although researchers differ in their opinions on etiology of RFM, unanimously it is accepted that expulsion of fetal membranes is an inflammatory process (Norman *et al.*, 2007; Jabbour *et al.*, 2009) and inflammatory mediators play a major role in separation of fetal membranes. Many reproductive processes display hallmark signs of inflammation during parturition (Goswami *et al.*, 2008). Inflammatory changes in utero-placental junction include a dramatic influx of immune cells, increased expression and secretion of pro-inflammatory cytokines and tissue remodeling (Ledingham *et al.*, 2001; Bollapragada *et al.*, 2009) and any aberrations in the pro-inflammatory pathway may result in RFM.

Several reports suggest that altered inflammatory process and lower levels of pro-inflammatory mediators are associated with RFM in cows (Beagley *et al.*, 2010; Streyl *et al.*, 2011; Walter and Boos, 2001; Boos *et al.*, 2003; Takagi *et al.*, 2007; Ghai *et al.*, 2012). Cytokines may be involved in the regulation of pre-term and term cervical ripening (Winkler and Rath, 1996). Thus, precisely timed activation of inflammatory pathway is important for

expulsion of fetal membranes as it has been reported in human that inappropriate early activation of the pro-inflammatory pathway may initiate preterm labour. In support to this, a recent study in human reported that the short chain fatty acids receptors (G protein coupled receptors GPR43 and GPR41) are more expressed in fetal membranes of women with pre-mature delivering preterm

compared to fetal membranes from normal delivery (Chiara *et al*., 2012). So, we can hypothesise that GPR41-GPR43-SCFAs interactions at the time of parturition might regulate inflammatory processes involved in fetal membrane expulsion and this modulation might vary between animal with and without RFM. The hypothetical model is shown in the figure (1).
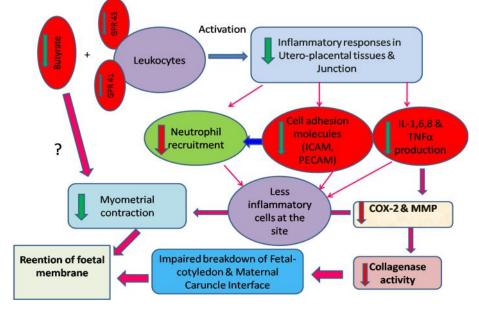

FIGURE 1: Hypothetical model for retention of fetal membranes in dairy cows, the SCFAs role in placental expulsion (MVSc. thesis, NDRI, Karnal, Boro, 2013)

Short chain Fatty acids (SCFAs) and RFM

Short chain fatty acids (SCFAs) *viz.* acetate, propionate and butyrate play a significant role in many pathways of human reproduction (Chiara *et al*., 2011). In addition to energy supply, fatty acids may present divergent effects depending on the cell types (Vinolo *et al*., 2011). Contradictory effects of SCFAs on different tissues as pro and anti-inflammatory has been reported (Huskonen *et al*., 2004). Fatty acid composition especially SCFAs like butyrate has been implicated in the pathogenesis of RFM (Boro *et al*., 2014). GPRs-SCFAs interactions may represent inflammatory pathways during labor. In humans, it is reported that SFACs modulate the inflammatory pathways in fetal membranes (Chiara *et al*., 2012). It includes increased mRNA expression of GPR41 and GPR43 (G-protein coupled receptors of SCFAs), cytokines (IL-1, IL-6, IL-8, TNF-), cell adhesions molecules (ICAM, LFA-1, PECAM, VCAM) and chemokines (Thomson *et al*., 1999; Osman, 2003; Chiara *et al*., 2012; Boro *et al*., 2014). Leukocytes in the myometrium, cervix, decidua and membranes express pro-inflammatory cytokines such as interleukin-1b (IL-1b), IL-6 and IL-8 (Young *et al*., 2002). Pro-inflammatory cytokine stimulate human uterine contractions (Tribe *et al*., 2003). A genomic study has confirmed that fetal membranes in labor have an acute inflammatory signature as there is a significant up-regulation of IL-1 and IL-6 in lab or (Haddad *et al*., 2006). This up regulation of inflammatory pathways in the utero-placental tissues increases the collagenase activity and myometrial contractions (Eiler *et al*., 1993; Beagley *et al*., 2010). These processes lead to the breakdown of

interface of utero-placental junction, consequently causing expulsion of fetal membranes from uterus. However, the mechanism is altered in the case of RFM as shown in the figure (1).

Mechanism of SCFAs in regulating inflammation and expression of some genes

Gut micro biota and chemo attractant receptor GPR43 up regulates inflammatory responses (Kendle *et al*., 2009). The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids (Browen *et al*., 2003). SCFAs act on leukocytes and endothelial cells through at least two mechanisms: activation of GPCRs (GPR41 and GPR43) and inhibiton of histone deacetylase (HDAC) (Vinolo *et al*., 2011). SCFAs regulate several leukocyte functions including production of cytokines (TNF- , IL-2, IL-6 and IL-10), eicosanoids and chemokines (*e.g*., MCP-1 and CINC-2). The ability of leukocytes to migrate to the foci of inflammation and to destroy microbial pathogens also seems to be affected by the SCFAs (Vinolo *et al*., 2011). GPR43 couples to Gi and Gq proteins, which interact with several proteins including adenylate cyclase, small G proteins (*e.g*., Rac and Rho), mitogen-activated protein kinases (MAPK), phospholipase C (PLC) and A2 (PLA2), ion channels and transcription factors and thereby leads to chemotaxis and ROS production. The main mechanism described for these effects is the attenuation of HDAC activity. Among the SCFAs, butyrate is the most potent, whereas acetate is the least potent inhibitor of HDAC (Vinolo *et al*., 2011; Zhang *et al*., 2007). So, SCFAs act on cells through inhibition of HDAC. This class of enzymes,

together with histone acetyltransferase (HAT), controls the acetylation state of histones and non-histone proteins including NF B, MyoD, p53 and N-FAT (Glozak *et al.*, 2005) and, consequently, modulates the transcription of several genes (Vinolo *et al.*, 2011) and causing inflammatory responses.

After all, SCFAs, of which butyrate is the most studied, modulate different processes including cell proliferation and differentiation, hormones secretion like leptin and peptide YY (Plaisancie *et al.*, 1996; Zaibi *et al.*, 2010) and activation of immune or inflammatory responses (Maslowski *et al.*, 2009; Vinolo *et al.*, 2011).

SCFAs Receptors and its role:

GPR41 and GPR43 are related members of a homologous family of orphan G protein-coupled receptors. GPR41 is primarily found in adipose tissues, whereas the highest levels of GPR43 are found in immune cells. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids (Browen *et al.*, 2003). GPR41 and GPR43 mRNA expression was higher in myometrium and fetal membranes collected from women after onset of labor and GPRs-SCFAs interactions may represent inflammatory pathways during labor (Chiara *et al.*, 2012). GPR43 receptor may specifically mediate SCFAs inflammatory effects (Maslowski *et al.*, 2009).

Role of SCFAs in premature birth in human and placental expulsion in bovines:

Inappropriate early activation of the pro-inflammatory pathway may initiate preterm labour, and thus strategies to up regulate the anti-inflammatory pathway are of interest in prevention or treatment of preterm birth (Jabbour *et al.*, 2009). As GPR43-SCFA interactions represents novel pathways that regulate inflammatory processes involved in human labor. Suppression of inflammatory pathways by SCFA may be therapeutically beneficial for pregnant women at risk of pathogen-induced preterm delivery. Hence**,** short-Chain fatty acids play a novel anti-inflammatory role in preterm human labor (Chiara *et al.*, 2011) and may play as an inflammatory role in separation of bovine fetal membranes.

CONCLUSION

Retention of Fetal membranes (RFM) has serious consequences on the reproductive health and subsequent productivity of cows. The cow need to be given due care to facilitate the expulsion of foetal membranes. The risk of developing uterine infection is very high if the animal is not managed properly, leading to increased calving interval and decreased reproductive efficiency. The expression of short chain fatty acids (SCFAs) receptors and pro-inflammatory cytokines in the utero-placental tissues is down regulated in RFM cows. The mRNA expression of genes of pro-inflammatory cytokines and Cell Adhesion Molecules also down regulated in RFM cows. Since, the available literature says that the levels of fatty acids (especially SCFAs) and expressions of their receptors, cytokines and CAMS are impaired in cows with RFM, modulating the levels of these molecules prior to parturition might help in reducing the incidence of RFM in cows.

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