

Identifying and Treating Uterine Disease in Dairy Cows

Klibs N. Galvão

Assistant Professor, Department of Large Animal Clinical Sciences,
College of Veterinary Medicine, University of Florida
PO Box 110136, Gainesville, FL 32610
galvaok@ufl.edu

Introduction

Uterine diseases can be classified as puerperal metritis, clinical metritis, clinical endometritis and subclinical endometritis (Sheldon et al., 2006). These diseases are highly prevalent in high producing dairy cows and have been associated with decreased pregnancy per AI, extended interval to pregnancy, increased culling, and economic losses (Bartlett et al., 1986; Sheldon and Dobson, 2004; Gilbert et al., 2005). Metritis affects about 20.0% of lactating dairy cows, with the incidence ranging from 8 to > 40% in some farms (Curtis et al., 1985; Galvão et al., 2009; Goshen and Shpigel, 2006; Hammon et al., 2006; Huzzey et al., 2007). Clinical endometritis also affects about 20.0% of lactating dairy cows, with the prevalence ranging from 5.0 to >30% in some herds (Galvão et al., 2009; LeBlanc et al., 2002; McDougall et al., 2007). Subclinical endometritis is the most prevalent of all uterine diseases; it affects ~ 30% of lactating dairy cows, with the prevalence ranging from 11 to >70% in some herds (Barlund et al., 2008; Galvão et al., 2009; Gilbert et al., 2005; Hammon et al., 2006; Kasimanickam et al., 2004).

Retention of fetal membranes is a condition where the cow fails to release the placenta 12 or 24 h after calving. Although retention of fetal membranes is not a disease per se, many researchers have tried to treat (systemically or intrauterine) this condition because it is a major risk factor for metritis (Drillich et al., 2006; Goshen and Shpigel, 2006; Risco and Hernandez, 2003). Although treatment has been found to prevent metritis (Risco and Hernandez, 2003), it has not been found to improve fertility or milk yield (Drillich et al., 2006; Goshen and Shpigel, 2006; Risco and Hernandez, 2003); therefore it will not be emphasized in this paper. Pyometra is characterized by a pus filled uterus in the presence of a corpus luteum (CL) and a closed cervix (Sheldon et al., 2006). Pyometra can be considered a sub-set of endometritis where cows ovulate in the presence of a contaminated uterus. Common treatment is administration of PGF2 α .

Identification

Metritis

Puerperal metritis is characterized by the presence of an abnormally enlarged uterus, a fetid watery red-brownish uterine discharge associated with signs of systemic illness, and fever (> 103 °F) within 21 days in milk (DIM). Animals without systemic signs but with an enlarged uterus and a purulent uterine discharge within 21 DIM may be classified as having clinical metritis (Sheldon et al., 2006). Metritis is diagnosed by a complete physical examination of the cow including attitude, hydration status, rectal temperature, and palpation of the uterus per

rectum to evaluate uterine discharge. Evaluation of rectal temperature should be performed before palpation per rectum. A Florida study (Benzaquen et al., 2007) observed that a high proportion (~ 60%) of cows did not have fever (> 103.0 °F) at the time puerperal metritis was diagnosed, indicating that this condition is not always accompanied by a fever. This finding suggests that diagnosis and treatment consideration for puerperal metritis should include the character of the uterine discharge (fetid or not) and the attitude of the cow, besides measurement of rectal temperature. Cows diagnosed with metritis without a fever were just as likely to later develop clinical endometritis as cows with metritis and a fever. This indicates that metritis without a fever might have the same negative effects on fertility as metritis without a fever (Benzaquen et al., 2007).

Cows diagnosed with metritis (puerperal or clinical) should be evaluated for concurrent metabolic or infectious disease (ketosis, displaced abomasum, mastitis, pneumonia, etc) since this conditions are associated (Curtis et al., 1985). Vaginal examination is not performed on a routine basis but can be performed to aid in diagnosis if a cow has a fever of unknown origin and no uterine discharge can be produced after palpation of the uterus per rectum. Care should be taken to wash the vulva with antiseptic solution (e.g. iodine scrub) and to use a clean well lubricated palpation sleeve (Williams et al., 2005). Dairies should have a clear standard operating procedure on when to evaluate cows for metritis and how to identify them. Metritis can occur at any time after calving, even after 21 DIM; however, most of the cases (~95%; 44/753); occur in the first 14 DIM with a peak around 5-7 DIM (**Fig. 1**).

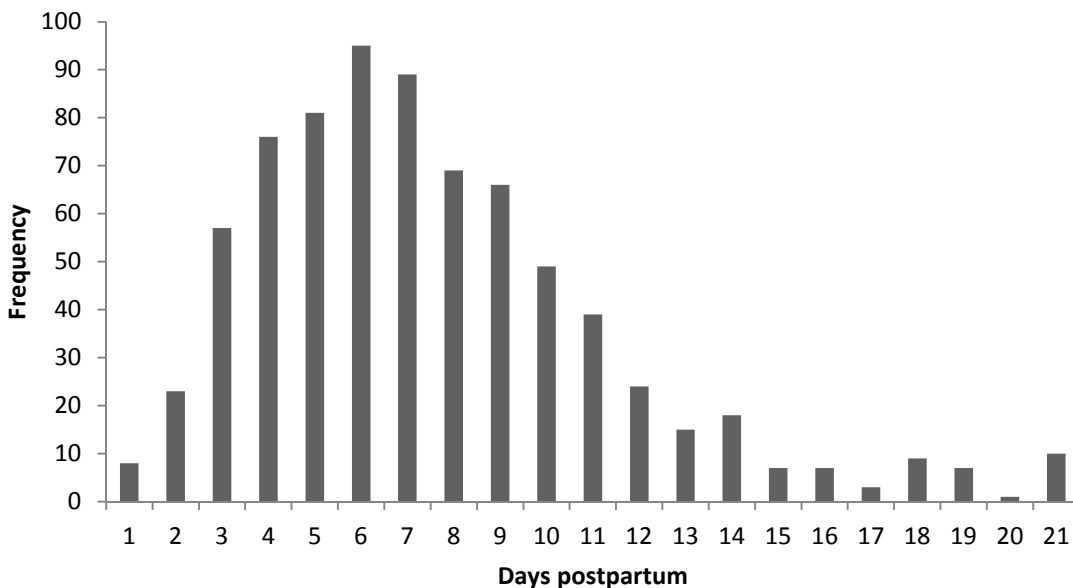


Figure 1. Frequency distribution of metritis incidence by days postpartum in a sample of 753 metritis cases that occurred over a one year period in dairies in Ohio, New York, and California.

Because of this concentration in incidence of metritis in the first 14 DIM, and in an effort to target monitoring of cows, different strategies have been proposed. Pfizer (Pfizer Animal Health, New York, NY) devised what is called the 100-day contract for health and reproductive management. Part of that program includes daily monitoring of fresh cows in the first 10 DIM. Although monitoring cows in the first 10 DIM would be sufficient to diagnose most of the cows, a substantial proportion (~20%; 140/753) would be missed. At the University of Florida Dairy Unit, a combination of targeted monitoring of all cows at 4, 7, and 12 DIM in combination with physical examination of cows with milk deviation of more than 12% or failure to increase milk yield at least 4 (primiparous) or 7% (multiparous) per day in the first 20 DIM have proven very efficacious in diagnosing cows with metritis and metabolic diseases (ketosis and displaced abomasum). Although the system has proven effective, it requires individual daily milk weights. Others have targeted the first 13 (Benzaquen et al., 2007) or 14 DIM (Galvão et al., 2009) for daily monitoring. Regardless of the monitoring regimen adopted, compliance with the protocol and skill of the evaluator is paramount to the success of the monitoring program.

Endometritis

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). Clinical endometritis is usually diagnosed by evaluation of uterine discharge detected in the vagina with the aid of a speculum (LeBlanc et al., 2002), the Metricheck tool (McDougall et al., 2006), or a gloved hand (Williams et al., 2005). When using either one of these methods, care should be taken to clean the vulva, to avoid introduction of contaminants into the vagina, and to use lubrication. When using vaginoscopy, the speculum should be introduced into the vagina up to the level of the external os of the cervix, and inspection of the discharge is performed with the aid of a flash light. When using the Metricheck tool (Metricheck, Simcro, New Zealand), the device should be introduced into the vagina up to the level of the external os of the cervix and the discharge should be scooped for evaluation after exteriorization of the device. When using a gloved hand, the hand should be introduced into the vagina up to the level of the external os of the cervix and the discharge should be scooped for evaluation after exteriorization of the hand.

In the absence of clinical endometritis, 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). Uterine cytology samples can be collected using the cytobrush (Kasimanickam et al., 2004) or the low-volume uterine lavage (Gilbert et al., 2005) technique. For the cytobrush, a Pap smear cytology brush is attached to a metal rod that is fitted through a metal pipe similar in diameter to an insemination pipette (**Fig. 2**). The tool is protected with a plastic sheath protector during insertion into the vagina, and then is exposed for passing through the cervix. At the uterine body, the cytobrush is exposed and the body wall is pressed slightly against the cytobrush while the cytobrush is rolled two or three times. After that, the tool is exteriorized, and the cytobrush is smeared onto a glass slide and air dried before staining using Diff-Quick stain.

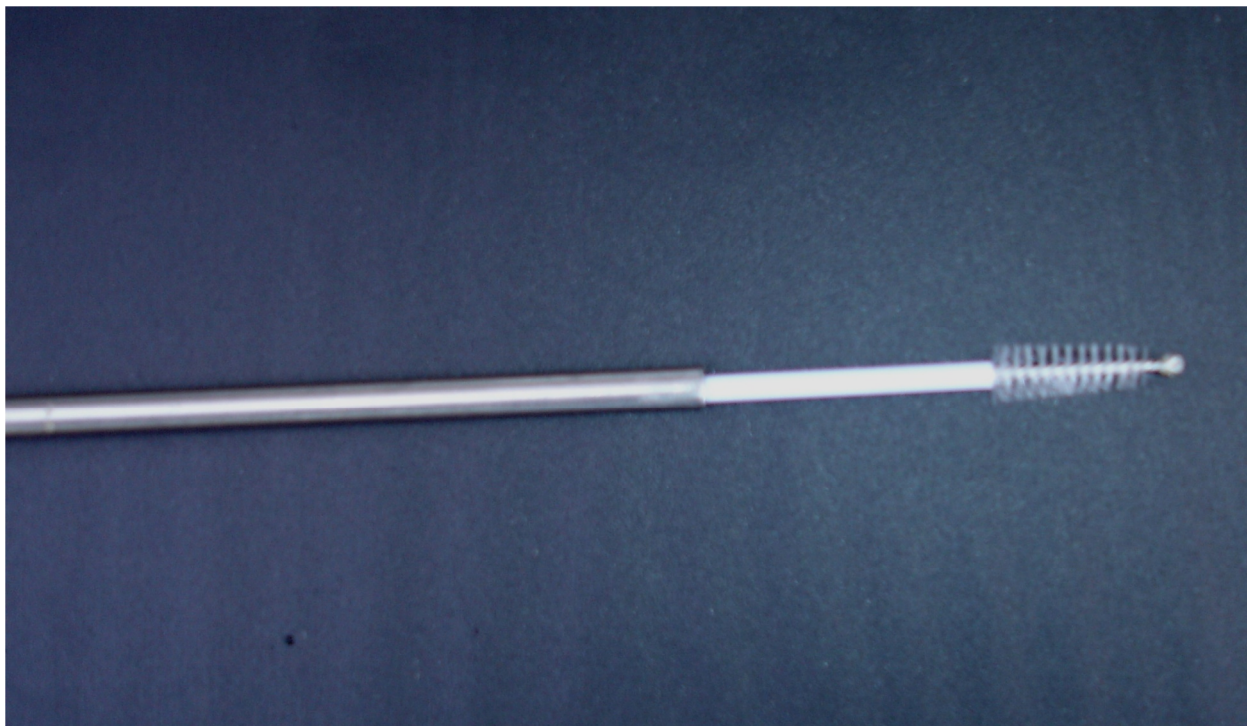


Figure 2. Cytology tool with cytobrush attached.

For the low-volume uterine lavage, an infusion pipette is protected with a sanitary chemise, which is punctured before the pipette is passed through the cervix. At any place in the uterus, 10-20 ml of sterile saline solution is infused, the uterus is then massaged and a portion (≥ 5 ml) is harvested. A folley catheter can also be used to perform a low volume lavage in a manner similar to embryo flushing (Galvão et al., 2009). After collection, the sample needs to be centrifuged in a conventional or cytospin centrifuge. If using a conventional centrifuge, most of the supernatant needs to be discarded and one drop of the remaining fluid is smeared onto a glass slide. For the cytospin, ~ 150 μ l of the collected sample is loaded in the cytospin container and centrifuged at 700 g for 5 min. Then, slides are air dried and stain using Diff-Quick. After staining, all cells, including epithelial cells but excluding erythrocytes, are counted under the microscope, and the proportion of PMN out of a total of 200 cells is calculated.

Endometritis has been diagnosed by detection of fluid in the uterus using ultrasonography (Kasimanickam et al., 20045). Nonetheless, this method was found to be less sensitive than endometrial cytology (Balund et al., 2008).

Treatment

Metritis

The most common method of treatment is either intrauterine (Galvão et al., 2009; Goshen and Shpigel, 2006; Kasimanickam et al., 2005; LeBlanc et al., 2002; Thurmond et al., 1993) or systemic (Chenault et al., 2004) antibiotic administration. Currently, in the USA, there is no

approved antibiotic for intrauterine administration in dairy cows. There is only one approved antibiotic for systemic administration for treatment of metritis in dairy cows; ceftiofur hydrochloride (Excenel[®], Pfizer Animal Health, New York, NY), which is a broad-spectrum third-generation cephalosporin in an oil suspension. The recommended dose is for treatment of metritis in postpartum dairy cows is 2.2 mg/Kg of body weight intramuscularly. Although systemic administration of ceftiofur hydrochloride improves clinical signs of metritis (Chenault et al., 2004), the effects on fertility have not been evaluated. On the other hand, intrauterine treatment with 5 g chlortetracycline twice weekly for 2 weeks prevented the negative effects of metritis on fertility and on milk yields in multiparous cows (Goshen and Shpigel, 2006); however, this treatment is not approved in the USA and would lead to long milk withdrawals. Assuming that the treatment would cost \$10.00 and milk would be discarded for 21 d, the overall cost would be \$ 199.00 (60 lbs x 21 x \$15.00 cwt = 189 + 10 = 199). Cows that received this treatment regimen produced 1438 lbs more milk and conceived 29 d sooner; therefore the return would be \$273.70 ((1438 / 100 x 15) + (29 x \$2.00 per additional day open)), and the net profit \$74.70.

Other ceftiofur products have been used in exchange for ceftiofur hydrochloride (Excenel[®]); namely, ceftiofur sodium (Naxcel[®]) and ceftiofur crystalline free acid (Excede[®]). Particularly Excede[®] has been widely adopted as the first antibiotic choice for treatment of metritis in many dairies because it has a long-acting formulation (5 days above the minimum inhibitory concentration for pathogens associated with respiratory disease). Nonetheless, producers and veterinary practitioners need to be aware that this product was not approved for the treatment of metritis; therefore, minimum inhibitory concentrations or dose of administration have not been established. With Excenel[®] for example, only the higher dose (2.2 mg/Kg of BW) was effective; therefore, more information is needed before Excede[®] can be indicated for the treatment of metritis.

Endometritis

A formulation containing 500 mg of cephalirin benzathine in 19 g emulsifier (Metricure[®], Intervet, Boxmeer, The Netherlands) is approved for treatment of clinical endometritis by intrauterine administration in Canada, Europe, New Zealand, Australia, and other countries around the world. Intrauterine infusion of Metricure[®] improved reproductive performance of cows with clinical endometritis (LeBlanc et al., 2002). In the same study, treatment with prostaglandin F_{2α} (PGF_{2α}) was found to be intermediate. Treatment with Metricure[®] was also found to improve fertility in cows with a history of retained fetal membranes, stillbirths, or a vulval discharge after 13 DIM (McDougall, 2001). Nonetheless, a formulation containing 125 mg of ceftiofur hydrochloride in 10 mL oil-based sterile suspension (Spectramast LC, Pfizer Animal Health, New York, NY) labeled for treatment of clinical mastitis was shown to reduce the bacterial contamination of dairy cows with clinical endometritis; however, it did not improve fertility (Galvão et al., 2009a).

Although there is no approved treatment for subclinical endometritis, Metricure[®] was found to improve reproductive performance of cows with SCE (Kasimanickam et al., 2005). Interestingly, in that study, PGF_{2α} had a similar beneficial effect (Kasimanickam et al., 2005). In another study, PGF_{2α} improved fertility in cows with subclinical endometritis at 35 DIM

(Fig. 3), but not in cows that still had endometritis at 49 DIM (Galvão et al., 2009b). Median days open for cows treated with PGF2 α was significantly decreased compared to controls (124 vs. 160 d; P < 0.05).

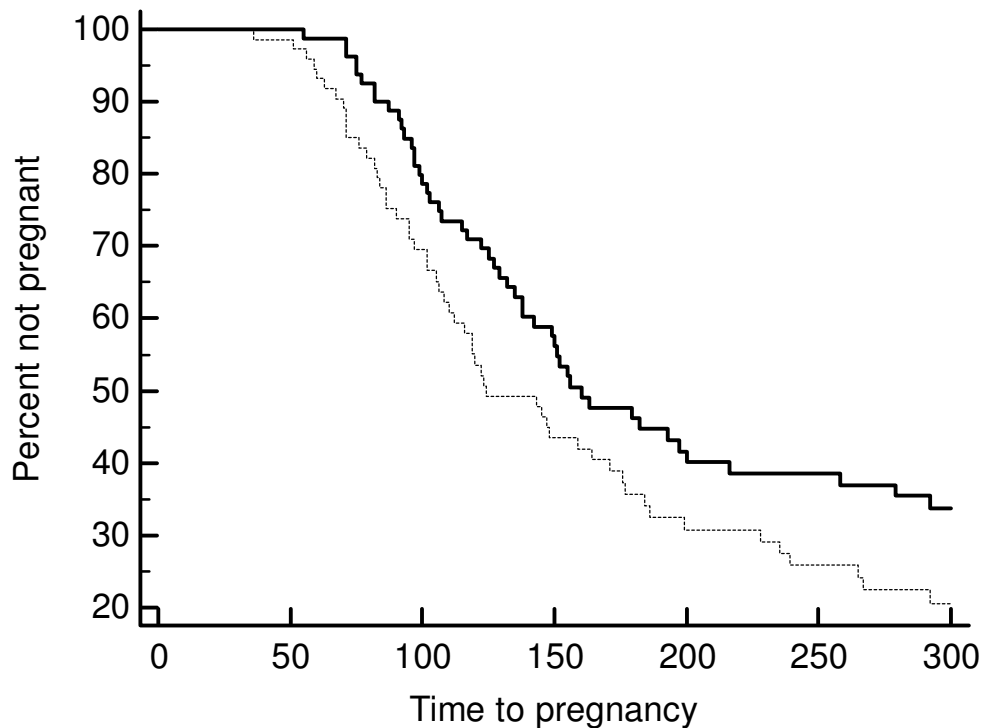


Figure 3. Survival analysis for time to pregnancy in cows that had subclinical endometritis at 35 DIM and did (dashed line) or did not receive PGF2 α at 35 and 49 DIM.

The benefit from PGF2 α administration is believed to arise from induction of estrus in cows having a PGF2 α -responsive corpus luteum; the estrus leads to physical expulsion of bacterial contaminants and inflammatory products as well as a possible improvement in the uterine defenses under low progesterone (Kasimanickam et al., 2005). It is generally agreed that a high-progesterone environment suppresses cervical mucus production, myometrial contractility, uterine-gland secretion and the phagocytic activity of uterine neutrophils (Frank et al., 1983; Hussain, 1989; Bondurant, 1999), and is therefore permissive to uterine infection. PGF2 α is not only luteolytic but also appears to have pro-inflammatory actions that might enhance neutrophil function (Lewis, 2004). Because there is increased concern about bacterial acquisition of antibiotic resistance, PGF2 α might provide an efficacious method of treatment of endometritis.

Conclusions

Uterine diseases are prevalent in high producing dairy cows, and require prompt diagnosis and treatment. Metritis can be successfully treated either by systemic or intrauterine antibiotic

treatment. Ceftiofur hydrochloride (Excenel[®]) intramuscularly was effective in treating metritis, and oxytetracycline intrauterine was effective in abrogating the negative effects of metritis on milk yield and fertility. Although ceftiofur crystalline free acid (Excede[®]) is routinely been used, more research is needed before this formulation can be safely recommended for the treatment of metritis. Intrauterine administration of cephalixin benzathine (Metricure[®]) or intramuscular administration of PGF₂ α seem effective in the treatment of endometritis (clinical or subclinical); although results are not consistent. Nonetheless, Metricure[®] is not available in the USA.

References

- Barlund CS, Carruthers TD, Waldner CL, and Palmer CW. 2008. A comparison of diagnostic techniques for postpartum endometritis in dairy cattle. *Theriogenology* 69:714-723.
- Benzaquen ME, Risco CA, Archbald LF, Melendez P, Thatcher MJ, and Thatcher WW. 2007. Rectal temperature, calving-related factors, and the incidence of puerperal metritis in postpartum dairy cows. *J. Dairy Sci.* 90:2804-2814.
- BonDurant RH. 1999. Inflammation in the bovine female reproductive tract. *J. Animal Sci.* 77(Suppl 2):101-110.
- Curtis CR, Erb HN, Sniffen CJ, Smith RD, and Kronfeld DS. 1985. Path analysis of dry period nutrition, postpartum metabolic and reproductive disorders, and mastitis in Holstein cows. *J. Dairy Sci.* 68:2347-2360.
- Drillich M, Reichert U, Mahlstedt M, and Heuwieser W. 2006. Comparison of two strategies for systemic antibiotic treatment of dairy cows with retained fetal membranes: preventive vs. selective treatment. *J. Dairy Sci.* 89:1502-1508.
- Frank T, Anderson KL, Smith AR, Whitmore HL, and Gustafsson BK. 1983. Phagocytosis in the uterus: a review. *Theriogenology* 20:103-110.
- Galvão KN, Greco LF, Vilela JM, Sá Filho MF, and Santos JEP. 2009a. Effect of intrauterine infusion of Ceftiofur on uterine health and fertility in dairy cows. *J. Dairy Sci.* 92:1532-1542.
- Galvão KN, Frajblat M, Brittin SB, Butler WR, Guard CL, and Gilbert RO. 2009b. Effect of prostaglandin F₂ α on subclinical endometritis and fertility in dairy cows. *J. Dairy Sci.* 92:4906-4913.
- Gilbert RO, Shin ST, Guard CL, Erb HN, and Frajblat M. 2005. Prevalence of endometritis and its effects on reproductive performance of dairy cows. *Theriogenology* 64:1879-1888.
- Hammon DS, Evjen IM, Dhiman TR, Goff JP, and Walters JL. 2006. Neutrophil function and energy status in Holstein cows with uterine health disorders. *Vet. Immunol. Immunopathol.* 113:21-29.
- Hussain, A. M. 1989. Bovine uterine defense mechanism: a review. *J. Vet. Med. B.* 36:641-651.
- Huzzey JM, Veira DM, Weary DM, and von Keyserlingk MA. 2007. Parturition behavior and dry matter intake identify dairy cows at risk for metritis. *J. Dairy Sci.* 90:3220-3233.
- Kasimanickam R, Duffield TF, Foster RA, Gartley CJ, Leslie KE, Walton JS, and Johnson WH. 2004. Endometrial cytology and ultrasonography for the detection of subclinical endometritis in postpartum dairy cows. *Theriogenology* 62:9-23.
- Kasimanickam R, Duffield TF, Foster RA, Gartley CJ, Leslie KE, Walton JS, and Johnson WH. 2005. The effect of a single administration of cephalixin or cloprostenol on the

- reproductive performance of dairy cows with subclinical endometritis. *Theriogenology* 63:818-830.
- LeBlanc SJ, Duffield TF, Leslie KE, Bateman KG, Keefe GP, Walton JS, and Johnson WH. 2002. Defining and diagnosing postpartum clinical endometritis and its impact on reproductive performance in dairy cows. *J. Dairy Sci.* 85:2223-2236.
- Lewis GS. 2004. Steroidal regulation of uterine immune defenses. *Anim. Reprod. Sci.* 82-83:281-294.
- McDougall S, Macaulay R, and Compton C. 2007. Association between endometritis diagnosis using a novel intravaginal device and reproductive performance in dairy cattle. *Anim. Reprod. Sci.* 99:9-23.
- Risco CA and Hernandez J. 2003. Comparison of ceftiofur hydrochloride and estradiol cypionate for metritis prevention and reproductive performance in dairy cows affected with retained fetal membranes. *Theriogenology* 60:47-58.
- Sheldon IM, Lewis GS, LeBlanc S, and Gilbert RO. 2006. Defining postpartum uterine disease in cattle. *Theriogenology* 65:1516-1530.
- Williams EJ, Fischer DP, Pfeiffer DU, England GC, Noakes DE, Dobson H, and Sheldon IM. 2005. Clinical evaluation of postpartum vaginal mucus reflects uterine bacterial infection and the immune response in cattle. *Theriogenology* 63:102-117.

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