Abstract

During the last two decades it has become clear that endometritis is a common postpartum disease of dairy cows, detrimentally affecting fertility and herd life. Endometritis is a separate and distinct condition from cervicitis; they may occur separately or together. Either condition may be associated with purulent vaginal discharge but need not be. A few cases of purulent vaginal discharge exist without evidence of endometritis or cervicitis. The effect on fertility of these conditions appears to be independent and additive. Endometritis is mostly mediated by negative energy balance in the periparturient period and cervicitis by obstetrical complications. The risk of both conditions is increased in cows that suffer puerperal metritis. Cephapirin specifically formulated for intrauterine infusion is effective in improving reproductive performance in affected cows but is not available in the USA. At present no other treatment has been convincingly shown to be effective.

Keywords: Cervicitis, cow, endometritis, postpartum, purulent vaginal discharge.

Introduction

In the early 1990’s there was disagreement on the importance of endometritis in bovine reproduction. While most believed intuitively that endometritis was bad for reproduction,1,2 this was certainly not universally accepted. In fact, at least one controlled study suggested that endometritis had no effect on reproduction of dairy cows3 and systematic studies of uterine bacteriology and histology concluded that endometritis was not a significant determinant of fertility in dairy cows.4 5 Closer examination, however, made it clear that there was no consistent definition of endometritis. The condition was diagnosed mainly by uterine palpation in North America, where the incidence of endometritis was generally reported to be less than 20%2,6,7 but in Europe, where vaginoscopy was a common procedure, endometritis was recognized in up to 40 % of postpartum cows.8 Since there was no consistent definition or diagnostic consensus, it is not surprising that effects of treatment were unclear to say the least. Intrauterine infusion of an array of compounds was routine practice but none were found to be efficacious in controlled studies. In fact, it was often argued that inclusion of an untreated control group would be unethical, a stance that substantially delayed the acquisition of the necessary evidence that many then-current treatments were not only ineffective but even detrimental. It is noteworthy that the first report that intrauterine infusion as then practiced was ineffective came from Charter Diplomate Steve Roberts, at Cornell more than 60 years ago.9 Given that intrauterine infusions were ineffective or harmful, the reports that prostaglandin treatment was as effective as intrauterine infusion10-12 were not encouraging.

Against that background, it seemed imperative to determine whether endometritis was in fact a common disorder of postpartum cows and whether it influenced fertility. If the condition could be defined and consistently diagnosed, epidemiology and risk factors could be elucidated and potential treatments could be methodically evaluated.

Diagnosis and prevalence of endometritis

Endometritis has always had a definition – it is inflammation of the endometrium. The problem seemed to be development of a sensitive, specific and practical diagnostic method. Brenda Bonnet had

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used endometrial biopsy and contributed a great deal to our knowledge of endometritis but reported that the biopsy procedure itself might impair fertility\textsuperscript{13-15}, an opinion that has been challenged recently. Endometrial cytology had long been established as a simple and reliable method of detecting endometrial inflammation in mares. We decided to apply the technique to cows, using an adaptation of the low volume flush method described by Barry Ball and others.\textsuperscript{16} Initially we targeted cows at 40–60 days postpartum since this was shortly before the breeding period and a time at which postpartum infection and inflammation were generally believed to have resolved. We found a surprisingly high proportion of cows with evidence of inflammation, and reported that presence of cytological endometritis impaired reproduction--at first service and throughout the lactation, leaving more cows open (and therefore likely to be culled) at 300 days in milk.\textsuperscript{17,18} These findings spurred much additional research on endometritis because the condition seemed both prevalent and detrimental, and therefore very costly to the industry, contentions soon confirmed by independent investigators.\textsuperscript{19,20} Ram Kasimanickam and others introduced the cytobrush as an alternative method of obtaining endometrial cytology samples.\textsuperscript{21} Using cytology as a gold standard, it was shown that ultrasonography,\textsuperscript{19,22} presence of leukocyte esterase, protein and pH of recovered fluid\textsuperscript{23} were useful but not excellent indicators of endometritis. Importantly, the process of obtaining endometrial samples is not itself detrimental to future reproduction.\textsuperscript{24,25}

**Purulent vaginal discharge and cervicitis**

Stephen LeBlanc and others at Guelph took a different approach to diagnosis of reproductive tract disease. They studied the relationship between clinically identifiable signs in the early postpartum period (21 to 35 days postpartum) and likelihood of pregnancy at 120 to 150 days in milk. They found that the presence of a purulent vaginal discharge after 21 days postpartum or a mucopurulent discharge after 28 days, or cervical diameter greater than 7.5 cm at this time significantly predicted poor reproductive performance.\textsuperscript{26} They labeled this condition “clinical endometritis” even though there was no direct evidence of endometrial inflammation. Importantly, over 40 % of cows diagnosed with clinical endometritis would have been missed had vaginoscopy not been performed—the vaginal discharge was not always externally visible.

Because vaginoscopy is regarded as cumbersome or time consuming by many practitioners, other methods were explored for detection of exudate in the vagina. Martin Sheldon’s group suggested “sweeping” the cranial vagina with a clean gloved hand and examining the recovered mucus.\textsuperscript{27} I am not in favor of this technique because I believe it has the potential to damage the vestibulovaginal junction, which is a critical anatomic feature in defense of the cranial tubular tract. However, a valuable contribution of this publication was the proposal of a classification system for scoring the recovered mucus (Table).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Clear or translucent mucus</td>
</tr>
<tr>
<td>1</td>
<td>Mucus with flecks of pus</td>
</tr>
<tr>
<td>2</td>
<td>Mucus with up to 50 % pus</td>
</tr>
<tr>
<td>3</td>
<td>Mucus with more than 50 % pus</td>
</tr>
<tr>
<td>3</td>
<td>Serosanguinous exudate, often malodorous</td>
</tr>
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A further innovation came from Scott McDougall and co-workers who introduced a device they called Metricheck\textsuperscript{\textregistered} to recover vaginal mucus samples.\textsuperscript{28} It consisted of a 50 cm stainless steel shaft at the end of which was a black rubber hemisphere. The device was inserted to the cranial vagina and when withdrawn the black “cup” collected mucus which could easily be evaluated. This device has been well tested and is now in common use.\textsuperscript{29-33}

At first it was assumed that cows with purulent vaginal discharge simply represented a more severe form of inflammation than those with cytological evidence of endometritis in the absence of
visible discharge. However, it soon became clear that some cows with obvious purulent discharge had no evidence of cytological endometritis. This situation was clarified by Jocelyn Dubuc, working under the supervision of Stephen LeBlanc. This group demonstrated that (cytological) endometritis and purulent vaginal discharge were separate and independent conditions, with additive detrimental effects on reproductive performance and separate risk factors. Purulent vaginal discharge was more likely to follow obstetrical complications and endometritis was associated with negative energy balance.

The source of vaginal exudate in the absence of uterine inflammation was briefly vexing but it has gradually become clearer that cervicitis is a common condition and independent of endometritis. It is noteworthy that enlarged cervical diameter was one of the clinical findings that LeBlanc found to predict poor reproductive performance.

**Current definitions of postpartum uterine disease**

Stemming from a conversation at the 2004 ICAR meeting in Porto Seguro, Brazil, Martin Sheldon, Stephen LeBlanc, Greg Lewis and I set about developing consensus definitions of postpartum uterine disease. The manuscript we wrote was circulated for their comments to 13 international colleagues to stress the consensus nature of the publication. This attempt provided definitions for puerperal metritis, retained fetal membranes, pyometra, subclinical endometritis and clinical endometritis. Unfortunately it was soon out of date. Puerperal metritis was defined as an abnormally enlarged uterus and a fetid watery red-brown uterine discharge, associated with signs of systemic illness (decreased milk yield, dullness or other signs of toxemia) and fever > 39.5°C, within 21 days after parturition. In fact, this condition almost always occurs within the first 10 to 14 days and the 21 day limit was introduced to avoid a “gap” between postpartum metritis and endometritis. Later evidence has made clear that there is a great deal of physiological inflammation still active around 21 days postpartum, so any diagnosis of a clinically relevant uterine inflammatory disease at this time should be made with great caution. This paper also introduced a distinction between puerperal metritis (accompanied by fever) and the similar but afebrile condition labeled “clinical metritis.” This distinction may be valid because there is evidence that reproductive performance is not impaired in cows with the afebrile form of the disease, although both puerperal metritis and clinical metritis are associated with reduced milk yield. This paper endorsed the concept of clinical endometritis characterized by vaginal exudate or enlarged cervix and of subclinical endometritis indicated by evidence of endometrial inflammation (usually by cytology) in the absence of visible exudate. Unfortunately, this paper perpetuated the notion that endometritis of clinical significance could be diagnosed around 21 days postpartum.

Once the independence of endometritis and purulent vaginal discharge had become clear, Dubuc et al. proposed updated definitions. He proposed using the term “purulent vaginal discharge” (PVD) to replace the former “clinical endometritis” and “cytological endometritis” for the condition where inflammation was confirmed to be present in the uterus. This certainly removed some of the former confusion. These investigators stressed that purulent vaginal discharge was a distinct and separate condition from cytological endometritis and not simply a more severe form of it.

However, the source of the purulent exudate remained elusive. The logical conclusion seemed to be that cervicitis existed as a separate entity and this attracted the attention of investigators. It soon emerged that cervicitis was indeed a distinct condition that could exist separately from endometritis. However, it was not the whole answer and, indeed, it seems that cervicitis affects about 15 to 40% of dairy cows. About half of cows with PVD have cervicitis and vice versa. About 50 to 75% of cows with endometritis have cervicitis. About 3% of cows at 35 days postpartum had PVD without any evidence of concurrent endometritis or cervicitis.

Currently, puerperal metritis, clinical metritis, and pyometra seem to be adequately defined. Clearly, there is overlap between endometritis, purulent vaginal discharge and cervicitis, which may occur independently or together. This requires additional investigation and clarification.
Epidemiology
In an attempt to clarify the causes of endometritis and illuminate possible preventive strategies some attention was devoted to understanding its epidemiology. Cheong et al. investigated endometritis in 38 dairy herds in Upstate New York and found the major risk factor for endometritis was clinical ketosis earlier in lactation. This was consistent with a report from Doug Hammon that cows affected with endometritis at five weeks postpartum had lower voluntary dry matter intake beginning in the prepartum period and continuing after parturition, accompanied by more severe negative energy balance and impaired neutrophil function. Dubuc confirmed the importance of negative energy balance for endometritis and showed that separate risk factors predisposed cows to purulent vaginal exudate, most importantly obstetrical complications. Puerperal metritis was a risk factor for endometritis and purulent vaginal discharge. At a herd level, Cheong et al. reported that risk of endometritis was reduced for cows calving on straw compared to other types of bedding.

Treatment
Establishment of clinical definitions of uterine disease laid the groundwork for systematic investigations of effective treatments to restore fertility. Prior to the 1990s an amazing array of compounds was infused into the uterus of cows despite the lack of evidence that any of these treatments was effective and some evidence that some treatments were in fact detrimental.

LeBlanc showed convincingly that cephapirin specially formulated for intrauterine administration (Metricure®, Merek Animal Health) was effective in partially restoring fertility in cows with purulent vaginal discharge. Simple disappearance of clinical signs occurred as often without treatment as with it, but improved fertility required treatment. This study compared intrauterine cephapirin to systemic administration of prostaglandin F2α (PGF) and it is instructional to examine the results closely. First, cephapirin treatment improved hazard of pregnancy only when cows were diagnosed and treated after four weeks postpartum. Treatment before this time was ineffective, consistent with the concept that inflammation at three weeks postpartum is often physiological. Prostaglandin treatment was not beneficial and tended to be detrimental in the absence of a palpable corpus luteum.

Kasimanickam examined the effects of the same two treatments in the case of cytological endometritis in cows without any signs of vaginal discharge, reporting that both cephapirin and cloprostenol improved reproductive performance of cows with endometritis but not of normal cows, when the cows were treated between 20 and 33 days postpartum. In contrast, Galvão et al. reported results of a larger study showing that although administration of PGF increased reproductive performance, it did not do so through curing or preventing endometritis; indeed, the greatest beneficial effect of prostaglandin treatment was in cows without endometritis. Because cephapirin for intrauterine administration is not available in the USA and PGF is not specifically effective in cases of endometritis, producers and veterinarians in the USA were left without effective treatments for endometritis.

Schuenemann and colleagues have reported beneficial effects of dextrose infusion on subsequent reproductive performance of cows with purulent vaginal exudates, a finding we were not able to replicate. More recently success has been reported with infusion of povidone iodine into the uterus of affected cows but the number of cows treated is too small to be convincing and this study requires confirmation especially since detrimental results have previously been reported with this treatment and intrauterine iodine infusion has been reported to impair local neutrophil function.

This leaves US producers and veterinarians without an effective treatment against endometritis. Many have pinned their hopes on systemic prostaglandin administration. Indeed, the evidence that PGF improves reproductive performance in dairy cows is quite strong. However, its role in endometritis is not so clear. In one study PGF was administered to cows at 21, 35 and 49 days postpartum. Cows were examined at the same times for presence of cytological endometritis and their reproductive outcomes were followed. Overall, cows given PGF did have better reproduction. However, cows receiving PGF were no more likely to recover from endometritis than untreated cows, and PGF 21 days did not reduce incidence of endometritis at 35 or 49 days postpartum. Furthermore, stratification of cows by presence of
endometritis indicated that the overall beneficial effect of PGF was limited to cows without evidence of endometritis.45

Conclusions
Research in the last two decades has done a great deal to clarify clinical definitions of postpartum uterine disease, which in turn has permitted credible study of epidemiology, pathogenesis, consequences and treatment of these conditions. Despite intensive study, however, little information of practical significance of producers and practitioners has emerged so far.

References