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Uterine diseases in dairy cows: understanding the causes and seeking solutions

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Abstract

Uterine diseases such as metritis and endometritis are highly prevalent in high producing dairy cows. These diseases lead to impaired welfare and fertility, and result in economic loss. The objective of this review article is to provide the current understanding of the underlying causes of uterine diseases and to provide some strategies to prevent them. The causes of uterine diseases are complex and multifactorial; therefore a holistic approach must be taken when trying identity the causes or prevent them. The dairy cow undergoes a state of negative energy, mineral and vitamin balance during the transition into lactation, which leads to immunosuppression and increased susceptibility to disease. The main risk factors for uterine diseases are primiparity (for metritis only), dystocia, male offspring, twins, stillbirth, abortion, prolapsed uterus, retained placenta (RP), ketosis, and hypocalcemia. Prevention strategies should be focused on maximizing cow comfort and dry matter intake (DMI), preventing hypocalcemia and hyperketonemia, preventing dystocia, prolapsed uterus, abortion, stillbirth and RP. Maximization of cow comfort and DMI can be achieved with appropriate housing and cooling. Management strategies to prevent metabolic and calving related problems include the use of anionic diets, the use of feed additives such as monensin and rumen protected choline, implementation of sound vaccination programs, and the use of sexed semen. Trace mineral and vitamin supplementation beyond what is fed in the diet is still controversial; however some trials have shown a decrease in RP and stillbirths. Prophylactic treatment of cows at high risk for metritis with PGF2α and/or oxytocin is not warranted because there is no beneficial effect. Prophylactic treatment of cows at high risk for metritis with NSAIDs is contraindicated because it has been found to decrease DMI and increase the degree of negative energy balance; therefore, leading to an increase in the risk of RP and metritis. Prophylactic treatment of cows at high risk for metritis with estradiol is contraindicated because there is no beneficial effect on the prevention of metritis and there is a negative effect on long term fertility. Prophylactic treatment of cows at high risk for metritis with antibiotics can reduce the incidence of uterine disease but has no positive long term effects on fertility; therefore, decision to implement prophylactic antibiotic treatment should be based on welfare, economic and legal considerations. Given that most treatments are not very efficacious, efforts should be focused on management strategies to decrease metabolic problems such as hypocalcemia and ketosis, and to prevent risk factors such as dystocia, male calves, abortions, stillbirths, and retained placenta.

Keywords: causes, dairy cows, solution, uterine diseases.

Introduction

Uterine diseases such as metritis and endometritis are highly prevalent in high producing dairy cows. Metritis is characterized by fetid red-brownish uterine discharge within the first 21 days in milk (DIM; Sheldon *et al*., 2006), and affects about 20.0% of lactating dairy cows, with the incidence ranging from 8 to >40% in some farms (Curtis *et al*., 1985; Goshen and Shpigel, 2006; Hammon *et al*., 2006; Huzzey *et al*., 2007; Galvão *et al*., 2009b). Clinical endometritis is characterized by the presence of purulent (>50%) uterine discharge after 21 DIM or mucopurulent (50% pus, 50% mucus) after 26 DIM (Sheldon *et al*., 2006), and also affects about 20.0% of lactating dairy cows, with the prevalence ranging from 5 to >30% in some herds (LeBlanc *et al*., 2002; McDougall *et al*., 2007; Galvão *et al*., 2009b). Subclinical endometritis is defined by the presence of >18% neutrophils (PMN) in uterine cytology samples collected between 21 and 33 DIM or >10% PMN between 34 and 47 DIM (Sheldon *et al*., 2006), and is the most prevalent of all uterine diseases; it affects approximately 30% of lactating dairy cows, with the prevalence ranging from 11 to >70% in some herds (Kasimanickam *et al*., 2004; Gilbert *et al*., 2005; Hammon *et al*., 2006; Barlund *et al*., 2008; Galvão *et al*., 2009a; Cheong *et al*., 2011). These diseases have been associated with decreased pregnancy per artificial insemination (AI), extended interval to pregnancy, increased culling, and economic losses (Bartlett *et al*., 1986; Sheldon and Dobson, 2004; Gilbert *et al*., 2005; Overton and Fetrow, 2008; Galvão *et al*., 2009a, b).

The decreased fertility is caused by negative effects in the uterus and in the ovary. Uterine diseases cause lesions in the endometrium (Bonnett *et al*., 1991), disrupt endometrial function (Sheldon and Dobson, 2004), and impair embryo development (Soto *et al*., 2003; Hill and Gilbert, 2008). Uterine diseases decrease luteinizing

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hormone, first dominant follicle size and growth, and follicular ability to secrete estradiol; therefore affecting ovulatory capacity (Peter *et al*., 1989; Sheldon *et al*., 2002; Williams *et al*., 2008). After postpartum ovulation resumes, cows that developed uterine disease present prolonged luteal phases (Opsomer *et al*., 2000; Mateus *et al*., 2002), which can decrease time to insemination and conception rates. In this review, we will focus on understanding the main causes of uterine diseases and present some solutions for the problem.

Causes

Like most diseases, uterine diseases are multifactorial; therefore it becomes extremely difficult to discuss all factors affecting its occurrence. Some of the traditional risk factors associated with metritis include primiparity, dystocia, male offspring, twins, stillbirth, abortion, prolapsed uterus, retained placenta (RP), ketosis, and hypocalcemia (Erb *et al*., 1981a, b; Dohoo and Martin, 1984; Markusfeld, 1984, 1985, 1987; Curtis *et al*., 1985; Gröhn *et al*., 1990; Correa *et al*., 1993; Kaneene and Miller, 1995; Goshen and Shpigel, 2006; Dubuc *et al*., 2010; Ospina *et al*., 2010; Hossein-Zadeh and Ardalan, 2011). Risk factors for endometritis include dystocia, male offspring, twins, stillbirth, abortion, RP, metritis, problems with vulval conformation, and ketosis (Gröhn *et al*., 1990; Galvão *et al*., 2009b; Dubuc *et al*., 2010; Potter *et al*., 2010; Cheong *et al*., 2011). Because of the multifactorial nature of uterine diseases, it is helpful to think of the disease triangle (Stevens, 1960) when trying to understand their causes. In that regard, for establishment of disease, it is necessary a susceptible host, a virulent pathogen, and an environment favorable for disease development.

Starting with the host, the dairy cow undergoes dramatic metabolic and physical challenges during the transition to lactation (3 weeks before to 3 weeks after calving). Regarding the metabolic challenge, the transition period is characterized by a state of negative energy, mineral, and vitamin balance (Goff and Horst, 1997) in which there is a decrease in dry-matter intake (DMI), leading to a sharp decrease in glucose, minerals (e.g. calcium, selenium) and vitamins (e.g. A and E) right after parturition, and an increase in body fat mobilization in the form of non-esterified fatty acids (NEFA). High mobilization of NEFA results in excessive uptake by the liver; therefore, leading to incomplete oxidation of this fatty acids and the accumulation of ketone bodies such as beta-hydroxybutyrate (BHBA) in the blood (Vazquez-Añon *et al*., 1994). This state of negative energy, mineral, and vitamin balance leads to immunosuppression (Kehrli and Goff, 1989; Gilbert *et al*., 1993; Cai *et al*., 1994) and increased susceptibility to disease (Trinder *et al*., 1973; Harrison *et al*., 1986; Hammon *et al*., 2006; Galvão *et al*., 2010, 2011, 2012; Martinez *et al*., 2012). The metabolic challenge is likely a result of preparation for and initiation of lactation (Kimura *et al*., 1999, 2006); however, dairy cows also have a high incidence of dystocia (11 to 29%; Meyer *et al*., 2001; Schuenemann *et al*., 2011a) which help breach the physical barriers such as the vulva and endometrium and probably affect DMI intake postpartum because of discomfort. We have observed (Vieira-Neto *et al*., 2013) that cows that suffer lacerations >2cm have a much greater incidence of metritis than cows with no laceration (63.0 *vs*. 35.2%; $P < 0.002$), while cows having laceration <2 cm were intermediate (43%). The higher incidence of dystocia in primiparous (29%) probably helps explain the higher incidence of metritis in primiparous cows (Meyer *et al*., 2001). Stillbirths are also highly correlated with dystocia (Meyer *et al*., 2001) and hypocalcemia (Martinez *et al*., 2012). Other risk factors such as twins, prolapsed uterus and RP are correlated among themselves and also associated with hypocalcemia (Risco *et al*., 1984, 1994; Kimura *et al*., 2002; Martinez *et al*., 2012). The RP may also work as a fomite and carry contaminants into the vagina. Abortion is a risk factor probably because of the underlying condition that caused the abortion in the first place and its association with RP.

The dairy cow is unique in the sense that virtually all cows are infected with bacteria in the days following calving (Sheldon and Dobson, 2004). Bacterial culture of the postpartum uterus yields a wide range of isolates (Elliot *et al*., 1968; Griffin *et al*., 1974; Sheldon *et al*., 2002; Galvão *et al*., 2009b). A complete list of isolates can be found in the work by Williams *et al*. (2005), but mainly *Escherichia coli* (*E. coli*), *Trueperella* (formerly *Arcanobacterium*) *pyogenes* (*T. pyogenes*), *Fusobacterium necrophorum* (*F. necrophorum*), and *Prevotella melaninogenica* (*P. melaninogenica*) were isolated from cows with metritis, whereas Streptococcus spp. Staphylococcus spp., and Bacillus spp. were isolated from healthy cows (Bonnett *et al*., 1991; BonDurant *et al*., 1999; Huszenicza *et al*., 1999; Gilbert *et al*., 2007). These four main bacteria are believed to work synergistically to cause uterine disease in dairy cows (Griffin *et al*., 1974; Ruder *et al*., 1981; Bonnett *et al*., 1991). In fact, *E. coli* increases the susceptibility of the endometrium to subsequent infection with T. pyogenes (Olson *et al*., 1984; Gilbert *et al*., 2007; Williams *et al*., 2007), and *T. pyogenes* acts synergistically with *F. necrophorum* and *P. melaninogenica* to enhance the severity of uterine disease (Griffin *et al*., 1974; Ruder *et al*., 1981; Bonnett *et al*., 1991). Recent work has highlighted the importance of *E. coli* on the development of metritis and endometritis (Bicalho *et al*., 2010, 2012; Sheldon *et al*., 2010; Machado *et al*., 2012a, b); especially the fact that it predisposes to infection with other pathogenic bacterium such as *F. necrophorum* and *T. pyogenes* (Bicalho *et al*., 2012; Machado *et al*., 2012a, b), increases the likelihood of developing metritis and endometritis, and decreases the likelihood of conception (Bicalho *et al*., 2010, 2012; Machado *et al*., 2012a).

Very few studies have tried to evaluate the

effect of the environment on the incidence of bacterial contamination of the uterus or the incidence of uterine disease. Noakes *et al*. (1991) compared the bacterial flora of the uterus from 26 cows from two herds with contrasting hygiene environments (one with poor hygiene and one with good hygiene), and found similar proportion of cows with uterine contamination and similar proportion of the main uterine pathogens. Based on these findings, the authors concluded that the environment had no influence on either the quantitative or qualitative uterine bacterial flora; therefore, uterine disease was due to other factors. This was a small and uncontrolled study; therefore the findings should be interpreted carefully. A larger study (Cheong *et al*., 2011) with 38 herds from upstate New York looked at the effect of bedding material in the calving pen and type of housing early postpartum. They found that herds that used straw in the calving pens had 10.7% ($P < 0.005$) lower incidence of subclinical endometritis compared to other types of bedding (sand, sawdust or paper). They also found that herds that housed their fresh cows in free-stalls had 16.7% (36.1 *vs*. 19.4%; $P < 0.005$) lower incidence of subclinical endometritis than herds that housed their cows in bedded packs. Although the results were significant, for type of bedding at the calving pen and type of housing early postpartum, a direct link between hygiene in the environment and incidence of disease could not be made; therefore, the authors warned the readers to interpret the results with caution. Although environment hygiene has not been associated with incidence of uterine disease, perineal hygiene at the time of calving has. In a study with 562 cows in Ohio (Schuenemann *et al*., 2011b), the hygiene of perineum of cows right before calving was scored using a 1-3 scale (1 = free of dirt-manure and completely dry; 2 = slightly wet, dirt-manure in 1-10% of the surface; 3 = moderately wet, covered with dirt-manure in >10% of the surface). Cows with scores 3 or 2 had greater incidence of metritis (22.4 ± 6% and 18.9 ± 4%, respectively) than cows with a score 1 (10.8 ± 3%; $P < 0.05$). These results indicate that contamination of the uterus might be coming from the cow herself and not from the environment.

An interesting observation is the difference in incidence of uterine disease in cows on free-stalls and cows on pasture. Certainly, there are many differences between the two types of cows besides the type of housing (milk yield and genotype being important ones). However, data recently generated in Florida (Ribeiro *et al*., 2013) shows that Holstein cows on pasture have much lower incidence of metritis (4.3 *vs*. 16.1%) and clinical endometritis (11.7 *vs*. 20.8%) than what is seen for cows in free-stalls (Santos *et al*., 2010), while other diseases such as mastitis (22.0 *vs*. 12.2%), pneumonia (2.4 *vs*. 2.0), and indigestion (3.9 *vs*. 2.8%) seem unaffected. In the study by Ribeiro *et al*. (2013), the authors speculated that the low incidence of uterine disease, especially metritis was due to the low incidence (8.5%) of calving problems (dystocia, twins, stillbirth or RP), which may be related to smaller calf size since most Holstein cows were bred with Jersey sires. This highlights the importance of calf size and consequently calving ease as a risk factor for uterine disease. One study pointed out that a male offspring, which is larger, had the highest influence (as measured by the population attributable fraction) in the incidence of endometritis (Potter *et al*., 2010). Mee (2012) summarized data on dystocia from several countries from 2000 to 2011 (Table 1) and found large differences in dystocia incidence in the Holstein-Friesian population of cows from different countries (the USA being the highest) and among different breeds of dairy cows; therefore, there is potential for reduction of dystocia incidence through genetic selection.

Table 1. International prevalence of dystocia in dairy heifers and cows (2000-2011).

Country	Breed of dam	Heifers, %	Heifers & Cows, %	Reference
Australia	Holstein-Friesian	9.5	4.1	McClintock, 2004
Canada	Holstein-Friesian	NR[a]	6.9	Sewalem *et al*., 2008
Denmark	Holstein-Friesian	8.7	NR	Hansen *et al*., 2004
Ireland	Holstein-Friesian	9.3	6.8	Mee *et al*., 2011
France	Holstein-Friesian & Normande	NR	6.6	Fourichon *et al*., 2001
New Zealand	Holstein-Friesian	6.5	3.8	Xu and Burton, 2003
Norway	Norwegian Red	2.7	1.1	Heringstad *et al*., 2007
Spain	Holstein-Friesian	3.1	2.5	Lopez de Maturana *et al*., 2006
Sweden	Swedish Red and White	3.9	1.9[b]	Steinbock, 2006
The Netherlands	Holstein-Friesian	NR	7.8[c]	Eaglen and Bijma, 2009
UK	Holstein-Friesian	6.9	2.0[b]	Rumph and Faust, 2006
USA	Holstein-Friesian	22.6	13.7	Gevrekci *et al*., 2006

[a]Not recorded, [b]Cows only, [c]Second calvers only. Adapted from Mee (2012).

Potential solutions

Although complete elimination of uterine disease does not seem possible with our current understanding of the pathophysiology of uterine diseases, there are management strategies that can be taken to mitigate the problem. Prevention strategies should be focused on maximizing cow comfort and DMI, preventing late term abortions with appropriate vaccination programs, favoring the birth of female calves with the use of sexed semen, preventing hypocalcemia and hyperketonemia, and preventing mineral and vitamin deficiencies. Prophylactic treatment with prostaglandin F2-alpha (PGF2α), oxytocin, estradiol, nonsteroidal anti-inflammatory drugs (NSAIDs), and antibiotics will also be discussed. Treatment of uterine diseases will not be discussed because it has been covered in previous publications (Galvão, 2012).

Dry matter intake is the single most critical factor of dairy production, and its effects on uterine health have been clearly demonstrated. Cows that develop metritis and endometritis have decreased dry matter intake starting up to two weeks before calving and remaining until four to five weeks after calving (Hammon *et al*., 2006; Huzzey *et al*., 2007). Critical areas of facility design related to cow comfort and DMI include access to feed and water, stall design and surface, supplemental lighting, ventilation, and cow cooling. A nice review of all these factors was put together by researcher at Kansas State University (Brouk and Smith, 2000). They emphasize that careful consideration must be made when designing facilities due to the fact that once they are built they will affect the performance of animals for the life of the facility (>20 years).

Maintenance of calcium homeostasis throughout transition is imperative for uterine health (Goff and Horst, 1997; Martinez *et al*., 2012). The use of anionic salts can reduce the incidence of clinical hypocalcemia (milk fever) to <2% in multiparous cows and also reduce the incidence of subclinical hypocalcemia in early postpartum (Horst *et al*., 1997). However, anionic salts must be used with caution because they may reduce dry matter intake, especially if >300 meq of anions/kg are fed (Charbonneau *et al*., 2006). They should also only be fed to close-up (usually 3 weeks before calving) dry cows. There is a debate to whether nulliparous cows should receive anionic salts (Horst *et al*., 1997) because of a potential decrease in DMI (Moore *et al*., 2000); however, with the availability of more palatable salts, feeding nulliparous cows should not be a problem (DeGroot *et al*., 2010). In order to achieve success using anionic salts, controlled feeding, precise ration formulation using the dietary cation-anion difference (DCAD) concept, and monitoring of urine pH are necessary. The goal is to have urine pH between 6 and 7. This can usually be achieved with a DCAD between -5 and -15 milliequivalents per 100 g of dry matter (Horst *et al*., 1997). Nevertheless, even with the use of anionic salts, between 20 and 50% of postpartum cows will be hypocalcemic (serum total Ca concentrations <8.5 mg/dl) early postpartum, and these cows will have a much higher incidence of metritis than normocalcemic cows (Martinez *et al*., 2012). In the same work (Martinez *et al*., 2012), it was observed that cows with dystocia, twins, stillbirth and RP had a greater decrease in calcium postpartum than cows without these risk factors; therefore, if an effective postpartum treatment was available, it would probably benefit this group of animals. The problem is that to this date, no effective treatment is available. Benzaquen *et al*. (2008) treated cows with dystocia with calcium propionate at 516 g of calcium propionate (providing 110 g of calcium and 400 g of propionate, 1.5 g of zinc, and 0.5 g of copper) at 6 and 72 h postpartum and actually found that calcium propionate treatment prevented the physiological increase in calcium concentration; therefore, resulting in lower calcium concentration on days two and three postpartum.

Trace mineral and vitamin deficiency early postpartum, particularly selenium and vitamin E have long been identified as a cause of uterine disease (Trinder *et al*., 1973; Harrison *et al*., 1986), probably because of the effect on neutrophil function (Cebra *et al*., 2003). Although selenium supplementation is recommended, the Federal Drug Administration (FDA) limits the supplementation of selenium to 0.3 ppm (mg/kg); therefore, because the upper limit of supplementation is set, the only options to try to supplement more is to change the source of selenium. Organic selenium (selenium yeast) is more absorbable then inorganic selenium (selenite and selenate). One study in Florida (Silvestre *et al*., 2006) and one in California (Rutigliano *et al*., 2008) compared the two sources of selenium. Only the study in Florida observed a decrease in clinical endometritis and an increase in conception rate to second service (Silvestre *et al*., 2006); nonetheless, neither study found any positive impact in the first service conception rate. Out of the two studies, blood concentrations of selenium were only increased in the study in Florida. The authors from the study in California pointed out that Selenium concentration in forages were quite high, which probably masked any benefits from selenium yeast. Therefore, it is important to know the selenium status of the ration as a whole before making a decision to adopt the supplementation of selenium yeast.

There is vast literature on the effect of vitamin E on milk quality (somatic cell count) and mastitis incidence; however, the evidence for an effect on uterine health and fertility is limited. Supplementation with 3000 IU vitamin E/cow/day in the late dry period is recommended because it is generally associated with decreased risk of mastitis postpartum (Politis, 2012).

Few studies have looked at the effect of vitamin E supplementation, beyond what is provided in the feed, on uterine health. In a review of the available literature, Allison and Laven (2000) stated that there appeared to be little benefit of high levels of vitamin E (at least 1000 iu per day) supplementation during the dry period on infectious diseases other than mastitis. They said that in herds with a history of selenium deficiency and a high incidence of RP, supplementation of vitamin E, in conjunction with selenium, could reduce RP, but the evidence for an effect of supplementation on other reproductive diseases was limited. In one study where 2100 mg of vitamin E and 7 g of sodium selenite were supplemented by intramuscular administration 2 weeks before calving and on the day of calving, there was a tendency (P = 0.055) for reduced incidence of RP, but there was no effect on time to conception (Bourne *et al*., 2008). In another study where daily supplementation with 1,610 mg of RRR-α-tocopherol (vitamin E) was performed from 4 weeks before to 2 weeks after calving, a reduction in the proportion of stillbirths was observed, but again no effect on long term fertility was observed (Persson *et al*., 2007).

Supplementation with injectable trace minerals has produced controversial results. Studies have found that additional supplementation of trace minerals can have a negative (Vanegas *et al*., 2004), positive (Sales *et al*., 2011), or neutral effect on reproductive performance (Vanegas *et al*., 2004). Vanegas *et al*. (2004) observed that trace mineral supplementation (Cu, Mn, and Zn) postpartum did not affect cow reproductive performance; however, supplementation pre and postpartum decreased reproductive performance. On the other hand, a recent study observed that trace mineral supplementation (Cu, Mn, Zn, and Se) before and after calving reduced the incidence of stillbirth and endometritis; nonetheless, it did not affect RP, metritis, or long term fertility (Machado *et al*., 2013). In a study performed with crossbred heifers, there was an increase in the conception rate (embryo survival) of heifers that received a trace mineral supplementation (Cu, Mn, Zn, and Se) 17 days prior to embryo transfer (Sales *et al*., 2011). An excellent meta-analysis was performed by Rabiee *et al*. (2010) on the effects of feeding organic trace minerals (OTM) on milk yield and reproductive performance in lactating dairy cows. They observed that feeding organic trace minerals significantly increased milk production by 0.93 kg/day, milk fat yield by 0.04 kg/day, and milk protein yield by 0.03 kg/day. However, the response to supplementation with OTM was not consistent across trial. Meta-regression analysis showed that milk production increased with the use of other supplements (e.g., monensin) and for 4-Plex versus Availa-4. Feeding OTM before calving and feeding for a full lactation after calving also increased milk production. Supplementation of cows with OTM reduced days open by 13.5 days and the number of services per conception by 0.27 units. The risk of pregnancy by 150 days in lactation was greater in cows fed OTM, but OTM had no significant effect on the interval from calving to first service or on the 21-day pregnancy rate. Although supplementation of vitamins and trace mineral remain controversial, there is a mounting body of evidence pointing to its beneficial effect.

Because of the importance of energy balance on the incidence of uterine disease, nutritional supplements that prevent ketosis may be an important component for the prevention of uterine diseases. Two nutritional supplements, monensin, and choline have shown consistent results on the improvement of energy balance and fat metabolism, respectively (Zahra *et al*., 2006). Monensin has been shown to increase glucose concentrations postpartum, and both monensin and choline have been shown to decrease ketosis postpartum; therefore, they are expected to have a positive impact on uterine health (Zahra *et al*., 2006; Lima *et al*., 2012). In one study (Lima *et al*., 2012), feeding rumen protected choline pre and postpartum reduced the incidence of clinical ketosis, and mastitis; however, it did not influence cyclicity or conception rates. Feeding rumen protected choline postpartum only, had mixed results.

Administration of a wide range of drugs (PGF2α, oxytocin, estradiol, NSAIDs, antibiotics) is commonly performed in dairy cows, particularly in cows with RP or dystocia, in an attempt to prevent uterine diseases. The benefits of such use are controversial. Because the mechanism of release of the placenta mainly involves the action of leukocytes and collagenase, the use of PGF2α or oxytocin are not expected to be helpful (Beagley *et al*., 2010). In two very nice reviews of the literature (Frazer, 2005; Beagley *et al*., 2010), both authors did not recommend the use of either PGF2α or oxytocin for prevention or treatment of RP because these hormones are not major players in the release of the placenta and they are already increased in cows with RP. Nonetheless, some studies have observed a reduction in the incidence of RP when either PGF2α (Stocker *et al*., 1993) or oxytocin (Mollo *et al*., 1997) are used; however, several other studies have found no effect (Garcia *et al*., 1992; Stevens and Dinsmore, 1997; Drillich *et al*., 2005; Palomares *et al*., 2010). In both reviews (Frazer, 2005; Beagley *et al*., 2010), it is recommended that manual removal should not be attempted because it decreases uterine defense mechanisms (Paisley *et al*., 1986; Peters and Laven, 1996) and impairs subsequent fertility (Bolinder *et al*., 1988). Nonsteroidal anti-inflammatory drugs are also commonly used in the attempt to prevent uterine diseases; however, counter intuitively, its use has caused a decrease in DMI and an increase in the degree of negative energy balance; therefore, leading to an increase in the risk of RP and metritis (Waelchli *et al*., 1999; Duffield, *et al*., 2009; Shwartz *et al*., 2009). For this reason, the prophylactic use of NSAIDs is not

recommended. Estradiol has also been used for prevention of metritis in cows with RP (Risco and Hernandez, 2003) and other risk factors such as dystocia stillbirth and twins (Overton *et al*., 2003); however, its use is not recommended because it does not prevent metritis (Risco and Hernandez, 2003; Overton *et al*., 2003) and is detrimental to fertility (Risco and Hernandez, 2003). The only known drug shown to release the placenta is collagenase. Administration of 20,000-200,000 U of bacterial collagenase into the umbilical artery has been shown to prevent RP or to hasten release of the placenta in several studies (Eiler and Hopkins, 1993; Eiler *et al*., 1997; Guerin *et al*., 2004); however, long term effects of uterine health or fertility have not been carried out. The most consistent results for prevention of metritis have been the treatment of cows with RP with antibiotics. Several studies have shown that the incidence of metritis (Overton *et al*., 2003; Risco and Hernandez, 2003; McLaughlin *et al*., 2013) or endometritis (Dubuc *et al*., 2011) can be decreased with systemic antibiotic administration; however, some studies have found no effect on the prevention of metritis (Drillich *et al*., 2006; Dubuc *et al*., 2012) and no study have found a positive impact of treatment of cows with RP on long term fertility, culling, or milk production (Overton *et al*., 2003; Risco and Hernandez, 2003; Goshen and Shpigel, 2006; Dubuc *et al*., 2011; McLaughlin *et al*., 2013). Furthermore, in the USA, the FDA has banned the use of ceftiofur (the only molecule with no milk withdrawal) for preventative treatment. Therefore, prophylactic antibiotic treatment should be based on welfare, economical, and legal considerations.

Conclusions

Given that most treatments are not very efficacious, efforts should be focused on management strategies to decrease metabolic problems such as hypocalcemia and ketosis, and to prevent risk factors such as dystocia, male calves, abortions, stillbirths, and RP.

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