Postpartum Uterine Diseases: Prevalence, Impacts, and Treatments

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Take Home Messages

- All cows deal with uterine bacterial contamination during the first days after calving but only a proportion of them will experience uterine diseases.
- Postpartum uterine diseases are associated with greater uterine bacterial contamination and reduced immune function.
- Cows affected by metritis should be treated with systemic antibiotic.
- Purulent vaginal discharge after 30 days in milk (DIM) is associated with a detrimental impact on subsequent reproductive performance, can be easily diagnosed on farms, and can be effectively treated with intrauterine infusion of cephapirin.
- Cytological endometritis after 30 DIM is associated with a detrimental impact on subsequent reproductive but is difficult to diagnose on farms and lacks a proven effective treatment.

Introduction

Reproduction is crucial in dairy production because of the necessity for a cow to calve on a regular basis in order to produce milk and provide economic sustainability to the farmer. Various factors can influence reproductive performance in dairy cows including estrus detection, breeding management, and postpartum uterine diseases. The objectives of this paper are to highlight the importance of postpartum uterine diseases and to review their prevalence, impacts and treatments.

WCDS Advances in Dairy Technology (2011) Volume 23: 255-267

■ Origin of Uterine Inflammation

During pregnancy, the uterine lumen is sterile. At calving, the cervix opens, allows the calf to be born, and remains open for many subsequent days. During this time period, bacterial contamination of the uterus will occur in greater than 95% of cows (Sheldon and Dobson, 2004). Based on these data, it is legitimate to assume that all cows are affected. A wide variety of bacteria can be isolated from uteri of postpartum cows, including aerobic and anaerobic bacteria (Sheldon, 2004). Bacterial contamination of uteri declines over the weeks following calving (Sheldon et al., 2006). In the first 10 DIM, bacteria frequently found include *Escherichia coli* (E. Coli), *Arcanobacterium pyogenes* (A. pyogenes), *Streptococcus* spp., *Staphylococcus* spp., *Pseudomonas* spp., *Fusobacterium necrophorum* (F. necrophoprum), *Prevotella melaninogenicus* (P. melaninogenicus), and *Clostridium* spp. (Sheldon and Dobson, 2004). Bacterial pathogens have been categorized as recognized uterine pathogens, potential uterine pathogens, and opportunistic contamination bacteria. This classification is somewhat subjective but is based on their relationship with endometrial inflammation and clinical uterine disease. Recognized uterine pathogens include A. pyogenes, E. coli, P. melaninogenicus, and F. necrophorum (Sheldon et al., 2006).

Presence of bacteria in the uterus is detected by receptors, such as the toll-like receptors (TLR) group. These TLR detect a wide range of pathogen-associated molecular patterns (Akira et al., 2006). For example, TLR-4 detects cell wall particles from Gram-negative bacteria, such as E. coli. Once detected, cells of the endometrium (inner layer of the uterus) release a great variety of chemical messengers that activate the immune response (Singh et al., 2008). Leukocytes, mainly neutrophils, respond to this activation by migrating to the infection site. Once on-site neutrophils ingest and destroy bacteria leading to a reduction of bacterial load over time.

■ Disease Definitions

Although the uterus of most cows is contaminated during the postpartum period, not all cows will develop uterine diseases. A prompt and adequate immune response plays an important role in controlling excessive bacterial growth. When bacterial growth exceeds the capacity of the immune system, clinical uterine disease appears. Metritis and endometritis are terms commonly used to describe uterine disease and are sometimes taken as equivalent or interchangeable. From a practical point of view, this discrepancy in terminology may appear trivial but it has a major impact when comparing results from studies using different terms. In order to address this situation, Sheldon et al. (2006) proposed standardized definitions of metritis and endometritis. Although it could be argued that these definitions might not be

totally accurate, they will be used in this manuscript because they represent the current state of the art.

Metritis is defined as an acute systemic illness due to bacterial infection of the uterus occurring within the first 20 DIM. It is characterized by a fetid brown-red watery vaginal discharge, fever, and signs of systemic illness (reduced milk yield and feed intake, dullness, dehydration).

Endometritis is defined as uterine infection or inflammation after 21 DIM without systemic signs of illness. Because severe illness or death cannot be used to diagnose the condition, studies have defined endometritis based on subsequent reproductive performance. In other words, diagnostic criteria associated with detrimental impacts on subsequent reproductive performance were determined and used. A recent study (Dubuc et al., 2010a) confirmed that 2 independent conditions can affect subsequent reproductive performance: 1) presence of purulent vaginal discharge (PVD) and; 2) presence of a high proportion of inflammatory cells in the endometrium (cytological endometritis; CYTO). Overall, data from that study suggested that both PVD and CYTO had individual detrimental impacts on reproduction, and that those effects were additive when present simultaneously. These data also suggested that PVD terminology may be more accurate than clinical endometritis (former terminology) because most cows affected by PVD did not have endometrial inflammation (endometritis) at the time of diagnosis.

Retained placenta (RP) is another condition considered as a uterine disease. However, RP has no impact on milk production, reproduction, and culling if the condition does not evolve to metritis, PVD, or CYTO. A complete and practical review of RP is beyond the scope of this paper but may be found elsewhere (LeBlanc, 2007).

■ Metritis

Prevalence

Prevalence of metritis may vary between studies depending on the disease definition used. Using proposed standardized definitions, metritis affects 10 to 20% of dairy cows in Canada and USA (Overton and Fetrow, 2008; Dubuc et al., 2010b). An important risk factor for metritis is RP. In fact, 30 to 50% of cows with RP will develop metritis (LeBlanc, 2007). Retained placenta is defined as retention of fetal membranes 24 hours after parturition (Kelton et al., 1998). The proposed contribution of RP in the development of metritis is in providing an ideal environment for bacterial growth, mainly because of the presence of a large amount of necrotic tissue and delay of its expulsion from the uterus (Kaneene et al., 1986; Bolinder et al., 1988; Sheldon, 2004).

Association between RP and metritis may also be explained by the impaired immune response occurring in both circumstances, which may presumably be linked (Gunnink, 1984; Hammon et al., 2006). Other reported risk factors for metritis include twins, dystocia, stillbirth, abortion, milk fever, negative energy balance, and deficiency in hygiene (Bartlett et al., 1986; Correa et al., 1993). Overall, risk factors for metritis can be summarized simplistically in two main categories: factors increasing uterine bacterial contamination and factors reducing immune function.

Impact

The impact of metritis on milk production remains unclear as some studies found a detrimental impact and others did not. When reported as detrimental, the effect of metritis is influenced by parity and stage of lactation. The magnitude of this impact in multiparous cows is between 2 and 13 kg of milk per day during a period that can vary from 2 to 20 weeks (Overton and Fetrow, 2008; Wittrock et al., 2009). Overall, it may represent a production loss of 100 to 2,000 kg per lactation. Milk production of primiparous cows was not affected by metritis in multiple studies (Wittrock et al., 2009; Dubuc et al., in press1). It is unclear why primiparous cows do not experience milk production losses compared to multiparous cows. It has been suggested that lactation curve difference between primiparous and multiparous cows may be involved (Dubuc et al., in press1).

The impact of metritis on reproduction and culling is unclear. Some data suggest that metritis decreases subsequent reproductive performance and increases culling (Gröhn et al., 1998). However, other data suggest that the impacts of metritis on reproduction and culling are from the increased risk of reproductive diseases later in lactation (PVD and CYTO; Dubuc et al., in press1). In summary, it may be assumed that metritis increases the risk of being culled in early lactation because of poor milk production performance. However, the impact of metritis on reproductive performance is likely mediated through PVD and CYTO.

Treatment

Numerous studies have investigated therapies for metritis. A lot of these studies had major weaknesses such as poor study design and small sample size. Disease definition is a major problem when comparing these studies because a clear case definition is not always presented. Nonetheless, 2 approaches are commonly used to treat metritis: systemic and intrauterine treatments.

Systemic Treatments

Systemic antibiotic therapy is the treatment of choice for cows affected by metritis. Penicillin and ceftiofur used as recommended by manufacturers in Canada (label) are efficacious for this purpose (Smith et al., 1998). Although fewer data are available, intramuscular administration of tetracycline may also represent a potential therapy (Schmitt et al., 2001). Currently, little evidence supports the use of anti-inflammatory drugs for alleviating the inflammatory process. However, this may change in the future as new studies are conducted. Conflicting data exist on repeated administration of prostaglandin (PGF) during the early postpartum period (<20 DIM). Overall, PGF was found to have very little success as therapy for RP and for the prevention of metritis (Archbald et al., 1990; Risco et al., 1994). Its use is not recommended.

Intrauterine Treatments

Although commonly used on farms, intrauterine antibiotic (oxytetracycline or ampicillin) or iodine therapies are not efficacious for treating metritis (Nakao et al., 1988; Stevens et al., 1995). Data from these studies even suggest that its use may be harmful or detrimental to subsequent reproductive performance. Intrauterine antibiotic therapy in addition to systemic penicillin or ceftiofur is not indicated because it does not improve efficacy compared to systemic antibiotic used alone (Drillich et al., 2001).

Practical Considerations

Diagnosis of metritis in fresh cows may be improved by performing systematic daily examination of these cows during the first 2 weeks after calving. When available, daily milk production and feed intake data may also serve as screening tools. Seeking an objective method for early detection and treatment, studies showed that rectal temperature monitoring alone during the postpartum period is inaccurate in predicting subsequent cases of metritis (Benzaquen et al., 2007). Focusing on cows with RP is a good idea as 30-50% of these cows will develop metritis. However, it is important to keep in mind that although RP is an important risk factor for metritis, only 35% of cows with metritis had an RP previously (Dubuc et al., 2010b). Once metritis is diagnosed in a cow, systemic antibiotic therapy is recommended. Standard treatment protocols should be developed with the help of your veterinarian. Data entry of disease information in farm records is crucial in order to assess the incidence of metritis at the herd level. Incidence greater than 15% in herds may indicate management issues that need to be addressed. Intuitively, preventive systemic antibiotic therapy on cows at high risk of having metritis (RP, dystocia, twins, stillborn) may seem appealing. However, numerous field clinical trials have failed to show a benefit of this for reducing the incidence of

metritis. Further research is needed to better identify cows that would benefit from preventive antibiotic therapy.

■ Purulent Vaginal Discharge

Prevalence

Purulent vaginal discharge was formerly known as clinical endometritis and reflects the presence of mucopurulent or purulent material in the vagina. It affects 20% of dairy cows between 21 and 40 DIM (LeBlanc et al., 2002a). Diagnosis of this condition can be performed by using a vaginoscope, a gloved hand, or a metricheck device. A metricheck device is a stainless steel probe with a semi-spherical rubber cup at the end. This device was invented in New Zealand and its use is becoming more popular in North America. Although there are some subtle differences, practically the use of any of these 3 techniques for diagnosing PVD provides similar results (Mcdougall et al., 2007; Runciman et al., 2009). Most commonly, vaginoscope and metricheck are used. Risk factors for PVD include RP, metritis, parity, and metabolic disorders such as ketosis, displaced abomasum, and hypocalcemia.

Impact

By definition, diagnostic criteria for PVD are established based on detrimental impact on subsequent reproduction. Therefore, PVD increases time to pregnancy by reducing pregnancy rate. The magnitude of this effect is similar between studies and is reported to be around 30 days (LeBlanc et al., 2002a; Dubuc et al., in press2). In other words, cows affected by PVD need on average 30 days longer to become pregnant than unaffected cows. This detrimental impact is important economically considering the cost of additional days open (roughly $3 per day per cow). Overall, it may represent a loss of $1,800 per year on an average 100-cow dairy farm. Because PVD is a localized chronic disease, it causes no direct loss of milk production or mortality (Fourichon et al., 1999). The impact of PVD on culling is not well described but it may be assumed that poorer reproductive performance may lead to greater risk of being culled in late lactation.

Treatment

Two main approaches are commonly used to treat PVD: 1) administration of one or more injections of PGF and; 2) administration of intrauterine antibiotic.

Use of Prostaglandin

The use of PGF for treating PVD is very common on dairy farms. However, a lot of conflicting data exist about such use and its efficacy remains unclear (Burton and Lean, 1995). There is little evidence to support the use of PGF before 3 weeks postpartum (Kristula and Bartholomew, 1998; Hendricks et al., 2006). Routine use of PGF after 30 DIM for treating PVD may be relevant but there is a lack of evidence to prove its efficacy. A major problem when performing studies investigating the impact of PGF for treating PVD is to avoid the use of PGF as an estrus synchronization protocol (i.e. to isolate the therapeutic effect on PVD from the estrus synchronization effect). In other words, using multiple injections of PGF for treating PVD and allowing cows to be bred after the last PGF injection may confer an advantage to the treated group of cows when evaluating subsequent reproductive performance. There are few well-designed large-scale studies that have addressed this issue. Studies that did so reported little to no benefit of using PGF (LeBlanc et al, 2002b; Dubuc et al., in press2).

Use of Intrauterine Antibiotic

The use of intrauterine antibiotic therapy for treating PVD has been studied at multiple times. No benefit was reported for infusing penicillin, ceftiofur, or tetracycline in the uterus after 25 DIM (Steffan et al., 1984; Sheldon and Noakes, 1998; Galvão et al., 2009b). On the other hand, intrauterine administration of cephapirin was shown repeatedly to improve reproductive performance in cows affected by PVD (LeBlanc et al., 2002b; McDougall, 2003; Runciman et al., 2008). These data support the use of cephapirin only after 26 DIM because no benefit was found earlier in the postpartum period (LeBlanc et al., 2002b).

Practical Considerations

Purulent vaginal discharge causes important economic losses in the dairy industry mainly because of its detrimental impact on reproductive performance. Fortunately, its diagnosis is simple (metricheck or vaginoscope) and can be performed systematically on all cows after 26 DIM. Cows presenting mucopurulent or purulent vaginal discharge benefit from treatment. The use of intrauterine infusion of cephapirin for treating these cows is strongly supported by literature. Systematic use of PGF after 21 DIM is beneficial as an estrus synchronization protocol but evidence is lacking for its benefit to treat PVD. In other words, cows given PGF show signs of estrus (which may include discharge from the uterus) but don't cure PVD at a greater rate than untreated cows.

■ Cytological Endometritis

Prevalence

Cytological endometritis is defined as an increased proportion of inflammatory cells in the endometrium after 21 DIM. This condition is often reported as subclinical endometritis. Although the reported prevalence of this disease is usually between 20 and 30%, some herds were found with a prevalence as high as 74% (Gilbert et al., 2005). Diagnosis of this condition is performed by obtaining a cytology sample from the endometrium (cytobrush or uterine lavage). Risk factors for CYTO are not as well studiedl as for PVD. It appears that risk factors for CYTO may be linked with decreased immune function during the postpartum period (Dubuc et al., 2010b).

Impact

Similarly to PVD, diagnostic criteria for CYTO are established based on subsequent reproductive performance. Most studies report that a proportion >5-10% of inflammatory cells in endometrial cytology after 30 DIM is associated with a detrimental effect on subsequent reproductive performance (Gilbert et al., 2005; Galvão et al., 2009a; Dubuc et al., 2010a). Affected cows have a lower pregnancy rate which leads to an increased time to pregnancy of 25 days on average. This condition is costly for dairy farmers. Assuming the cost of an additional day open of $3, this may represent a loss of $2,000 per year in an average 100-cow dairy farm. It may also represent a loss of $5,500 in a herd of similar size but with a greater proportion of cows being affected. Cytological endometritis has no impact on milk production. Little data exist about the impact of CYTO on culling but cows with poorer reproductive performance may presumably be at higher risk of being culled in late lactation.

Treatment

Similarly to PVD, two approaches are used for treating CYTO: the use of PGF and of intrauterine antibiotic.

Use of Prostaglandin

Based on currently available data, the use of PGF after 20 DIM might help to mitigate the detrimental impact of CYTO on reproductive performance (Kasimanickam et al., 2005). However, 2 larger similar studies investigating the same question did not find any benefit (Galvão et al., 2009a; Dubuc et al., in press2). It remains unclear is PGF is beneficial or not but current data suggest a lack of efficacy for treating CYTO.

Use of Intrauterine Antibiotic

Little data are available about the efficacy of intrauterine antibiotic use for treating CYTO. Intrauterine administration of cephapirin was suggested to be beneficial but the study was not repeated (Kasimanickam et al., 2005). Intrauterine administration of ceftiofur does not improve reproductive performance (Galvão et al., 2009b). Further research is needed to improve our knowledge on this topic.

Practical Considerations

Cytological endometritis is a disease that causes important economic losses to dairy farmers, mainly by its detrimental impact on reproductive performance. Diagnosis of the condition is not commonly performed on farms for 2 main reasons. Firstly, current diagnostic techniques cannot provide an immediate result (cow is affected by CYTO or not) so that it can be used as a convenient on-farm cow-side test. Secondly, there is little evidence of an effective treatment for CYTO. Current data suggest that intrauterine cephapirin may be beneficial, but further research is needed to confirm it. Practically, CYTO is of little interest for dairy farmers and veterinarians until a cow-side test is developed and a treatment is proven efficacious.

■ Conclusions

Postpartum uterine diseases cause important losses to dairy farmers. As for any important diseases affecting livestock, a systematic procedure to diagnose them becomes relevant only if subsequent action can be undertaken in an efficient and economical manner (e.g. treatment, culling, etc.). Metritis and PVD affect a large proportion of cows, have detrimental impacts on milk production and reproduction, can be easily and accurately diagnosed, and can be treated effectively. Thus, dairy farmers should be aware of these diseases and discuss with their veterinarians the establishment of diagnostic and treatment protocols. Cytological endometritis affects a large proportion of cows and has detrimental impact on reproduction, but cannot currently be easily diagnosed on farms and treated effectively. Thus, dairy farmers should be aware of this disease but no action should be undertaken until research provides further information.

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