Retention of Fetal Membranes and its Clinical Perspective in Bovines

R. V. Patel¹, Sanjay C. Parmar²
¹Sabarmati Ashram Gaushala, Bidaj, Kheda, Gujarat, India
²Anand Agricultural University, Anand, Gujarat, India

*Corresponding Authors
Name: Sanjay C. Parmar
Email: dr.sanjayparmar@yahoo.in

Abstract: Retention of the fetal membranes (RFM) or Retention of Placenta (ROP) in the cow is normally defined as the condition in which the fetal membranes are not expelled within a period of 12 hours after expulsion of the fetus. Primary retention of fetal membranes results from a lack of detachment from the maternal caruncles whereas secondary retention is related to a mechanical difficulty in expelling already detached fetal membranes. There are a number of risk factors associated with RFM, including induced parturition, shortened gestation, abortion, twinning, dystocia, fetotomy, cesarean section, nutritional deficiencies such as vitamin E, selenium and carotene, infectious agents such as bovine viral diarrhea virus and immunosuppression. The most commonly used hormonal products in treating RFM are prostaglandins and oxytocin and these hormones play a role in uterine contraction and could be effective in treating retention of the fetal membranes.

Keywords: Caruncles, Cotyledons, Fetal membranes, Parturition, Placenta, Puerperium

INTRODUCTION

Retention of the fetal membranes (RFM) comprises of failure of dehiscence and a lack of expulsion of fetal membranes within the duration of physiological third stage of labour. Primary retention of fetal membranes results from a lack of detachment from the maternal caruncles whereas secondary retention is related to a mechanical difficulty in expelling already detached fetal membranes e.g. uterine atony [1, 2]. Retention of the fetal membranes (RFM) or Retention of Placenta (ROP) in the cow is normally defined as the condition in which the fetal membranes are not expelled within a period of 12 hours after expulsion of the fetus[3]. Failure of the placenta to be expelled during the third stage of labour is a common postpartum complication in ruminants particularly in cattle which is due to failure of the fetal villi to detach themselves from the maternal crypts [4]. Retention of fetal membranes is one of the most common conditions occurring in dairy cows following parturition. It is commonly followed by delayed involution of the uterus; drop in milk production and infertility resulting economic loss to the owner [5]. Retention of placenta has been associated with a vast range of factors such as abortion, forced labor, delayed gestation, early parturition, uterine atony, infections, and seasonal and hormonal disorders. In addition, it is well known that deficiencies of some vitamins and minerals induce or predispose animals to ROP [6].

Calcium concentration, which maintain adequate contraction of the uterus, may cause ROP, increase the risk of dystocia and delay the involution of the uterus[7]. Metritis and pyometra are more common occurrences in such animals where the placenta is not removed manually. However, manual removal has been opposed as it may favor the entry of infection, which may be more harmful. Premature induction of parturition with glucocorticoids and prostaglandins increases the cases of placental retention. Moreover, it may be caused as a result of low plasma estrogen concentration. Deficiency in vitamin E and selenium also has an impact on retention of placenta [8]. The Chemotactic activity of the placental tissue immediately after parturition determines placental expulsion and may even be a decisive factor. Major Histocompatibility Complex (MHC) incompatibility between dam and calf would facilitate the expulsion of placenta and accordingly MHC compatibility would be associated with retention [9].

Incidence

RFMs are a common abnormality in dairy cows, occurring in 5-10% of normal calvings. It is regarded as a major cause of reproductive disorders in the puerperal and post puerperal period and may lead to significant economic losses at the herd level [10]. The incidence rate of retention of fetal membranes in buffaloes was 22.8 per cent [11] and in dairy cows was 19.44 per cent.

Etiology

There are a number of risk factors associated with RFM, including induced parturition, shortened...
gestation, abortion, twinning, dystocia, fetotomy, caesarean section, nutritional deficiencies such as vitamin E, selenium, and carotene, infectious agents such as bovine viral diarrhea virus, and immunosuppression[12]. The multiple hormonal and biochemical changes leading to normal placental delivery suggest that an interruption in one or more of these events can lead to placental retention. The role of immunosuppression in RFM, as it relates to leukocyte activity, antioxidant capacity and steroid synthesis [13]. Maintenance of pregnancy requires suppression of the immune response to avoid rejection of the fetal-placental unit and RFM might result from a failure to switch off these immunoprotective mechanisms, either because of immunosuppression or an interruption of the normal prepartum hormonal changes. Cows with RFM after normal parturition had decreased leukocyte chemotaxis and phagocytic activity before parturition[14].

There are differences in protease activity within placentomes in retained versus non-retained placentas, suggesting that alterations in enzyme activity play a role in the etiology of RFM [2]. For example, cotyledon collagenase is decreased and type III collagen persists in cows with RFM. These enzymes may be important for the breakdown of cotyledon-caruncle links and release of fetal membranes [15]. Interruption of normal hormonal changes in the uterine environment may inhibit protease release from the epithelium, and immunosuppression could inhibit leukocyte protease activity. Either scenario could then lead to RFM caused by decreased protease activity. Induction of labour with dexamethasone, with or without prostaglandin, is an established risk factor for RFM in cattle. It has been suggested that glucocorticoids could have a direct inhibitory effect on collagenase activity. Also, dexamethasone inhibits PGF2α synthesis within cotyledon cells and administering prostaglandin along with dexamethasone reduces but does not eliminate the occurrence of RFM[16]. Induced labor associated with the incidence of RFM was also reduced when relaxin was administered along with dexamethasone or cloprostenol, presumably because of relaxin promoting collagenase activity that could counteract the inhibitory effects of dexamethasone [17].

Numerous associations between RFM and hypocalcemia have been made. In cows fed anionic diets those with RFM had significantly lower total plasma calcium than cows without RFM [18]. Calcium is required for collagenase activity, but the decreased blood calcium levels found in RFM cows were not low enough to preclude collagenase activity. While hypocalcemia can predispose cows to dystocia and uterine atony can interfere with the final step of placental delivery [19]. Many of the risk factors for RFM involve trauma to the uterus including dystocia, fetotomy, and caesarean section. Trauma can result in edema of chorionic villi that could impair separation at the cotyledon-caruncle interface. Normal detachment of the bovine placenta involves separation of the finger-like cotyledon villi from the caruncle crypts. Thus, bigger oedematous villi might not be able to disarticulate from the crypts as easily. In addition, trauma to the uterus can cause an increase in heparin release from mast cells at the site of injury. Heparin inhibits collagenases and can also delay uterine involution, whereby both could contribute to RFM. Dystocia and uterine trauma have also been associated with uterine atony that could inhibit expulsion of membranes and lead to secondary retention. After a caesarean section, treatment of cows with a nonsteroidal anti-inflammatory drug (flunixin meglumine) increased the risk of RFM. Flunixin meglumine is a cyclooxygenase inhibitor and it has been suggested that the higher incidence of RFM is mediated through a reduction of prostaglandin synthesis [20].

Pathophysiology

Cattle have cotyledonary placentas, wherein the fetal cotyledons are attached and envelop the maternal caruncles, forming the placentome. This connection is facilitated by villi from the cotyledons and microvilli interactions at the cotyledon-caruncle interface. Collage links the interface together at several sites and the breakdown of this collagen is likely a key factor in placental separation [21]. The normal sequence of events initiating parturition involves fetal cortisol induction of placental enzymes that direct steroid synthesis away from progesterone and toward estrogen. Increased estrogen level results both in the upregulation of oxytocin receptors on the myometrium and secretion of PGF2α. Prostaglandin initiates myometrial contractions and results in lysis of the corpus luteum (CL). Lysis of the CL leads to secretion of relaxin and a further decline in progesterone. Both the secretion of relaxin and the decline of progesterone promote collagenase activity. Relaxin is well known for causing collagen lysis resulting in softening of the cervix and relaxation of the pelvic ligaments. Thus, relaxin might also promote collagen breakdown at the fetal cotyledon-maternal caruncle interface [17]. Conversely, progesterone promotes myometrial quiescence and suppresses collagenase activity. Thus, the decline in progesterone during the prepartum period could allow for the enzymatic activity necessary for placental separation [22].

The processes leading to normal separation and delivery of the placenta are multifactorial and begin before parturition. For example, it has been suggested that serotonin might also play a role in regulating bovine placental attachment [23]. High fetal and placental serotonin during pregnancy could help to maintain placental attachment by promoting placental cell proliferation and inhibiting matrix metalloproteinase (MMP) activity. Maturation of the fetal monamine oxidase enzyme system close to parturition results in the metabolization and subsequent
decrease in serotonin, which in turn could promote placental separation and parturition. In addition to changes in the hormonal environment that favour enzymatic break-down of cotyledon-caruncle linkages, activation of the maternal immune response against the fetal membranes can play an important role in the breakdown of the placenta. Increased leukocyte chemotaxis and activity occur in cows with normally expelled placentas and the cytokine interleukin-8 can play a role as a neutrophil chemoattractant in the cotyledon during parturition[24].

Maternal immunological recognition of fetal major histocompatibility complex (MHC) Class I molecules also contributes to placental separation and parturition[25]. These molecules, absent in early pregnancy, are expressed by fetal trophoblast cells in the 3rd trimester of pregnancy and could play a role in initiating an inflammatory response that ultimately dissolves the adhesions between maternal and fetal portions of the placenta. Further support for this theory comes from the observation that placental retention after normal parturition was more common when there was MHC Class I compatibility between the dam and calf [9]. They proposed that this MHC Class I compatibility, which implies a genetic similarity in the MHC locus between fetus and dam, results in deficient all reactivity of the maternal immune system against fetal antigens. Subsequently, this leads to a lack of cytokine production (eg, interleukin-2 and tumour necrosis factor a), necessary for the maturation and eventual shedding of the placenta. The approach of labour is characterized by increased prostaglandin and oxytocin synthesis and release resulting in mechanical contraction of the uterus that is vital for normal delivery[26]. Contraction persists into stage 3 of labour and is responsible for the mechanical expulsion of fetal membranes.

Delivery of the fetus results in a sudden decrease in blood flow through the placenta and subsequent shrinking of the villi. Uterine contraction could further contribute to detachment of the cotyledons from the maternal caruncles, although the lack of damage to fetal villi in normally expelled membranes suggests the process is not purely mechanical. The current thought is that while uterine contraction is necessary for the final removal of fetal membranes, primary myometrial dysfunction is not an important prerequisite of RFM[27].

Therapeutic Management

A variety of methods have been used in the treatment of bovine RFM, although the efficacy of many of these treatments is questionable.

Manual Removal

Manual removal of the placenta remains a common practice despite numerous studies that fail to demonstrate a beneficial effect on reproductive performance. Drillich et al.; [28, 29]studied comparing manual removal and intrauterine antibiotic therapy along with systemic treatment of febrile cows found no difference in reproductive outcomes when compared with the use of systemic therapy of febrile cows alone. The implication of these studies is that intrauterine treatments can result in additional time, cost, and unnecessary antibiotic use without improving reproductive outcome.

Manual removal can result in more frequent and severe uterine infections, when compared with more conservative treatment and manual removal prolonged the interval from calving to 1st functioning CL by 20 days [30]. Additionally, intrauterine pathogenic bacteria were found in 100 per cent of cows with manually removed RFM versus 37 per cent of untreated cows at 3 weeks postpartum and further 37 per cent of treated versus 12 per cent of untreated cows at 5 weeks postpartum. While current evidence does not support manual removal as an effective treatment for RFM, it is still commonly practiced. This is likely due both to aesthetic benefits, including parlor hygiene and removal of offensive odours and perceived benefits, which have been called into question by current research. Perceived benefits include the idea that removing the placenta eliminates a potential source of infection and will thus reduce endometritis and subsequent negative effects on fertility.

It is more likely that removal of an attached placenta causes damage to the endometrium and suppresses uterine leukocyte phagocytosis, both of which encourage bacterial invasion. In addition, it is difficult to ensure that the entire placenta has been removed, with necrotic portions left behind further contributing to bacterial invasion of the damaged endometrium. Necropsy examinations of cows after manual removal of the placenta revealed uterine haemorrhages, hematomas and vascular thrombi, as well as macro- or microscopic evidence of fetal cotyledon tissue attached to caruncles even when removal was thought to be complete. The combination of damage to the endometrium, bacterial invasion and suppression of leukocyte phagocytosis can result in an increased likelihood of developing postpartum metritis and subsequent negative effects on fertility.

Antibiotics

The use of antimicrobial therapy in the treatment of RFM has demonstrated conflicting results [30]. Postpartur metritis is common sequelae of RFM, and the rationale behind antibiotics for RFM is to prevent or treat metritis and its subsequent negative effects on fertility. The use of intrauterine chlorotetracycline was found to be beneficial only in active cases of clinical metritis [31]. It was speculated that intrauterine antibiotics could control local bacterial growth, but in doing so could actually interfere with the necrotizing process that is responsible for the eventual

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release of RFM [32]. Tetracycline antibiotics commonly used for intrauterine treatment in cattle, inhibit MMPs and might therefore interfere with the normal placental detachment mechanisms [15]. Systemic antibiotics are believed to be beneficial in RFM cases[33].

Hormones

The most commonly used hormone products in treating RFM are prostaglandins and oxytocin. These hormones play a role in uterine contraction and could be effective in treating RFM because of uterine atony. However, it is thought that uterine atony accounts for a very small percentage of retained placenta cases and numerous studies have not supported their use as a general treatment for RFM [34]. Additionally, the use of prostaglandins or oxytocin at the time of parturition for prevention of RFM had no effect on the incidence of RFM in dairy cows. Conversely, a higher percentage of cows (80 vs. 58.5 %) expelled the complete placenta within 12 hours if they were treated with prostaglandins[35].

Collagenase Enzyme

The breakdown of collagen plays a role in placental detachment and infusion of collagenase can be helpful in breaking the caruncle-cotyledon bond in RFM. Injection of 1 litre saline containing 200,000 IU of bacterial collagenase into the umbilical arteries of retained placentas caused earlier placental release than untreated contemporaries. If applied within 24 to 72 hours after calving, collagenase treatment was shown to cause release of membranes in cows within 36 hours. This treatment is targeted specifically at correcting the lack of cotyledon proteolysis and might be more effective than traditional therapies[15].

While collagenase therapy shows promise as a means of treating retained placenta in a variety of species, these techniques are not widely used. In cattle, the procedure can be performed by a skilled veterinarian within 25 minutes, and is more difficult in a recumbent animal or if the umbilical cord and arteries cannot be retracted outside of the vulva. However, the cost required might preclude its use except for valuable breeding or show animals. Additional studies on dosages, efficacies, and long-term production outcomes of collagenase treatments in cows with RFM would be helpful in determining if this would be an economically advantageous treatment for RFM.

Preventive Measures

Specifically link transition cow management in terms of nutrition and cow comfort with decreases in the incidence of retained placenta. These management objectives should be considered as a way of preventing this disease [36]. High producing dairy cows deal with severe physiological and immunological challenges and nutritional management in the prepartum period helps reduce other peri- and postpartum diseases [37].

Evidence that decreases in immune function play important role in the mechanism of placental retention as well as supplementation of vitamin E and selenium in deficient cows reduces incidence of RFM, further highlight the importance of nutrition and stress management strategies. The focus of bovine veterinary medicine is shifting from the treatment of disease in individual animals to herd prevention strategies, and RFM is a prime example of a disease in which prevention might be easier and more economical that treatment[36].

Sequelae and its effect on puerperium

It is the period after completion of parturition, including the third stage of labour, when genital system is returning to its normal non-pregnant stage. Four major events of the puerperium are uterine involution, restoration of endometrium, resumption of ovarian activity and elimination of bacterial contamination of the reproductive tract.

RFM delayed uterine involution with consequent postpartum anoestrus as well as long open days and calving intervals [38]. Placenta retention is usually accompanied by delayed involution of the uterus and adversely reproductive performance. Cows with reproductive disorders had longer interval from calving to first service and to conception. Thus required more service per conception and leads to lower pregnancy rate. The intervals from calving to first service and conception were prolonged with retained placentas. Milk yield was suppressed for about 4 weeks after calving with retained placenta. RFM have been associated with increased risk for endometritis, metritis and mastitis. These diseases can in turn lead to decreased fertility and potential losses in milk production[4].

Under metabolic stress, retained membranes release inflammatory biochemical that in the uterus cause Immunosuppression, increased vascular permeability (histamine, prostaglandins), increased lysosomal activity (proteolysis), endometrial damage (including release of heparin by mast cells), decreased chemotaxis and leukocyte migration that lead to metritis and decreased fertility, inflammatory biochemical from RFM may cause systemic effects that are mediated by hypothalamic centers, including control of hormones, causing decrease appetite and milk secretion and possibly delayed uterine involution. Bacterial colonization is increased favouring release of both bacterial endotoxin and inflammatory biochemicals by RFM. Physical mass of the retained membranes (approx. 3 to 4 Kg) within uterus may contribute to delayed uterine involution, leading to clinical complication and reduces reproductive performance [2].

Conclusions

Prevention of RFM in cattle includes cow comfort, reducing stress around parturition and careful
nutritional management particularly during the transition period. Season of calving, dam’s weight, number of parity, sex, weight of calves born and feeding system has pronounced effects on incidence of retained placenta. Lack of exercise, low vitamin-A level in feed and infections like brucellosis may also contribute to the higher incidence. Ayurvedic preparation as ebolic and collagenase injection may be useful in treatment of RFM. Supplementation of vitamin-E and selenium may be an effective as preventive measure and the case with RFM has to be treated with appropriate antibiotics for 3 to 5 days to prevent the puerperal diseases.

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