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Revisión bibliográfica

Uterine inflammation affects the reproductive performance of dairy cows: A review [1]

La inflamación uterina afecta el desempeño reproductivo de las vacas lecheras: una revisión

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Abstract:

Incidence of post- partum uterine disease is an important concern in dairy cattle, because it affects its reproduction. Therefore, the objective of this review of literature was to generate a multifactorial overview about uterine diseases, and the reproductive performance of dairy cows, from a zootechnical approach. Dairy cows face multiple challenges around parturition. Immune suppression around calving, exposition to trauma and uterine bacterial contamination, metabolic diseases, lactation, and changes in management make dairy cows susceptible to uterine diseases. Most cows are able to eliminate uterine infection after calving, however, some cows keep uterine disease. Uterine disease may show clinical signs, but also silent signs that affect fertility as well. Poor reproductive performance is not caused by those signs by themselves, but due to alterations in ovarian and uterine function. Also, the problem of this silent signs is that farmers become aware of the disease when it has already caused negative effects on the reproductive performance. Sometimes, uterine disease is still present at the moment of the first service after calving. Uterine disease make it harder for cows to get pregnant because it affects the establishment and maintenance of pregnancy, being another cause for infertility, increasing the cull rate and decreasing incomes from the dairy industry.

Keywords: endometritis, uterine diseases, fertility, risk factors, reproductive performance.

Resumen:

El ganado lechero, entre otros desafíos, presenta enfermedades uterinas post parto que afectan su reproducción, por tanto, el objetivo de esta revisión de literatura fue generar una visión desde múltiples aristas acerca de las enfermedades uterinas y el desempeño reproductivo de la vaca lechera desde un enfoque zootécnico. La vaca lechera enfrenta múltiples retos en el momento del parto. Inmunosupresión alrededor del parto, exposición a trauma y contaminación uterina, enfermedades metabólicas, lactancia y cambios en el manejo, hacen a la vaca lechera un animal vulnerable de sufrir algún tipo de enfermedad uterina. La mayoría de las vacas pueden eliminar la infección uterina después del parto, sin embargo, un porcentaje de los animales mantienen la infección uterina. Esta infección puede presentarse con signos clínicos o subclínicos que también afectan la fertilidad. El pobre desempeño reproductivo no se da por causa de dichos signos, sino más bien por alteraciones en la función ovárica y uterina. Además, el problema para los ganaderos, es que se dan cuenta de la enfermedad uterina subclínica, hasta que la misma generó las consecuencias negativas sobre el rendimiento reproductivo del animal. Algunas veces, la enfermedad uterina está presente incluso hasta el momento del primer servicio post parto. Esta enfermedad hace más difícil que la vaca quede preñada, debido a que afecta tanto el establecimiento como el mantenimiento de la preñez, lo cual constituye una fuente de infertilidad que eleva el desecho de animales y disminuye los ingresos en la actividad lechera.

Palabras clave: endometritis, enfermedades uterinas, fertilidad, factores de riesgo, eficiencia reproductora.

Introduction

Dairy cows face significant challenges around parturition. These include calving, the initiation of lactation, the transition from dry to lactating cow management, diminished dry matter intake, high nutrient demand,

body reserve mobilization and uterine involution. All these changes produce a cow that is more vulnerable to get sick. Metabolic diseases such as sub-acute ruminal acidosis, fatty liver, clinical and subclinical hypocalcemia and ketosis are part of the risks after calving (Mulligan and Doherty, 2008). Al these challenges after calving make the cows vulnerable to develop a uterine disease, for example, diseases such as metritis and endometritis that collectively affect biological and productive parameters on dairy farms (Esposito et al., 2014).

Many factors have been clearly identified such as risk factors for uterine disease (Dubuc et al. 2010). They determined that high non-esterified fatty acids (NEFA) concentration pre-partum, dystocia, retained placenta and greater haptoglobin are the major risk factors for metritis, these factors are a combination of trauma, inflammatory reactions and good environment for bacteria colonization. Twinning, dystocia, metritis and increased haptoglobin are associated with purulent vaginal discharge (PVD), whereas low body condition score (BCS) at calving, hyperketonemia, and increased haptoglobin during the first week post-partum were the identified risk factors for subclinical endometritis (SCE).

High producing dairy cows are, additionally challenged, perhaps by milk production itself or through a sum of metabolic changes. High producing cows are more susceptible to uterine disease. Williams (2013) reported, for example, that cows producing more than 35 kg of milk per day have a greater incidence of uterine disease. Cows with uterine inflammation have poor reproductive performance which is translated into diminished pregnancy rates, more days open and more pregnancy losses (Galvão et al., 2009; Vieira-Neto et al., 2014).

Infection takes place in the uterus of the cow right after calving. The cow is usually able to clear the infection within a few days after calving but if this does not happen then metritis can develop, but also other forms of uterine disease and inflammation such as subclinical endometritis will take place (Bittar et al., 2014).

The short or long terms effects of uterine disease on ovarian structures and ovarian and uterine responses are not completely elucidated, however, there is evidence about uterine disease affecting fertility in dairy cows, possible consequences of prolonged inflammatory reactions are responsible for the diminished reproductive performance (LeBlanc, 2008; de-Boer et al., 2014; LeBlanc, 2014; Eckel and Ametaj, 2016).

Subclinical endometritis is a uterine disease that does not present clinical signs and cannot be easily diagnosed on farm site. But as a form of uterine disease, it is producing deleterious effects on reproduction in dairy cows. The objective of this review was to generate a multifactorial overview of uterine diseases, inflammation and reproductive dairy cow performance within the animal science approach.

Definition and incidence of uterine disease

There are different types of uterine diseases. Metritis is a uterine infection that manifests as clinical disease. It typically presents fetid vaginal discharge between three to nine days after calving. The cow may also present fever, which makes it a systemic illness, that reduces cow performance in a short time (Esposito et al., 2014; LeBlanc, 2014), also it presents inflammation on the entire uterine wall, infiltration of defense cells and tissue degeneration (Sheldon et al., 2006). The definition of the infection changes according to the presence of clinical symptoms and time postpartum. Clinical endometritis has been defined as uterine inflammation without systemic illness after twenty days in milk (DIM). A mucopurulent vaginal discharge may also be present (Esposito et al., 2014), the inflammation is restricted to the endometrium, no deeper than the stratus spongiosum. It presents infiltration of defense cells, fibrosis, and endometrial glands atrophy as well (Sheldon et al., 2006). Pyometra is another uterine infection characterized by an accumulation of purulent content into the uterine lumen with the presence of a persistent corpus luteum (Knudsen et al., 2015). Cows with metritis and cows experiencing problems at calving have an increased incidence of endometritis and subclinical endometritis (SCE), which is a silent disease (Bittar et al., 2014). Although, metritis tends to be associated with purulent vaginal discharge (PVD) and mixed bacterial infection, SCE is not usually

associated with PVD or bacterial infection (LeBlanc, 2014). Subclinical endometritis does not present any clinical symptoms, leucocyte infiltration, mainly polymorphonuclear neutrophils (PMN), and edema are the main signs of this disease. Diagnosis of SCE is commonly done by techniques such as cytobrush or uterine flushing (Esposito et al., 2014). Cervicitis is the inflammation of the cervix, the relation between cervicitis, uterine inflammation and fertility is not clear, but when cervicitis and uterine inflammation are present, fertility declined (Hartmann et al., 2016).

The reported incidence of disease in dairy cows from calving to artificial insemination is 42% (Ribeiro et al., 2015). This percentage includes diseases with a local infection such as uterine infection, but also systemic diseases such as digestive and respiratory diseases. Uterine disease, specifically, metritis is present from 2 to 37% of cows after parturition and between 37 to 75% of cows, develop endometritis (Knudsen et al., 2015), so that, some cows are able to clear infection by two or three weeks postpartum, but some do not. These diseases in dairy cattle decrease fertilization and conceptus development (Ribeiro et al., 2015). The incidence of PVD and SCE at 35 (DIM) was 17.1 and 36.2%, respectively (Denis-Robichaud and Dubuc, 2015a). de-Boer et al. (2015) reported 10, 15 and 7% incidence of PVD at 0, 21 and 42 DIM, respectively. Prunner et al. (2014a) reported an incidence of SCE of 21% from 20 to 30 DIM. In a crossbred dairy herd, between 32 to 70 DIM, 26% of cows were diagnosed with SCE by cytobrush (cutoff = 5% PMN) (Carneiro et al., 2014). At 65 DIM cows were assessed for SCE by cytobrush, and a threshold of 5% of PMN was used. The average of polymorphonuclear neutrophils (PMN) (PMN are the first cell line of defense during infection, the percentage of PMN along luminal epithelial cells is an indicator of SCE) for SCE cows was 16.02% and for control, cows were 3.7% (Brodzki et al., 2014). The incidence of pyometra is around 5% after parturition (Knudsen et al., 2015) because of this low incidence, pyometra is out of the scope of this review.

Subclinical endometritis in repeat-breeder cows has not been evaluated as fully as in first service cows. Pothmann et al. (2015) studied cows with three or more unsuccessful services in a row and assessed SCE by cytobrush technique (cutoff: 5% PMN). The incidence of SCE was 12.7%. More than 90% of the diagnosed SCE was found in multiparous cows. These findings indicate that uterine disease affects significantly dairy herds.

Uterine disease and reproductive outcomes

It is known that uterine disease causes impaired reproductive performance. Subclinical endometritis evaluated by cytobrush or uterine lavage at 35 or 49 DIM, showed that its incidence increases the number of days open and reduces pregnancies per artificial insemination (P/AI) (Vieira-Neto et al., 2014). During the same period (35 and 49 DIM) Galvao et al. (2009) reported thirty and forty more days open which is consistent with the 30-day delay reported by Madoz et al. (2013). Also, conception rate at the first service was reduced.

The effect of uterine disease on reproductive performance has not been the same for all categories of cows. Multiparous cows are more susceptible to metritis. This uterine disease results in delayed time to first insemination and more days open in multiparous cows but it did not affect primiparous cows (Toni et al., 2015). In the case of SCE diagnosed by cytobrush at 35 DIM with a cutoff of 5% PMN, the hazard to pregnancy was 27% lower than healthy cows. Also, days open were 42-days longer in cows with SCE than in healthy cows (Bicalho et al., 2016). Not only are cows less likely to get pregnant when associated with uterine disease, there are also greater pregnancy losses. Clinical endometritis and retained placenta (which is the abnormal retention of fetal membranes after calving) also increased the probability of pregnancy losses. Cows with retained placenta had 3.36 times greater odds and cows with clinical metritis had 2.16 times greater odds of losing pregnancy than cows without those diseases (Machado et al., 2015).

Evaluation of PVD by gloved hand at day 26 showed that cows with PVD had delayed resumption of cyclicity when compared with healthy cows. Pregnancies per artificial insemination were greater in healthy

cows than cows with PVD. The purulent vaginal discharge was associated with more pregnancy losses (Maquivar et al., 2015). In beef cows, based on the percentage of PMN from uterine lavage between days 28 to 68 post-partum, SCE caused a 40-days delay to conception compared with healthy cows (Ricci et al., 2015).

The percentage of PMN along luminal epithelial cells cannot be interpreted by itself, it is important to consider the DIM when the diagnostic test is done. When cows presented ≥25% of PMN at 0 DIM, for instance, they had a better chance of pregnancy than cows with less than 25% (de-Boer et al., 2015). Cows with greater percentages of PMN at 21 DIM, however, had 20% less chance of pregnancy. This shows that an early strong immune response increases fertility, but a protracted inflammatory response decreases fertility (de-Boer et al., 2015). This was confirmed by Peter et al. (2015) who showed that cows with endometritis around 48 DIM (late response) presented the greater concentrations of biomolecules related to the inflammatory response. Heppelmann et al. (2016) also found greater expression of IL1A, IL1B and TNFα in cows with endometritis than in healthy cows from d 0 to 65 after calving. This provides evidence for protracted inflammatory response in cows with endometritis.

The pathway through which uterine disease causes reproductive failure is not totally elucidated, however, alterations in ovarian function explains partially the reproductive performance. It is known that endotoxins from bacteria, may play a role. An *ex vivo* model was developed to evaluate the effect of LPS, on theca cells of different stages of ovarian follicular development (Magata et al., 2014); the theca cells of pre-selected follicles were more susceptible to LPS, when stimulated luteinizing hormone (LH), LPS suppress progesterone secretion from theca cells, this effect was only on cells from post-selected follicles (in this case, pre or post-selected follicles to refer to follicular wave stages). Lipopolysaccharide effect on progesterone secretion was not found when theca cells were stimulated with estradiol instead of LH. Steroid metabolism through the mevalonate pathway is altered by LPS, the endotoxin diminishes steroid production, for instance, steroid reproductive hormones. Actually, intervention on the mevalonate pathway is proposed, such a possible therapeutic strategy to mitigate LPS effects on reproduction (Healey et al., 2016).

Development of uterine disease

Parturition opens a window for uterine infection, bacteria are present in the uterus right after calving. Jeon et al. (2015) evaluated the population of bacteria in the uterus by using metagenomics. The first sampling was within the first twenty minutes after calving. The uterine environment was rich in bacteria. They found that metritic and healthy cows share similar bacteria after calving, but quickly differ for cows that develop metritis at that time. Bacteria such as *Bacteroides* spp. and *Fusobacterium* were the most common genus identified in metritic cows in the first six days after calving. But also, *Candidatus blochmannia*, *Scherichia Sneathia* and *Pedobacter* spp. were associated with uterine health (Jeon et al., 2015).

Concomitant with the bacteria, dairy cows have metabolic disturbances such as elevated non-esterified fatty acids (NEFA) and low glucose concentrations (LeBlanc, 2014). Abnormal metabolic profiles are associated with delayed clearance of bacteria. The metabolic status affects neutrophil function and generates inflammatory factors such as tumor necrosis factor α (TNFα) and interleukin 6 (IL6) (LeBlanc, 2014). Neutrophils are the primary immune cells attempting to clear the bacterial infection. So that, recruitment and activation of PMN is the main immune response to bacterial infection in the uterus. The function of PMN is vital to clear the infection and avoid the transition from physiological to pathological infection which is crucial to avoid poor reproductive performance (Kimura et al., 2014). The immune system of cows is affected by all the challenges of the transition period, including impaired neutrophil function, low lymphocyte and antibody responsiveness and diminished cytokine releases (Esposito et al., 2014). A successful immune response in a healthy cow is able to resolve the inflammatory state postpartum to a regular or homeostatic state within a period of one to three weeks. Cows that develop endometritis or SCE are not able to do this and maintain the inflammatory response for a longer period (Foley et al., 2015).

Bacterial colonization or growth within the uterine tissue releases endotoxins called pathogen associated molecules (PAM). Gram negative bacteria, for instance, release a lipopolysaccharide (LPS). Endometrial cells have receptors that are able to detect PAM. Once a receptor is activated, it triggers cytokines and chemokines to recruit and activate immune defense cells and inflammatory reaction (Healy et al., 2014).

Diagnosis of uterine disease

Different methods for diagnosis of reproductive tract disease in cows have been used. Vaginoscopy, it is an instrument that allows the exploration of vagina and cervix to evaluate color, content and inflammation signals (Hartmann et al., 2016). Transrectal palpation (Hartmann et al., 2016) and transrectal ultrasonography (Polat et al., 2015; Toni et al., 2015) allows to palpate or look at the reproductive organs, texture, size, and content, ultrasonography gives a more accurate diagnosis than palpation. Uterine flush (Bicalho et al., 2016), cytobrush (Madoz et al., 2014; Denis-Robichaud and Dubuc, 2015b; Ledgard et al., 2015; Pascottini et al., 2015; Polat et al., 2015; Hartmann et al., 2016), cytotape (Pascottini et al., 2015) and biopsies (Hartmann et al., 2016) (Madoz et al., 2014) are more invasive methods, uterine flush consist in the introduction of fluid into the uterus to retrieve it with the uterine content sample. The cytobrush and cytotype techniques have to reach the uterine lumen to collect the content of the endometrial walls, the cytobrush uses a small brush to collect the samples, meanwhile, the cytotype is a modification of the cytobrush technique where the sample is collected by a piece of tape. When biopsy technique is used, pieces of endometrial tissue are taken by using biopsy forceps, all these techniques require laboratory work for evaluation of the uterine samples. Cow-side methods such as metricheck device (Denis-Robichaud and Dubuc, 2015b; Ledgard et al., 2015; Bicalho et al., 2016) and gloved hand (Toni et al., 2015) are also methods to evaluate the vaginal content. These methods are used to assess different uterine diseases such as metritis, clinical or subclinical endometritis, and even cervicitis.

In some cases, depending to the used method, the diagnosis is affected by the estrous cycle stage, for example, plasma estradiol concentrations have shown to affect the sensitivity of vaginal discharge (metricheck and gloved hand) and ultrasound evaluations (presence of fluid into the uterus and diameter of the cervix) for the diagnosis of uterine disease (Silper et al., 2016). Polymorphonuclear neutrophils, however, are considered good indicators for SCE because they are not significantly affected by the estrous cycle stage or circulating progesterone concentrations (Madoz et al., 2013). In addition, another advantage of PMN evaluation, specifically, cytology methods, is that the percentage of PMN from uterine cytology showed a high correlation with gene expression related to inflammatory response. Genes with a high correlation were C–X–C motif chemokine receptor 2 (CXCR2), Interleukin-1A (IL1A), Interleukin–1B (IL1B) and Interleukin–8 (IL8) where the correlation was above 0.6 (Peter et al., 2015). This correlation opens a series of molecular biology approaches to diagnose uterine disease. For example, the presence of PMN in luminal epithelial cells is an indicator for SCE. But some biomolecules are currently used to diagnose uterine diseases as well. Gene expression of cytokines such as IL1A, IL6, IL17A, TNFα, and enzymes such as prostaglandin H synthase type – 2 (PGHS2) and prostaglandin E synthase (PGES) are highly correlated with the percentage of PMN in the uterus between 29 to 36 DIM. The cytokines are involved in PMN recruitment and inflammatory responses (Johnson et al., 2015). Specifically, IL1A has been recognized as the signal that triggers inflammation in response to a combination of endometrial cell damage and bacteria (Healy et al., 2014).

The location where the sample is taken from the cow can also affect the diagnosis, for instance, the interpretation related with the reproductive outcome. Brodzki et al. (2014) sampled the uterus and also, collected peripheral blood; they found that the local sample gave different immune mechanisms than the systemic sample for healthy and SCE cows at 65 DIM, however diagnosis of the uterine disease was clear.

Intrauterine, cervical or vaginal sampling can also give a different diagnosis (Madoz et al., 2014; Hartmann et al., 2016).

The transcriptome in SCE cows depended on sample location as well. Subclinical endometritis altered gene expression in liver and adipose tissue. Subclinical endometritis was associated with changes in liver transcription for genes related to coagulate cascade, steroid hormone synthesis, apoptosis, inflammation and oxidative stress. In adipose tissue, inflammation, oxidative phosphorylation, dynamics of long chain fatty acids and others were also altered in cows with SCE, however, independently of the different biomarkers found, the result indicated decrease fertility (Akbar et al., 2014). Similar results were found by Salilew-Wondim et al. (2016) but dysregulation of genes was more severe in cows with metritis than SCE cows.

Metagenomics analysis to evaluate the population of bacteria also differ by the type of sample evaluated. Cows analyzed at weeks 1, 4 and 7 after calving presented different bacteria population during each week, but also was different if the sample was from a uterine flush or biopsy (Knudsen et al., 2016).

Different types of uterine samples have been used to evaluate these biomolecules, and they have also been evaluated in peripheral blood. In cows with SCE, from peripheral blood samples, mononuclear cells, B-cells, natural killer cells (NK-cells) and CD172α positive monocytes were elevated. At the same time, mRNA expression was greater for CXCL8, TNF, and IL12 (Duvel et al., 2014) so that, these evaluations are potential indicators for SCE from peripheral blood samples because they were in agreement with a diagnosis from uterine samples.

Some proteins have been correlated with the percentages of PMN as well. Ledgard et al. (2015) found a strong correlation between percentages of PMN and cathelicidin, PGLYRP1, SERPINB1, and S100A9. These proteins are products of immune cells in response to a current infection and during a prolonged inflammatory response.

In addition to gene expression analyses, ELISA tests have been used to determine concentrations of biomolecules as potential markers for uterine disease, however, more investigation is needed because studies present contradictions. For example, when Brodzki et al. (2015b) evaluated TNFα, IL6, IL10, haptoglobin, and serum amyloid A (SAA), in healthy and sick cows (SCE cows), they reported these molecules as candidates for biomarkers of uterine disease, but Brodzki et al. (2015a) could not totally support it. These molecular biology approaches, also fail to differentiate between SCE, clinical metritis and healthy cows (Kasimanickam et al., 2014; Johnson et al., 2015). These potential biomarkers are also sensible to the type of sample, evaluation of TNFα, IL6, and IL10 from uterine washes revealed a different diagnosis than the same evaluation done in serum samples (Kim et al., 2014).

The mRNA expression of cytokines (IL1A, IL1B, IL6, and TNFα) have shown expected changes with respect to the resolution of uterine disease over the time. Cytokine concentrations were less in cows categorized as mild, moderate and severe metritis at 42 DIM than 4-days after calving. These results are consistent with the expected infection resolution of uterine disease (Heppelmann et al., 2015).

In order to evaluate short and long-term effects of uterine diseases on reproductive performance, the transcriptome of specific genes has been analyzed in healthy, SCE and clinical endometritis cows. A greater mRNA expression of chemokines and enzymes such as prostacyclin synthase and prostaglandin D2 synthase (enzymes related to prostaglandin synthesis) was found in cows with endometritis than in healthy cows. Additionally, cows with SCE showed greater expression of inflammatory markers until 48 DIM than healthy cows. This demonstrates a strong late immune response in cows with endometritis (Peter et al., 2015).

Acute phase proteins, such as haptoglobin allows to distinguish metritic than healthy cows early postpartum (10 DIM) but not later, it also worked only in multiparous but not in primiparous cows (Burfeind et al., 2014; Yasui et al., 2014).

There is not a lot of information about the uterine disease in repeat breeder cows, however, Kasimanickam et al. (2014) suggested the evaluation of MUC1, IGF1, IGFBP2 to differentiate between repeat breeder cows and normal cows.

Risk factors associated with uterine disease

Nutritional and metabolic factors

The effect of trace minerals on retained placenta, metritis and clinical endometritis were evaluated. Calcium, Mg, Mo and Zn were lesser in cows with retained placenta. Calcium, Mo, P, Se, and Zn were lesser in cows with metritis and Ca, Cu, Mo, and Zn were lesser in cows with SCE compared with healthy cows (Bicalho et al., 2014b). Salehi et al. (2016) found greater expression of genes associated with inflammation in cows with SCE (IL1B, IL8, IL10) and TNFα but did not find any differences when healthy and SCE cows were supplemented with oilseeds which are recognized to suppress inflammation. Other supplements such as monensin and high starch diets improved the activity of immune cells (PMN, phagocytes, and monocytes), but they did not improve uterine health in cows with SCE diagnosed by uterine lavage at 8 and 47 DIM. Further investigation must be done to determine the effects of increased immune cell activity on conception risk (Yasui et al., 2015).

Metabolic pressure after calving, negative energy balance, and metabolic diseases such as ketosis increase the incidence of uterine disease (Williams, 2013). Metabolites such as NEFA and beta hydroxyl butyrate (BHB) were not different from three weeks before to three weeks after calving in cows that developed endometritis from 40 to 60 DIM. Energy balance pre-partum (based on intake of Mcal/d) was similar, but negative energy balance was more severe in the first three weeks postpartum in cows with endometritis than in healthy cows. Energy balance was positive at week six for both groups but significantly greater in healthy cows (Yasui et al., 2014). The severity of negative energy balance influences uterine involution postpartum and the ability to clear the infection. Repair and regeneration of uterine tissue during involution is mediated by metabolic actions and hormones at the cellular level (Wathes et al., 2009). Wathes et al. (2007) reported that severe negative energy balance is associated with more uterine inflammation and altered tissue remodeling and immune response.

Supplementation with selenium and vitamin E have shown to diminish retained placenta, which also means less uterine infection and inflammation (Bourne et al., 2008; Moeini et al., 2009).

Low body condition score has been associated with greater incidence of SCE (Carneiro et al., 2014). In addition to low body condition score (BCS), glucose concentration and blood urea nitrogen (BUN) are associated with the incidence of SCE as well. Cows diagnosed with SCE between weeks 5 to 7 post-partum had low BCS, low glucose concentration and greater BUN (Senosy et al., 2012). Other studies failed to link BCS with SCE, for example, Akbar et al. (2014) did not find an association between SCE and BCS. Interestingly, milk yield and blood metabolites such as NEFA, protein, albumin, globulin, magnesium, glutamate dehydrogenase and aspartate aminotransferase did not differ for healthy cows and cows with SCE diagnosed between 22 and 25 DIM (threshold of 18% of PMN) (Akbar et al., 2014). Düvel et al. (2014) also reported that concentration of Ca, BHB, NEFA, and progesterone in serum did not differ between the healthy and SCE cows.

Infectious factors

The presence of bacteria affects conception. The process through which bacteria exerts its effects is still uncertain. It is clear that the presence of bacteria is related to clinical and/or subclinical uterine inflammation (Ghanem et al., 2015). The presence of specific bacterial populations in the uterus is also a factor involved in uterine disease. Cows with Trueperella pyogenes had a greater risk of presenting PVD, purulent uterine lavage, SCE and poor reproductive performance (Prunner et al., 2014a; Ghanem et al., 2015; Wagener et al., 2015; Bicalho et al., 2016). It is known that *T. pyogenes* secrete an exotoxin called pyolysin. This toxin causes hemolysis and cytological lysis in a cholesterol-dependent manner. Stromal cells have greater contents of cholesterol, so they are more susceptible to pyolysin than luminal epithelial cells or immune cells. *T. pyogenes* will also cause more severe effects when luminal epithelial cells are damaged (Amos et al., 2014).

In addition to *Eschericha coli*, *T. pyogenes*, and *Bacillus* spp., Streptococcus uberis is associated with uterine health in postpartum dairy cows. Cytobrush samples were taken at 3, 9, 15 and 21 DIM (Wagener et al. 2014). They also demonstrated that the presence of *S. uberis* at day three increased the risk of T. pyogenes infection at day nine after calving.

The effect of bacteria can vary according to the physiological stage of the cow. Prunner et al. (2014b) found that the presence of *T. pyogenes* during the first four weeks after calving was associated with clinical metritis in primiparous cows but not in multiparous cows. Also, they found that *E. coli*, *T. pyogenes*, *Streptococcus* spp., *Staphylococcus* spp., *Corynebacterium* spp. and *Bacillus* spp. were the most frequent bacteria isolated from the uterus between 20 to 30 DIM. Their work is in agreement with Heppelmann et al. (2015), who found that *E. coli*, *Bacillus* spp. and *T. pyogenes* were the most common. Isolation of *E. coli* at 0 DIM did not have an effect at 21 DIM on the isolation of *T. pyogenes* but *T. pyogenes* was associated with PVD (de-Boer et al., 2015; Ledgard et al., 2015).

Twenty-seven percent of cows with SCE between 45 to 55 DIM showed the presence of *E. coli*, but none tested positive for *T. pyogenes* (Düvel et al., 2014). Brodzki et al. (2014) found that SCE cows were similar in bacteria population at 5 DIM, but significant differences were shown at 22 and 40 DIM. *E. coli*, *T. pyogenes*, *F. necrophorum*, *P. melaninogenicus*, *Staphylococcus* spp. and *Streptococcus* spp. were isolated at 5 DIM, but only *T. pyogenes* was isolated from healthy cows at 22 and 40 DIM. Subclinical endometritis cows presented the same type of bacteria at 22 and 40 DIM compared with 5 DIM except for the absence of *Streptococcus* spp. at 40 DIM.

Bacteriology has been used as a tool to diagnose SCE, but negative bacterial samples are sometimes positive for SCE when assessed by biopsy or cytobrush (Madoz et al., 2014). This finding opens the discussion about the nature of inflammation in SCE cows, whether sterile inflammation is present without current infection or bacteriology has some limitations. Prunner et al. (2014b) reported that from endometrial samples taken from 20 to 30 DIM for bacterial growth, only 60% had growth indicating that either a sterile environment existed or the culture technique had failed.

Bovine herpesvirus 4 (BoHV4) is the only virus directly associated with endometritis after calving. It attacks macrophages and produces chronic infections. It spreads easily in endometrial cells causing damage to endometrial epithelial and stromal cells (Sheldon et al., 2009a).

Management factors

Management factors and complications at parturition can increase the incidence of uterine disease. Retained placenta, calving difficulty, and calving assistance have been identified as risk factors for clinical and subclinical endometritis and increases in days open (Healy et al., 2014; Prunner et al., 2014b; Wagener et al., 2014). The vaginal laceration score (VLS) which is related to calving difficulty, was evaluated by Vieira-Neto et al. (2016). Cows with severe vulvovaginal laceration were also cowed more susceptible to develop the uterine disease.

Cows suffering from dystocia tend to have a greater population of bacteria three weeks after calving and a greater concentration of inflammatory signals such as IL8, IL1B, and IL1A (Healy et al., 2014).

Type of housing also affected the incidence of SCE in beef cows. Cows allocated and inseminated in tie stalls had a greater incidence of SCE than cows inseminated in free stalls. In the same study, parity was not a factor associated with SCE (Ricci et al., 2015). Stocking density at 100 and 80% of headlocks was evaluated in dairy cattle but no effects were found for retained placenta, metritis or PVD (Silva et al., 2014).

Genetic factors

A study evaluated sire predicting transmitted ability (PTA) for milk production and its association with health including the association with metritis, but no effect was found (Bicalho et al., 2014a). Whereas, Moore et al. (2014) showed that cows selected for high fertility had a lesser PVD and cytological endometritis than cows with low fertility traits.

Changes in DNA methylation have not been associated with SCE, so changes in gene expression are not believed to occur through an epigenetic mechanism. Genes that regulate immune response are more highly expressed in SCE cows than in healthy cows. Bacteriological findings do not correlate with the expression of inflammatory mediators in cows that had cleared bacteria previously. This suggests a lack of control of the immune system once infection has been cleared (Walker et al., 2015).

Immune response

Progesterone and estradiol may affect immune response. Specifically, *E. coli* and LPS response were tested on endometrial tissue from beef and dairy cattle. Endometrial tissue was tested in an *ex vivo* model, whereas endometrial epithelial samples, stroma cells, and peripheral blood leucocyte cells were evaluated by an *in vitro* model. In regard to progesterone and estradiol, cattle breed, *E. coli* or LPS stimulation had no effect on inflammatory mediators such as IL1B, IL6, and IL8. Data indicate that immune responses *ex vivo* and *in vitro* differ from *in vivo* evaluations wherein all cases bacteria and endotoxins increase inflammation (Saut et al., 2014).

The impaired immune response is also a major factor for the development of uterine infection and inflammation in dairy cows. A group of cows was assessed by cytobrush at 5, 22 and 40 DIM. Subclinical endometritis was diagnosed at 22 DIM by using a cutoff of 18% PMN. Cows with SCE showed the lesser phagocytic activity of granulocytes and monocytes than control cows. Some biological markers such as CD4 +, CD14 + and CD25 + leukocyte cells were in lesser concentrations in cows with SCE in peripheral blood. CD21 + and CD8 + lymphocyte cells were significantly decreased in SCE cows from uterine flushes (Ghanem et al., 2015).

Effects of uterine disease on ovarian structures and their physiology

Metritis delays ovarian activity after calving (Vercouteren et al., 2015). The same effect was seen for SCE (> 8% PMN at 25 DIM). Cows with SCE had delayed resumption of ovarian activity after calving (Salehi et al., 2016).

Some studies have examined the effects of uterine disease on ovarian structures and associated hormones. It is still unclear how uterine disease mediators affect ovaries, pituitary or hypothalamic function. A combination of all possible candidates may be necessary (Sheldon et al., 2009b).

The delay in the resumption of cyclicity in cows with the uterine disease is related to changes in ovarian activity. The number of ovarian follicles in healthy cows was shown to be greater than in cows with PVD. Additionally, healthy cows had a lower incidence of cystic follicles (Maquivar et al., 2015). Tsousis et al. (2009) also had found a greater incidence of ovarian cysts in cows with clinical endometritis diagnosed from 14 to 42 DIM.

Anovulation is associated with SCE in dairy cows. Cows diagnosed with SCE at 42 DIM were less likely to ovulate between 63 to 70 DIM than healthy cows (Burke et al., 2010). The onset of ovarian function was also altered by SCE. Dubuc et al. (2012) showed that cows with SCE had a delayed resumption of ovarian activity after calving.

Early cyclicity post-partum is related to health and fertility, however, studies report different outcomes with respect to uterine disease and cyclicity. Galvao et al. (2010) reported that cows that started to cycle by 21 DIM had less incidence of SCE by 49 DIM and greater pregnancy per artificial insemination than anovulatory cows by 49 DIM. Carneiro et al. (2014) did not find any relationship between SCE, cyclicity, parity or DIM. Cows resuming ovarian cyclicity sooner after calving showed greater cytokine mRNA expression of inflammatory signals at 40 to 60 DIM than cows that started to cycle later (Heppelmann et al., 2015).

The effect of metritis on luteal size, progesterone concentration, and enzymes involved in steroidogenesis during the first four estrous cycles after calving were tested. The concentration of progesterone was similar

over time. The size of the corpus luteum was smaller in the metritic cows but only for the first estrous cycle. The amount of luteal RNA for steroid acute regulatory protein (StAR), Cytochrome P450 and 3B - hydroxyl steroid dehydrogenase (3β – HSD) was similar for healthy and metritic cows (Struve et al., 2013). Sheldon et al. (2009b) reported that uterine disease causes a decrease in follicular size and estradiol concentrations. Progesterone concentrations were affected as well.

Long-term effects of SCE on ovarian function have been identified. Green et al. (2011) showed that cows diagnosed with SCE at 21 DIM (cutoff: 18% PMN) had a self-cure rate of 81% by 42 DIM, but the initial SCE affected pre-ovulatory follicles at 63 DIM. Estradiol, dehydroepiandrosterone and androstenedione concentrations were significantly less in 8 to 10 mm follicles. Cortisol tended to be greater and testosterone lower in this same category of follicles.

Different approaches to evaluate reproductive disorders related with the uterine disease have been used, Senosy et al. (2011) evaluated the effect of ovarian structures on the incidence of endometritis. The presence of corpus luteum from week 3 to 7 after calving or follicular size was not associated with the incidence of endometritis. Delayed uterine involution was associated with the presence of endometritis in weeks 6 and 7 after calving.

Uterine pathogen load is also associated with ovarian structures and reproductive performance early postpartum. On 13 and 15 DIM, cows with greater uterine pathogen load had a lesser concentration of estradiol and smaller follicles. On 24 and 26 DIM, the diameter of the corpus luteum was less and progesterone concentrations were reduced in cows with greater uterine pathogen load (Williams, 2013). The effect of *Arcanobacterium pyogenes* on endometrial and ovarian function was evaluated. Explants of epithelial and stromal endometrium were exposed to heat-killed *A. pyogenes*. Killed bacteria did not affect the production of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or PGE_2. Whereas, when explants were exposed to bacteria-free filtrate from A. pyogenes, $PGF_{2\alpha}$ and PGE_2 concentrations increased. The effect of intrauterine infusion of bacteria free filtrate from A. pyogenes on the estrous cycle was also evaluated. The infusion was done during the first nine days of the estrous cycle. No differences were found in the emergence of the follicular wave, dominant follicle and corpus luteum size. Peripheral plasma concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, progesterone, metabolites of prostaglandins and acute phase proteins were unchanged (Miller et al., 2007). Kaneko and Kawakami (2008) confirmed that uterine infusion of A. pyogenes in cyclic cows did not change follicular dynamics or follicular size, however, uterine bacteria inoculation was associated with rapid regression of corpus luteum and an increase in prostaglandin F metabolite (PGFM).

The endotoxin LPS has been associated with extended luteal phases of estrous cycles. Lipopolysaccharide induces inflammatory mediators that shift the production of $PGF_{2\alpha}$ to PGE (Sheldon et al., 2009b). Herath et al. (2009) also showed *in vivo* and *in vitro* evidence for production of PGE compared with $PGF_{2\alpha}$ in cows with *E. coli* infection. Lüttgenau et al. (2016), however, found the opposite effect in heifers. Intrauterine infusion of LPS decreased progesterone concentrations and reduced the lifespan of the corpus luteum in the cycle when LPS was infused, but also in the subsequent cycle.

Effects of uterine disease on estrous synchronization response

Synchronization of estrous cycles can give different reproductive outcomes with respect to uterine disease. The effect of clinical and subclinical endometritis at the initiation of a Presynch - Ovsynch protocol for timed artificial insemination (TAI) was tested. The uterine disease was diagnosed by ultrasonography and visual evaluation of vaginal discharge. Pregnancy rate at first service did not differ for cows with clinical and subclinical endometritis compared with healthy cows (Kasimanickam et al., 2006). Uterine disease, however, affected the response to estrous synchronization when a controlled internal drug release (CIDR) was used. Cows without uterine disease were 1.9 times more likely to respond to a synchronization protocol using a

CIDR and two times more likely to be pregnant after artificial insemination than cows with uterine disease (McNally et al., 2014).

Effects of uterine disease on the uterus

Uterine disease induces a protracted inflammatory response with the recruitment of immune cells chemokines and cytokines that are combating uterine disease but also are causing uterine tissue disruption. This prolonged inflammatory stage can affect the transport of spermatozoa, failures in embryonic attached and poor placental development (Sheldon et al., 2009a).

Angiosclerosis is a degenerative vascular lesion with deposition of collagen and/or elastic fibers in the vessel wall. It is also an effect of endometritis that has not been studied in full extent in dairy cows. Heppelmann et al. (2016) found that cows with endometritis presented the greater incidence of angiosclerosis on the endometrium than uterine healthy cows, which possibly affects uterine functions.

Treatment of uterine disease

Systemic and local treatments have been used to treat uterine diseases. Cephapirin, which is a first-generation cephalosporin antibiotic, is an approved treatment for purulent vaginal discharge in some countries. Denis-Robichaud and Dubuc (2015b) used the uterine infusion to treat PVD and endometritis at 35 DIM. Cephapirin infusion did not reduce the prevalence of uterine disease or ovarian activity. Pregnancy at first service in cows with PVD, endometritis or both was always greater in cows receiving the Cephapirin infusion. These results were in agreement with the work of Runciman et al. (2008) where intrauterine infusion with Cephapirin did not affect cure of endometritis. When cows had a major risk of severe uterine disease, within the first 21 DIM, however, the use of Cephapirin improved conception at first service. Other uterine infusions such as Formosulphatiazole have been compared with Cephapirin to treat endometritis diagnosed at 28 DIM. Formosulphatiazole and Cephapirin were treatments and propylene glycol uterine infusion was used as a control. Both antibiotic treatments improved the uterine health of endometriotic cows. Bacteriology culture and clinical scores for endometritis were significantly greater for the propylene glycol group. Reproductive outcomes were not reported in this study (Mari et al., 2012).

Ceftiofur, a third generation Cephalosporin antibiotic, has been used to treat uterine disease. It was shown to decrease the incidence of endometritis. Ceftiofur was effective only in cows that did not suffer retained placenta and with two or more births. A positive effect was not found in other categories of cows (Dubuc et al., 2011). The large variation among studies for dose, route of administration, and duration of treatment do not enable a clear position with respect to the effectiveness of Ceftiofur to treat metritis. Furthermore, the definition of the uterine disease, the definition of cure, reproductive outcome and experimental designs lack consistency in studies using Ceftiofur (Reppert, 2015).

Other antibiotic therapies for metritis have included the use of intramuscular amoxicillin and intramuscular amoxicillin plus oxytetracycline uterine infusion. The use of amoxicillin plus oxytetracycline uterine infusion produced better reproductive performance than only intramuscular amoxicillin in cows with metritis diagnosed during the first 21 DIM. The combined treatment increased the percentage of pregnant cows at first service and decreased the percentage of open cows at 150 DIM (Armengol and Fraile, 2015).

The use of antimicrobials and other drugs to treat uterine diseases such as retained placenta, clinical endometritis and puerperal metritis in cattle and other species, has been reviewed by Pyorala et al. (2014).

Subclinical endometritis does not have a treatment. Dini et al. (2015) proposed uterine lavage as an alternative to reduce the presence of PMN in the uterus but this treatment has to be tested for reproductive

outcomes in larger studies. Up to 90% of self-cure has been reported for SCE in dairy grazing cows (Priest et al., 2013).

Subclinical endometritis includes a uterine inflammatory response. Non-steroidal anti-inflammatory drugs (NSAID) have been evaluated, therefore, to treat SCE. Carprofen, which is an NSAID, was tested in cows with SCE diagnosed at 14 DIM (cutoff: 14% PMN). The SCE cows received three injections of Carprofen between 21 to 31 DIM. The treatment did not affect the percentage of PMN, anovulatory interval or milk production at 42 DIM. Pregnancies per artificial insemination were similar between groups at 42 DIM as well, however, cows with more than 14% of PMN at 14 DIM (severe SCE) had better conception when treated with Carprofen than cows in the same category without the Carprofen treatment (Priest et al., 2013).

Hormonal treatments for the uterine disease have been also tested. The use of $PGF_{2\alpha}$ has been the most studied but its outcomes are not clear enough. Drillich et al. (2005) suggested $PGF_{2\alpha}$ as the gold standard for treatment of chronic endometritis. Galvao et al. (2009) and Dubuc et al. (2011), however, showed that treatment with $PGF_{2\alpha}$ did not improve the condition of clinical or subclinical endometritic cows. Galvao et al. (2009) reported no effect of $PGF_{2\alpha}$ on endometritis but they indicated that $PGF_{2\alpha}$ improved the overall conception rate in endometritic cows.

Diet supplementation with selenium was tested with respect to its effect on SCE. Supplementation with different sources of selenium in diet before and after calving did not reduce the incidence of SCE at 30 DIM but cows with SCE had lower fertilization rate than healthy cows (Cerri et al., 2009).

Some lactic acid bacteria (LAB) have shown to decrease the infection and inflammation in cultured endometrial cells, but more research using *in vivo* models is needed to see if the uterine infusion of LAB can improve uterine health status (Genis et al., 2016).

Homeopathic remedies have been used as alternatives to prevent instead of cure endometritis. Different homeopathic treatments were tested from the first day of calving until 27 DIM. Intramuscular administration of these remedies did not decrease the incidence of endometritis at 21 and 27 DIM (Arlt et al., 2009).

Final considerations

The understanding of how uterine disease affects reproductive physiology by its effects on the uterus, ovaries and hormone profiles is basic to develop alternatives to mitigate deleterious effects of uterine disease on dairy cow fertility.

Over the years, risk factors for uterine disease susceptibility have been identified, dystocia, retained placenta, calving assistance, nutritional and metabolic disorders, environment and additional factors, affects the incidence of disease. Some theories are elucidated about effects of uterine disease on ovaries, less information is available about effects on the uterus of the dairy cow, but short and long-term consequences are still unclear about effects on the uterus and interaction within the hypothalamus-hypophysis-ovary axis. Although there are still some gaps to be filled such as to how uterine diseases affect reproduction, what is clear, is that uterine diseases diminish the general reproductive performance of the dairy cow.

Cow-side methodologies and laboratory assays are used to diagnose the different types of uterine disease. The test used for diagnosis and the moment when the sampling is done affects the results, treatments for uterine disease have a wide range of response from no response to cure, but also, uterine disease has shown a strength self-cure rate, so that, this combination makes difficult to handle uterine disease in the dairy cattle industry.

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Notes

1 This review was part of the first author MSc. Thesis at the University of Missouri, Columbia, MO, USA.

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