Postpartum metritis in cattle: A review of the condition and the treatment

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The diagnosis and management of postpartum metritis in cattle has been a controversial subject for many years. Different approaches are related to a number of factors: the different types of cattle and levels of productivity, how the condition is defined, the multitude of risk factors associated with metritis (Table 1), the lack of well-designed or well-controlled studies evaluating treatment effectiveness, and differences in the endpoints being monitored in the available studies. This issue of Large Animal Veterinary Rounds reviews the etiology, signs, and treatment of postpartum metritis and describes a research project in progress at the Western College of Veterinary Medicine.

Metritis is defined as inflammation of both the endometrial and muscular layers of the uterus.1,2 The most serious cases occur during the first 10-14 days post-calving and are sometimes referred to as toxic puerperal metritis.1,2 Affected animals are ill and exhibit varying degrees of depression, inappetence, and decreased milk yield. Economic losses occur due to decreased milk production, drug costs, milk withdrawal, impaired reproductive performance, and even death of the animal.2,3 A recent American study pegged the per lactation cost of a case of metritis at $106.00 US.4 Inappetent postpartum dairy cattle are also predisposed to develop a displaced abomasum; this is always a concern for producers and a common reason for seeking veterinary assistance.5 Veterinarians often feel compelled to try to do something for their clients and their animals in an attempt to reduce the severity of metritis and its sequelae. Many have thought that they had the “magic bullet” treatment for postpartum metritis only to discover that the protocol offered no advantage, or in some cases, was even more harmful than simply doing nothing.

The role of retained placenta in the development of metritis

Retained fetal membranes (RFMs, retained placenta) are the most significant predisposing factor for metritis in cattle (Figure 1).6-8 The incidence of postpartum metritis in cows with RFMs may be as high as 90%.9 The odds of a cow with RFMs developing metritis are 6 times the odds of those without RFMs and are much higher than any of the other risk factors (Table 1). As well as an independent risk factor for metritis, twinning is the greatest natural cause of RFMs in cattle.6-8 Rates of twinning in Holsteins have been increasing in recent years, primarily due to selection for increased milk production.10,11 High-producing cows are thought to have increased rates of steroid hormone metabolism as a result of increased blood flow to the rumen and ultimately, the liver. Estradiol from the dominant follicle is metabolized too rapidly and therefore, does not suppress follicle stimulating hormone levels sufficiently. Ancillary follicles are allowed to develop to maturity, resulting in multiple ovulations.11

The smelly, unsightly nature of RFMs combined with the risk of metritis often obligates both veterinarians and cattle producers to prevent or treat RFMs. A research paper, published in 1921, stated that “the presence of the great necrotic and putrefying mass of membranes” was likely “a menace to the health and life of the patient,” which may have led to the idea that manual removal might be beneficial. However, in many cases, manual removal may only make benign cases more serious.12 It is now well accepted that the manual removal of RFMs is contraindicated. Numerous studies have demonstrated a negative effect of removal on future fertility, especially in cows with metritis, since the uterus in cows with RFMs is friable and prone to damage.13 Despite this information, veterinarians are still commonly pressured to do something about the sick postpartum cow with RFMs, which usually implies doing something to remove the membranes.
Retained fetal membranes alone have mild effects on future fertility. Problems occur when cases are complicated by metritis. Any therapy for RFMs should focus on preventing postpartum metritis. Most attempts to speed up the loosening process are futile as the normal breakdown mechanisms within the placentomes begin weeks before parturition. The use of intrauterine antibiotics in cases of RFMs should be avoided because they will impair the putrefactive processes necessary for dissolution of the membranes. Ecbolic agents such as PGF$_2\alpha$, fenprostalene, cloprostenol, ergot derivative, and oxytocin have largely met with failure as means of speeding up the expulsion of the placenta. If the sight and smell of the placenta are a concern then there is no harm in cutting off the exposed portion at the vulva.

Causative bacteria

The postpartum uterus is a good environment for bacterial growth because it is warm, fluid filled, and contains a variable amount of necrotic debris. A variety of bacteria have been cultured from the uterus of postpartum cows (Table 2). Infections commonly involve *Arcanobacter pyogenes*, coliforms, and the Gram-negative anaerobes, *Fusobacterium* and *Bacteroides* species. Most of the other bacteria tend to be transient invaders that result in no or only minor inflammatory lesions that do not appear to affect subsequent fertility. Mixed infections of *Fusobacterium* and *Bacteroides* species together with *Arcanobacter pyogenes* are common. Through leukotoxins, inhibitors of phagocytosis, and various growth promoters, they enhance the growth of each other. These 3 infectious agents are probably the main causes in cases of persistent metritis and are associated with impaired fertility. The coliforms are of gastrointestinal origin and are very frequently isolated, but their true significance is unknown. They are likely incidental contaminants in the postpartum genital tract. Coliforms comprise 36% of bacterial isolates from normal postpartum cows and tend to be encountered more frequently in the early postpartum period. In cows demonstrating signs of metritis, (eg, depression and a fetid uterine discharge), coliforms were isolated in 29% of cases.

*Clostridium* species deserve comment because they have been isolated from the uteri of nearly all postpartum cows in studies where careful anaerobic culturing techniques were employed. Other investigators have had considerable difficulty recovering this species, which may be due to its strict anaerobic nature. These bacteria are associated with a toxic, gangrenous metritis that typically culminates in death. Some dairy farms reportedly have a great deal of difficulty with pathogenic *Clostridium* species, necessitating the use of specific preventive and treatment programs.

Normal uterine involution

Uterine involution requires 25 to 50 days for completion and entails a reduction in uterine size, necrosis and shrinking of the caruncle, and re-epithelialization of the endometrium. Size reduction begins immediately after the calf is delivered and is relatively modest during the first 10 days compared to the reduction between 10 to 14 days postpartum. This initial shrinkage is largely due to oxytocin-generated uterine contractions that occur every 3–4 minutes during the first day and possibly persist up to the third day postpartum. Suckling is associated with a much more frequent release of oxytocin from the pituitary than milking and is probably the reason beef cattle tend to have a shorter period of involution than dairy cattle. When palpated transrectally, the normal postpartum uterus should have prominent longitudinal ridges or rugae owing to the substantial reduction in size (Figure 2).

Involution of the bovine uterus is not a sterile process since a large quantity of lochia is expelled over a few weeks. Two weeks after calving, 85% to 93% of cows have uterine infections, but only 5%–9% remain infected at 45–60 days. Phagocytic leukocytes have an important role in the cleanup and defense of the postpartum uterus. Neutrophils and macrophages are largely responsible for the phagocytosis of bacteria and debris that usually begins on the second day postpartum.
Antibodies against immunity in the defense and cleanup of the postpartum uterus. 30% of heifers versus 6% of cows, 10 days postpartum.7

Ap yogenes

Heifers may not have adequate levels of antibody against eral weeks after calving despite their presence in the serum. were not found in the vaginal mucus of heifers until sev-

Fluid may be detected within the uterine lumen and may be expelled by exerting pressure on the uterus. However, caution is advised because rectal palpation tends to be very subjective and it may be difficult to differentiate the uterus undergoing normal involution from postpartum metritis, especially in the first 2 weeks after calving.1,6

**Treatment**

Postpartum metritis is usually treated with antibiotics or hormones, alone or in combination. Antibiotics are typically delivered systemically or are infused directly into the uterine lumen. In severely-affected animals, anti-inflammatory agents and intravenous fluid therapy should also be employed.

The value of supportive care must never be underestimated. In a retrospective analysis of the management in 78 cases of postpartum metritis, it appeared that all that was needed for recovery was to administer therapy for life-threatening changes while the uterus healed itself.1 It is still controversial whether cattle without signs of systemic illness should be treated. Results of a variety of studies have been conflicting, likely due to several factors: the differences in criteria used to diagnose metritis, the postpartum stage of the animals, the outcome variables being measured, and the route and frequency of administration of the various drugs used in each trial.17 The prophylactic use of antibiotics in cases of retained placenta may be useful, but there are few controlled trials evaluating their ability to prevent metritis, especially in relation to their cost and appropriate withdrawal times.8

Intrauterine infusions: A variety of agents, antiseptic or otherwise, have been infused into the uterus in an attempt to destroy bacteria, enhance uterine defense mechanisms, or increase uterine tone and blood flow. The infusion of iodine solutions in water or saline is the most common. Few studies have evaluated the potential harmful effects of iodine infusion on future reproductive performance. It has been reported that a single infusion of as little as 50-100 mL of 2% polyvinylpyrrolidone-iodine (povidone-iodine) solution, as a routine therapy 30 days postpartum, has a detrimental effect on fertility in cows with endometritis compared to non-treated animals.16 Several years ago, clinicians at WCVM advocated the infusion of 1 L of a 50% dextrose solution into postpartum cows. The dextrose apparently caused increased uterine tone, but no critical studies have been published. The increase in tone was likely due to the hypertonicity of the solution, which might be accomplished with any hypertonic solution (eg, saline) (Dr. Frank Bristol, personal communication). It is unknown whether the infusion of an agent to increase uterine tone is of any benefit for uterine involution or helpful for the treatment of metritis.

The ideal treatment should remove harmful bacteria from the uterus without damaging the uterus or impairing its defense mechanisms. Although there are several articles extolling the virtues of intrauterine therapy, several trials have found no benefits. As a rule, intrauterine antibiotic infusion should be avoided as a treatment for postpartum metritis.17 When antibiotics are infused into the uterus, it is often uncertain whether the drug is distributed throughout all layers of the uterus. Moreover, because many agents administered into the uterus may be systemically absorbed to some extent, there are concerns about appropriate meat and milk withdrawal periods.7,17 Most common drugs are not registered for intrauterine use and many are rendered ineffective in the postpartum uterus. For example, aminoglycosides require an aerobic environment to be effective, not the anaerobic environment of the postpartum uterus. Necrotic tissue and purulent debris

**Figure 2: A normally involuting uterus with longitudinal rugae.**

Normal lochia is reddish brown to white and lacks a significant odour. Uterine infections are characterized by a fetid, watery, reddish brown discharge. Affected cows may be so smelly that they can be detected as soon as one enters the housing area. Other clinical signs include depression, reduced appetite or anorexia, dehydration, and a decline in milk production. Fever is common, with temperatures easily exceeding 39.4°C. Since this organism was cultured from the uterus of cows with postpartum metritis, it appeared that all that was needed for recovery was to administer therapy for life-threatening changes while the uterus healed itself. It is still controversial whether cattle without signs of systemic illness should be treated. Results of a variety of studies have been conflicting, likely due to several factors: the differences in criteria used to diagnose metritis, the postpartum stage of the animals, the outcome variables being measured, and the route and frequency of administration of the various drugs used in each trial. The prophylactic use of antibiotics in cases of retained placenta may be useful, but there are few controlled trials evaluating their ability to prevent metritis, especially in relation to their cost and appropriate withdrawal times.

A normally involuting uterus with longitudinal rugae.
reduce the efficacy of sulfonamides and aminoglycosides.17 Penicillin family of drugs7,17 and the cephalosporins17 tend to perform poorly when infused in the first 30-days postpartum because there are a number of organisms producing inactivating (β-lactamase) enzymes. Streptomycin and the tetracyclines7,17 are very irritating to the bovine uterus and most formulations should not be used for intrauterine therapy. All intrauterine antibacterials have been found to have a negative affect on leukocyte function17,18 and their placement risks iatrogenic contamination or further injury to the uterus.

**Systemic antibiotics:** Systemic antibiotic therapy appears to offer many advantages. Withdrawal times are generally well-established, distribution to all layers of the uterus is possible, and systemic antibiotic use appears to be less harmful to the uterine environment (Table 3).17 Penicillin is the preferred antibiotic for postpartum metritis as it penetrates all layers of the uterus, is inexpensive,17 and most of the bacteria penetrating the endometrium and causing septicemia are sensitive to penicillin.7,17,18 A typical dose is 21,000 IU/kg procaine penicillin G IM once–a–day for 3 to 5 days. Milk should be withheld for at least 96 hours and the animal should not be slaughtered for food use until 10 days after the last treatment. Alternatively, ceftiofur sodium at 1 mg/kg IM or SQ may be administered for 3 to 5 days with no withdrawal requirement. Ceftiofur sodium has been found to concentrate in uterine tissues at levels exceeding the mean inhibitory concentrations for *Arcanobacter pyogenes*, *Fusobacterium necrophorum* and *Escherichia coli*.17 Oxytetracycline is also commonly used for the treatment of postpartum metritis, especially in cattle demonstrating only mild signs of systemic involvement (eg, slight depression). Intravenous dosages of 11 mg/kg oxytetracycline IV administered twice daily maintained a mean tissue concentration >5 µg/g in the uterine wall for the first 4 hours after the first treatment, reaching a maximum of 9 hours by the 5th day of treatment. Slightly higher and more persistent concentrations were found in the caruncles and endometrium for longer periods of time.19 Concentrations in the uterine wall were far below those of blood. The minimum inhibitory dose for *Arcanobacter pyogenes* in uterine isolates is reported to be 20.4 µg/mL.17 Together, this information suggests that parenteral oxytetracycline is an inadequate treatment for postpartum metritis.

**Hormone therapy:** Hormone therapy offers another alternative in the treatment protocol. The desired effect of hormone use is to increase expulsive uterotonoc contractions and/or induce an estrogenic state. The benefits of estrus are well-recognized since neutrophil function, uterine resistance to infection,17 and myometrial contractility20 are all reduced under the influence of progesterone.

Prostaglandin F2α (PGF) is produced by caruncles in the early postpartum period.1,17 Plasma levels of a PGF metabolite have been found to peak at day 4 postpartum15 and decline thereafter, reaching baseline levels by 14 to 20 days postpartum.13 Some reports suggest that higher and more prolonged concentrations have been associated with more rapid uterine involution.1 Both PGF and various analogs have been widely used for the treatment of postpartum metritis. The rationale for PGF or PGF analog use in the immediate postpartum period, primarily, has been in an attempt to increase uterine tone. However, it is unlikely that PGF has any effect unless there is luteal tissue on the ovary.17,20 Use of cyclooxygenase inhibitors (eg, flunixin meglumine) will reduce PGF production, but the rate of reduction in size of the uterine horn and cervix is unaffected by as much as an 80% decline in endogenous PGF production.20 Many studies outlining the benefits of PGF therapy for the treatment of RFMs and metritis have been refuted. Intramuscular (IM) doses of PGF as high as 50 mg have not had any apparent effect on uterine tone. Intravenous (IV) doses (15 mg Dinoprost) have been much more effective, but only up to 4-days postpartum.20 This may be because IM injections are absorbed more slowly and, once absorption occurs, PGF is metabolized on a single pass through the lungs. A readily available PGF analog, cloprostenol (250 µg) administered IV was found to be minimally uterotonic. Another analog, fenprostalene (no longer available), has a very long half-life of 18–23 hours. Dosages of fenprostalene as high as 2 mg SQ did not significantly affect uterine tone or contractility when administered repeatedly to cows from 12– to 84-hours postpartum; IV injection yielded similar results. The role of elevated PGF levels in the postpartum cow is largely unknown. Oxytocin and PGF are involved in a complex feedback loop in the periparturient cow, each leading to an increase in the other. The administration of flunixin meglumine will attenuate the effects of exogenous oxytocin through its effect on prostaglandin synthesis, but apparently it has no effect on involution. The benefits of prostaglandin in the postpartum cow may relate to its role in the inflammatory process, but this hypothesis has yet to be validated.20

Estrogens, particularly estradiol cypionate (ECP), have been used to stimulate the formation of oxytocin receptors in the postpartum uterus. Most of the evidence supporting this concept has been extrapolated from other species and from cycling cattle. It has been demonstrated that estradiol will speed up the process of oxytocin receptor expression in cyclic cattle, but it is not essential for the process. Furthermore, the use of 5 mg of ECP IM 18-hours post-

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dose/Route</th>
<th>Treatment Interval</th>
<th>Withdrawal Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procaine Penicillin G</td>
<td>21,000 IU/kg IM</td>
<td>Once per day</td>
<td>96 hrs</td>
</tr>
<tr>
<td>Ceftiofur Sodium</td>
<td>1 mg/kg IM/SQ</td>
<td>Once per day</td>
<td>0 days</td>
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Table 3: Appropriate systemic antibiotics, dosages, and withdrawal times for treating postpartum metritis.
parturition was found to negatively affect the frequency and duration of uterine contractility for at least 5 days. When 25 units of oxytocin was administered IV 6 hours after the ECP injection, there was a slight depression in contractility that was lower than when 20 units of oxytocin was used alone. In addition, repeated daily dosing with oxytocin following the single ECP injection did not produce a demonstrable benefit. Numerous studies have demonstrated that under the influence of estrogen, uterine contractions are largely cervico-tubal. This is likely to facilitate the movement of sperm; however, this movement has been suggested as the reason for the high incidence of salpingitis in a study where cows with metritis were treated with 10 mg of ECP IM. An increased incidence of cystic ovarian disease has also been associated with ECP use. In a recent study, 33 cows with retained placenta were treated with 4 mg ECP IM 24-hours postpartum. Cows treated with ECP were just as likely to develop metritis, but were 0.40 times as likely to conceive and had a median time to pregnancy was found in a study of 122 normal cows treated with 4 mg of ECP IM 24-hours postpartum. Any beneficial effects of ECP are likely to be outweighed by negative effects on reproductive performance.

Oxytocin is very inexpensive, but is thought to be relatively useless as an aid to uterine clearance in the postpartum cow. It has long been assumed that there is a loss of oxytocin receptors in the myometrium after parturition and that oxytocin would not be effective after 48-hours postpartum. Another problem with oxytocin is its short duration of response. When 25 IU oxytocin was administered IV to cows on days 1 to 4 postpartum, the increased uterine contractility lasted only 2 hours and dropped to 1.5 hours by day 5. It is probable that a continuous slow IV infusion (ie, 100 IU oxytocin in saline over 6 hours) would have been more appropriate, but this regime is seldom practical in most large animal situations. Many veterinarians have used oxytocin post-dystoica or post-caesarean to treat uterine atony, aid placental expulsion, and prevent uterine prolapse. Most preparations contain 20 IU (U.S.P) per ml and the label dosage for obstetrical manipulations in cattle is typically, 50–100 IU IM, IV, or SQ. With oxytocin, veterinarians often ascribe to the “more is better” philosophy and administer doses as high as 200 IU. To date, little has been done to determine the most appropriate dose; however, in a study evaluating oxytocin as a treatment for RFMs, doses as low as 60 IU were found to result in non-rhythmic, uterine spasm. Contractility of this nature is not useful in terms of expelling uterine contents and possibly represents an overdose. In the first 6-days postpartum, IV doses of 2 to 40 IU have been used and all have resulted in increased, myometrial contractility. As the dose increased so did the contraction frequency, but the 40 IU dose tended to cause an initial uterine spasm that lasted 6–10 minutes, especially when used within the first 3 days. By day 10 postpartum, only the 40 IU dose produced a detectable response. The increased frequency of contractions has been said to be similar to a cow in early stage II of parturition. Most of the studies have involved IV administration of oxytocin. Similar responses have been recorded following IM or SQ use of 20 to 40 IU. A suggested treatment plan has been to administer 20 IU every 3 hours IM, or more practically, 3 times between milkings for the first 2–3 days postpartum. The dose could be increased to 30 IU by day 4 postpartum and administered as frequently as every 2 hours. Oxytocin is arguably the most physiologic hormonal treatment for postpartum metritis; however, critical, scientific evaluation has yet to be done to determine its effectiveness. A research group at WCVM is beginning to evaluate this treatment and the work is described in the next section. Another possibility is the use of a long-acting formulation that reportedly produces sustained uterine contractions and is available in some countries.

Case Study: Research in progress

Experiment: Evaluation of multiple oxytocin injections combined with IM penicillin therapy for the prevention of postpartum metritis in cows with RFMs.

Background: The study population is composed of approximately 50 milking cows with a rolling herd average for milk production of over 12,000 kg, up from 10,500 in 2000. In 2000, 2001, and 2002 the twinning rate was 4%, 3%, and 11.6%, respectively, and to date in 2003, it is 10.7%. Virtually all of the cows in this herd with RFMs develop metritis and become seriously systemically ill. In response, a protocol was designed to evaluate the effectiveness of multiple oxytocin injections to prevent or at least ameliorate the systemic illness associated with metritis. The farm staff felt that something must be done for all cows, so all were assigned a treatment, however, only some received oxytocin. A reasonable protocol incorporating penicillin and oxytocin was devised.

Protocol: A cow is considered to have RFMs if expulsion has not occurred by 24-hours postpartum. Two of 3 cows with RFMs receive both the oxytocin and penicillin treatment for 5 days; 1 of 3 receives only procaine penicillin G for 5 days. From the first morning milking after making the diagnosis of RFMs to 4-days postpartum, cows receive 20 IU oxytocin IM after morning milking (5:00 AM), at 10:30 AM, after afternoon milking (3:30 PM), and at evening check (10:00 PM). On day 5, oxytocin treatment is increased to 40 IU. Procaine penicillin G (300,000 IU/mL) is administered at a dose of 7 mL/100kg IM in at least 2 sites at the morning milking.

Measured endpoints: Morbidity, days to 1st service, times bred, days open.

Results: Only 5 cows have been treated with penicillin and oxytocin to date. However, none became systemically ill during the postpartum period. One of the 5 was sold for unrelated reasons. Of the 4 remaining cows: 1 became pregnant to 1st service at 77 days in milk; the second at 75 days, but later aborted twins; the third is 154 days in milk and still open; and the 4th cow is not yet ready to be bred. It is too early to determine if this treatment is consistently better than the control therapy. One cow, treated with penicillin alone, did not experience postpartum illness, and became pregnant at 101 days in milk.
Summary

Postpartum metritis is an economically important disease occurring in the first 2 weeks after calving. Affected animals have a fetid, reddish brown uterine discharge and varying degrees of depression, reduced appetite, dehydration, and decreased milk production. RFMs are the most significant predisposing factor for metritis; they provide an excellent substrate for bacterial growth. *Fusobacterium* pyogenes and the Gram-negative anaerobes, *Prevotella* and *Bacteroides* species, are the most significant pathogens involved. Treatment is usually based on antibiotics alone or in combination with hormone therapy; IV fluid therapy and anti-inflammatory agents should also be used for those animals demonstrating severe systemic illness. Antibiotic use should be limited to the use of systemic penicillin or ceftiofur, paying attention to appropriate withdrawal requirements. Treatment is usually based on systemic penicillin or ceftiofur, paying attention to appropriate withdrawal requirements. Treatment is usually based on systemic penicillin or ceftiofur, paying attention to appropriate withdrawal requirements.

References


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