Review
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Physiology and Treatment of Retained Fetal Membranes in Cattle

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Retained fetal membranes (RFM) in cattle have adverse effects on fertility and production. Understanding the pathophysiology and causes of RFM is important for managing this disease. The hormonal processes that lead to normal placental separation are multifactorial and begin before parturition. A variety of risk factors, including early or induced parturition, dystocia, hormonal imbalances, and immunosuppression, can interrupt these normal processes and result in retention of the placenta. Current research does not support the efficacy of many commonly practiced treatments for RFM. Systemic administration of antibiotics can be beneficial for treating metritis after RFM, but antibiotic administration has not been shown to significantly improve future reproduction in cows with RFM. Collagenase injected into the umbilical arteries of retained placentas specifically targets the lack of placentome proteolysis and might enhance placental release. However, such therapy is costly and its benefits in terms of improving subsequent reproductive function have not been evaluated.

Key words: Cattle; Placental detachment; Risk factors; Treatment.

Retention of fetal membranes (retained fetal membranes [RFM]) in cattle can lead to adverse health effects that ultimately affect reproductive performance. The definition of RFM is varied, ranging from retention of the placenta for 8[1] to 48 hours[2] postpartum. Most studies define RFM in cattle at 12 to 24 hours,[3–5] and therapy is usually instigated during this time. The majority of cattle (66% in one study) will pass the placenta within 6 hours after parturition.[1]

Negative sequelae to RFM include delayed uterine involution, longer time to 1st service,[6] increased services per conception,[7] decreased pregnancy rates,[8] and increased days open.[6,7] RFM have been associated with increased risk for endometritis, metritis, ketosis, and mastitis.[9–12] These diseases can in turn lead to decreased fertility[13] and potential losses in milk production.[14] In a meta-analysis of studies analyzing the effects of disease on reproduction, RFM were associated with 2 to 3 more days to 1st service and 4 to 10% lower conception rates at 1st service, resulting in an average of 6 to 12 additional days to conception in cows with RFM versus cows without RFM.[3] However, only 5 of the 13 included studies found decreased milk production associated with RFM.[15] It should be noted that a variety of factors, including case definitions, other associated diseases, and culling risk, complicate the interpretation of impact of RFM on both reproduction and milk production.

Knowledge of the placental anatomy and physiology is helpful to understand causes of RFM and formulate treatment plans accordingly. The following review focuses on the normal placental detachment, causes and risk factors for RFM, and therapeutic options.

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Abbreviations:

CL	corpus luteum
MHC	major histocompatibility complex
MMP	matrix metalloproteinase
PGF2α	prostaglandin F2 alpha
RFM	retained fetal membranes

Physiology of Placental Detachment

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. Collagen links the interface together at several sites, and the breakdown of this collagen is likely a key factor in placental separation.[16]

The normal sequence of events initiating parturition involves fetal cortisol induction of placental enzymes that direct steroid synthesis away from progesterone and toward estrogen.[17] Increased estrogen results both in the upregulation of oxytocin receptors on the myometrium and secretion of prostaglandin F2 alpha (PGF2α).[18] Prostaglandin initiates myometrial contractions and results in lysis of the corpus luteum (CL).[19] Lysis of the CL leads to secretion of relaxin and a further decline in progesterone.[20]

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.[20] 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.[21]

The processes leading to normal separation and delivery of the placenta are multifactorial and begin before parturition (Fig 1). For example, it has been suggested that serotonin might also play a role in regulating bovine

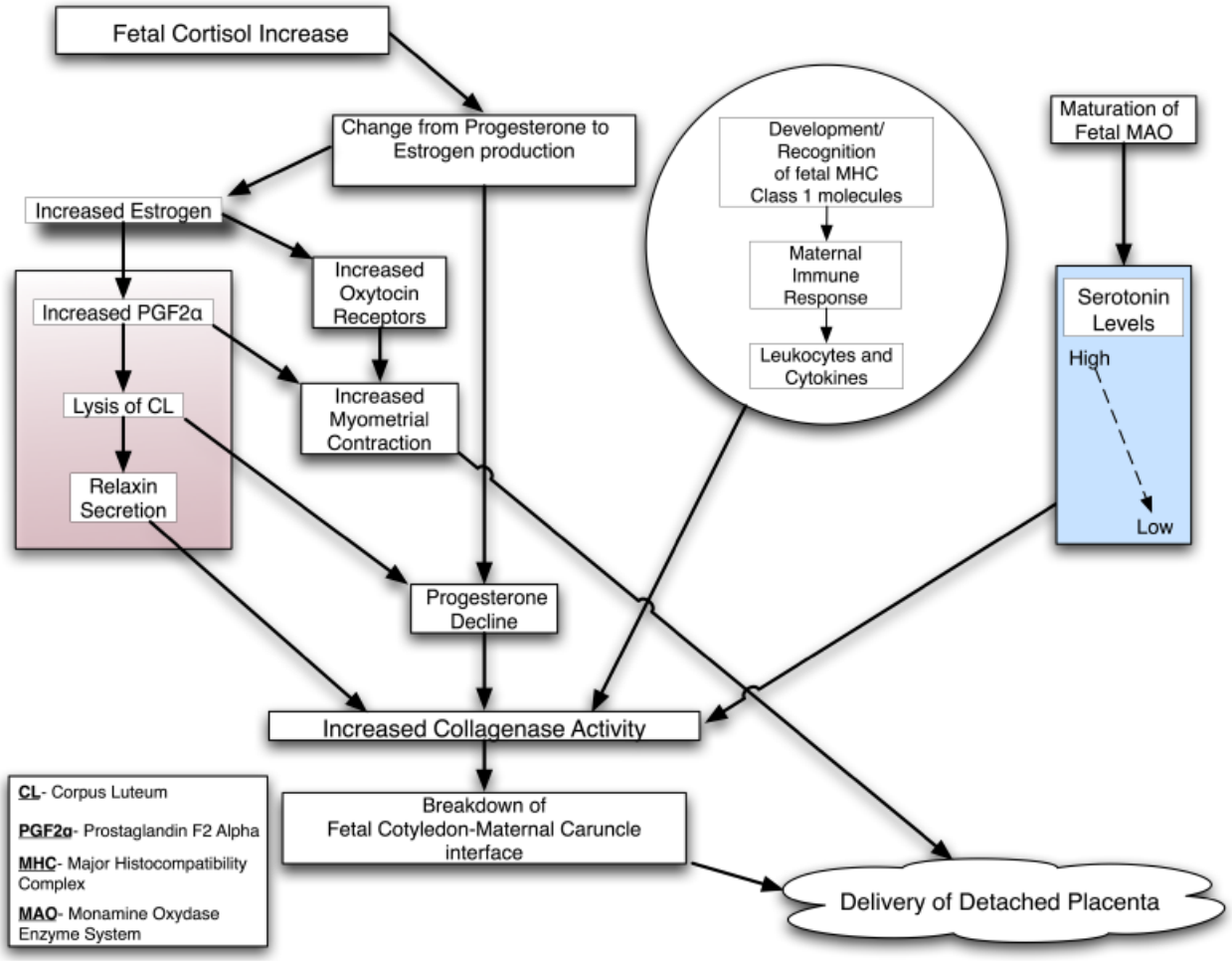

Fig 1. Physiologic processes leading to the detachment of the placenta in cattle.

placental attachment.[22] High fetal and placental serotonin during pregnancy could help to maintain placental attachment by promoting placental cell proliferation[22] and inhibiting matrix metalloproteinase (MMP) activity.[16] 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.[22]

In addition to changes in the hormonal environment that favor 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,[23–25] and the cytokine interleukin-8 can play a role as a neutrophil chemoattractant in the cotyledon during parturition.[25]

Maternal immunological recognition of fetal major histocompatibility complex (MHC) Class 1 molecules also contributes to placental separation and parturition.[26] These molecules, absent in early pregnancy, are expressed by fetal trophoblast cells in the 3rd trimester of pregnancy,[27] and could play a role in initiating an inflammatory response that ultimately dissolves the adhesions between maternal and fetal portions of the placenta.[26] 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.[28] They proposed that this MHC Class I compatibility, which implies a genetic similarity in the MHC locus between fetus and dam, results in deficient alloreactivity of the maternal immune system against fetal antigens. Subsequently, this leads to a lack of cytokine production (eg, interleukin-2 and tumor necrosis factor α), necessary for the maturation and eventual shedding of the placenta.[26]

The approach of labor is characterized by increased prostaglandin and oxytocin synthesis and release resulting in mechanical contraction of the uterus that is vital for normal delivery.[19,29] Contraction persists into stage 3 of labor and is responsible for the mechanical expulsion of fetal membranes.[14] However, the entire role of uterine contraction in placental separation is unknown. Delivery of the fetus results in a sudden decrease in blood flow through the placenta and subsequent shrinking of the villi.[14] 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.[30] 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.[5,31]

Risk Factors and Causes of RFM

There are a number of risk factors associated with RFM, including induced parturition,[32] shortened gestation,[33] abortion,[34,35] twinning,[33,36] dystocia,[34,37] fetotomy,[34,38] Cesarean section,[34] nutritional deficiencies such as vitamin E, selenium, and carotene,[39,40] infectious agents such as bovine viral diarrhea virus,[41] and immunosuppression.[14] While the mechanisms behind these factors are not completely understood, 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. Analysis of risk factors in light of the physiology of placental separation helps to determine the various etiologies of bovine RFM.

The role of immunosuppression in RFM, as it relates to leukocyte activity, antioxidant capacity, and steroid synthesis, is not completely understood.[23–25,42] 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.[23–25] 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.[25] In addition, interleukin-8, an important chemotactic agent for neutrophils, was lower in cows with RFM than cows that expelled their placenta normally. These studies suggest that decreased neutrophil activity at the placenta may be a part of the mechanism for placental retention.

Decreases in the antioxidant enzyme capacity of the placenta during pregnancy may also contribute to the etiology of RFM.[43,44] Lower prepartum levels of placental superoxide dismutase and plasma estrogen were found in cows that subsequently developed RFM.[43] Investigators proposed a pathway of placental retention starting with an imbalance of the antioxidant capacity at the placenta, followed by a decrease in the production of estrogen, resulting in decreased PGF2α production and accumulation of arachodonic and linoleic acids within placental tissue.[43] A meta-analysis that looked at 44 studies comparing RFM incidence in cows treated with vitamin E and untreated cows found that overall vitamin E supplementation decreased the incidence of RFM,[45] although the benefits of supplementation could depend on whether cattle had marginal or adequate serum vitamin E before supplementation.[46,47] In addition to improving antioxidant capacity, vitamin E and selenium may increase chemotaxis and leukocyte numbers at the fetomaternal junction, thus contributing to the normal expulsion of fetal membranes.[45]

There are differences in protease activity within placentomes in retained versus nonretained placentas,[48,49] suggesting that alterations in enzyme activity play a role in the etiology of RFM. For example, cotyledon collagenase is decreased and type III collagen persists in cows with RFM. In addition, cows with RFM have decreased activity of MMP-9 and lack some forms of MMP-2.[21] These enzymes may be important for the breakdown of cotyledon-caruncle links and release of fetal membranes.[50] The cellular source of collagenases and other proteases in the cow is unknown, although cotyledon or caruncular epithelium and leukocytes are possibilities.[48,50] 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 labor with dexamethasone, with or without prostaglandin, is an established risk factor for RFM in cattle, although the exact mechanism for this is unclear.[48] It has been suggested that glucocorticoids could have a direct inhibitory effect on collagenase activity.[51] Also, dexamethasone inhibits PGF2α synthesis within cotyledon cells,[52] and administering prostaglandin along with dexamethasone reduces but does not eliminate the occurrence of RFM.[48,53] Induced labor associated with the incidence of RFM was also reduced when relaxin was administered along with dexamethasone or cloprostenol,[20] presumably because of relaxin promoting collagenase activity that could counteract the inhibitory effects of dexamethasone.

Numerous associations between RFM and hypocalcemia have been made.[54,55] In cows fed anionic diets, those with RFM had significantly lower total plasma calcium than cows without RFM.[55] Calcium is required for collagenase activity, but the decreased blood calcium levels found in RFM cows were not low enough to preclude collagenase activity.[48] Furthermore, it should be noted that comparisons of calcium levels between cows with and without RFM have primarily focused on only total calcium,[55] rather than the biologically active ionized form. For example, total calcium levels can be affected by other factors, such as hypoalbuminemia, in the face of normal ionized calcium levels. No decrease in calving-related disorders, including RFM, was found when cows on anionic diets were supplemented with oral calcium and energy.[10] While hypocalcemia can predispose cows to dystocia,[56] and uterine atony caused by hypocalcemia can interfere with the final step of placental delivery, the direct role of calcium in placental separation is not clear.

Many of the risk factors for RFM involve trauma to the uterus, including dystocia, fetotomy, and Cesarean section. Trauma can result in edema of chorionic villi that could impair separation at the cotyledon-caruncle interface.[14,31] Normal detachment of the bovine placenta involves separation of the finger-like cotyledon villi from the caruncle crypts. Thus, bigger edematous 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.[48] Heparin inhibits collagenases[57] and can also delay uterine involution, whereby both could contribute to RFM.[49] Dystocia and uterine trauma have also been associated with uterine atony that could inhibit expulsion of membranes and lead to secondary retention. After a Cesarean section, treatment of cows with a nonsteroidal anti-inflammatory drug (flunixin meglumine) increased the risk of RFM compared with controls. Flunixin meglumine is a cyclo-oxygenase inhibitor and it has been suggested that the higher incidence of RFM is mediated through a reduction of prostaglandin synthesis.[58]

Treatment and Prevention

Unfortunately, there are few effective treatment options for RFM, whereby choices tend to be based more on tradition than evidence. 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 of the placenta remains a common practice despite numerous studies that fail to demonstrate a beneficial effect on reproductive performance or milk yield.[59–62] Recent prospective studies 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.[62,63] 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.[64] Bolinder et al[64] found that manual removal prolonged the interval from calving to 1st functioning CL by 20 days. Additionally, intrauterine pathogenic bacteria were found in 100% of cows with manually removed RFM versus 37% of untreated cows at 3 weeks postpartum, and further 37% of treated versus 12% 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.[65] This is likely due both to aesthetic benefits, including parlor hygiene and removal of offensive odors, 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. In reality, it is more likely that removal of an attached placenta causes damage to the endometrium and suppresses uterine leukocyte phagocytosis,[66] both of which encourage bacterial invasion.[5,65] 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 now damaged endometrium. Necropsy examinations of cows after manual removal of the placenta revealed uterine hemorrhages, 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.[5] 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.

The use of antimicrobial therapy in the treatment of RFM has demonstrated conflicting results.[65] Postpartum metritis is a common sequelae of RFM, and the rationale behind antibiotics for RFM is to prevent or treat metritis and its subsequent negative effects on fertility. Local antimicrobials, typically given as uterine infusions or boluses, have not been shown to reduce the incidence of metritis or improve fertility.[65] In one study, cows either received no intrauterine treatment, local antibiotics, manual removal, or a combination of local antibiotics and manual removal.[63] In addition, cows that had elevated rectal temperatures, regardless of treatment group, were given systemic ceftiofur. While the groups treated with intrauterine antibiotics did show a reduced incidence of postpartum fever, no differences were found among treatment groups in terms of milk yield or reproductive performance.[62,63] Another study evaluated the use of intrauterine chlortetracycline for the treatment of RFM and clinical metritis in terms of reproductive performance and milk yield.[67] Treatment was found to be beneficial only in active cases of clinical metritis, and no difference in either milk yield or reproductive performance were found between treated and untreated RFM cows. These results suggest that while intrauterine antibiotics can be beneficial in treating metritis, it is unlikely that they either cause earlier release of membranes or prevent metritis in cows with RFM.

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 release of RFM.[35] Tetracyclines, antibiotics commonly used for intrauterine treatment in cattle, inhibit MMPs,[68] and might therefore interfere with the normal placental detachment mechanisms.[50]

Systemic antibiotics are believed to be beneficial in RFM cases where fever was also present.[62,69,70] Systemic antibiotics alone were just as effective as systemic antibiotics combined with intrauterine treatment.[62] However, because all febrile cows were treated systemically, it is unclear whether the resolution of fever was caused by the antibiotics or to the cow's own immune defense mechanisms. There are currently no known trials in which cows with RFM and fever were left untreated.[69]

Treating all RFM cows with systemic ceftiofur regardless of temperature was not superior, in terms of occurrence of fever, shedding of RFM, or subsequent reproductive parameters, to selective antibiotic treatment of only febrile cows.[71] In this study daily temperatures were taken on all RFM cows and treatment was initiated immediately upon development of fever. In general, it appears that unnecessary antibiotic usage can be avoided by only treating febrile cows, assuming this is done in a consistent and systematic manner.

While there is no direct evidence for a benefit of treating all RFM cows with systemic antibiotics, antibiotic treatment has been shown to be beneficial in cases of acute postpartum metritis.[72,73] Metritis has been identified as one of the main reasons for reduced fertility in RFM cows.[14] Treating RFM for 5 days with 2.2 mg/kg of systemically administered ceftiofur was superior in preventing metritis when compared with estradiol or no treatment, although no significant improvements in reproductive performance were found.[70]

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,[14,31] and numerous studies have not supported their use as a general treatment for RFM.[6,74] PGF2α also had no positive impact on RFM resolution or reproductive performance.[74] 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.[6,75] Conversely, a higher percentage of cows (80 versus 58.5%) expelled the complete placenta within 12 hours if they were treated with PGF2α after Cesarean section.[76]

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 L of 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 85% (23 of 27) of cows within 36 hours, whereas none of the 24 control cows infused with saline released their membranes within this time period. This treatment is targeted specifically at correcting the lack of cotyledon proteolysis and might be more effective than traditional therapies.[16] Untreated RFM undergoes autolysis but can not be expected to be released before 6 to 10 days after calving.[5]

While collagenase therapy shows promise as a means of treating retained placenta in a variety of species,[16,77,78] 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. Type-XI crude collagenase from *Clostridium histolyticum* has a proteolytic activity ranging from 1,650 to 2,200 U/mg.[16] Current prices for *Clostridium histolyticum* Type XI collagenase (>1,200 U/mg) are US$2,210 for 5 g of powder.[a] At 200,000 U per cow, the cost of collagenase per cow would be about US$74 at 1,200 U/mg and US$40 at 2,200 U/mg, for the collagenase alone. It is unknown whether lower dosages or different preparations of collagenase would be effective in treating RFM, which could lower the cost. While it has been shown that collagenase treatments result in earlier release of membranes,[16] no studies exist that compare production losses in cows treated with collagenase versus untreated cows. 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.

Few field trials exist that 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.[79] High-producing dairy cows deal with severe physiological and immunological challenges,[80,81] and nutritional management in the prepartum period helps reduce other peri- and postpartum diseases.[82–86] Evidence that decreases in immune function[23–25] play an important role in the mechanism of placental retention as well as evidence that supplementation of vitamin E and selenium in deficient cows reduces incidence of RFM[45] 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.[79]

Summary

Placental detachment and expulsion are complex processes that begin with prepartum hormonal and biochemical changes. Disturbances in any of these normal processes may result in placental retention. An understanding of the physiology of placental retention allows discussions about the link of risk factors to specific causes that will aid in the critical appraisal of treatment protocols and prevention of bovine RFM. Thus, RFM can be thought of more as a syndrome with possibly multifactorial causes as well as reflecting herd management.

Many common therapies for RFM have not been shown to be effective, and some could actually have a negative impact on future reproduction. Manual removal, local antibiotics, and prostaglandins are used treatments, although current evidence does not support their use.[6,65] When cows become febrile, systemic ceftiofur has been the most widely evaluated antibiotic, and appears to be beneficial in reducing disease and aiding in the return to normal reproductive function. Collagenase might prove to be valuable in achieving faster release, although cost-prohibitive in many cases. New therapies should be aimed at correcting specific causes of RFM.

The limited availability of effective treatment options emphasizes the importance of prevention. Current recommendations for prevention of RFM in cattle include cow comfort, reducing stress around parturition, and careful nutritional management, particularly during the transition period. Recent evidence suggests supplementing vitamin E and selenium may be an effective preventive measure.[45] As we learn more about the various etiologies of placental retention, more detailed

recommendations for both treatment and prevention will become available.

Footnote

[a] Sigma Chemical Co, St Louis, MO

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