New Advances in the Management of Uterine Diseases

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Take Home Message

- Nearly 50% of dairy cows develop uterine diseases, which reduces pregnancy per AI, increases pregnancy loss, prolongs interval from calving to pregnancy, and diminishes the cow's productive lifespan and profitability.
- Peripartum metabolic stress compromises energy and calcium homeostasis, hindering optimal endometrial inflammatory defenses to resist pathogens.
- Treatment of uncomplicated cases of retained fetal membranes (RFM) is not usually justified, but supplementation of vitamin E, selenium, and beta-carotene can reduce RFM incidence. Metritis needs treatment with antibiotics; endometritis can be treated with intrauterine cephapirin and potentially dextrose; pyometra can be resolved with prostaglandin F2α ($PGF_{2\alpha}$).
- The threat of antimicrobial resistance has led to the development of a new wave of therapeutics and preventives for uterine diseases. The list includes an essential oil (carvacrol) that efficaciously cured metritis in organic dairy farms; two new vaccines for metritis (one had promising results); intravaginal lactic acid bacteria, chitosan microparticles, and recombinant IL-8 have also been explored.
- Prevention of compromised immunity at peripartum is critical to reducing uterine infections. Thus, strategies such as optimizing dry matter intake, cow comfort and environment, calcium homeostasis, adequate immunization, selection for smaller calves, and minimizing contamination of the uterus at any interventions are essential to managing uterine diseases successfully.

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Introduction

Uterine diseases occur in nearly 50% of dairy cows after parturition leading to disruptions in endocrine signaling, oocyte and follicle development, embryo quality, conceptus development, and maternal recognition of pregnancy, which hinders fertility, increases culling and causes substantial economic losses for dairy producers (Bromfield et al., 2015). The most common types of uterine diseases include RFM, metritis, endometritis, and pyometra. This manuscript aims to review the definition, incidence, significance, risk factors, and treatments of uterine diseases, as well as discuss the most recent advances and novel therapies and strategies under development to mitigate the adverse impact of uterine diseases in dairy cows.

Defining Uterine Diseases

Retention of fetal membranes is characterized as a failure to release the fetal membranes within 12 or 24 h after calving (McNaughton and Murray, 2009). Puerperal metritis is characterized by an enlarged, flaccid uterus, a fetid, watery red-brown discharge, and usually fever and other signs of systemic illness, such as depression or decreased milk yield and feed intake within ten days post-calving (Sheldon et al., 2006). Endometritis is classified as clinical or subclinical. Clinical endometritis is defined by the presence of purulent vaginal discharge detectable 21 days or more after parturition, or mucopurulent discharge detectable in the vagina after 26 days postpartum. Subclinical endometritis is characterized by inflammation of the endometrium measured by the relative presence of polymorph nuclear leukocytes (PMNL) in a uterine sample (collected by flushing or cytobrush) in the absence of clinical disease (Sheldon et al., 2006). The term for clinical endometritis has been questioned because a large proportion of cows presenting pus in vaginal discharge do not have concurrent neutrophil infiltration and pus in the endometrium (Dubuc et al., 2010). Thus, purulent vaginal discharge (PVD) was suggested as an alternative name for clinical endometritis (Dubuc et al., 2010). Also, the term cytological endometritis has been proposed as a “global” definition of endometritis based on the presence of PMNL in the uterine lumen with or without PVD (Dubuc et al., 2010). Pyometra is characterized by the accumulation of purulent contents within the uterus with a concurrent persistent corpus luteum and a closed cervix (Sheldon et al., 2006)

What is the Incidence of RFM and Uterine Diseases?

Retained fetal membranes affect 7.8% of the US dairy cow population (NAHMS, 2009) and reported incidence in other regions vary from 5% to 15% (reviewed by Gilbert, 2016). The incidence of metritis in dairy cows ranges from 10 to 36% (Lima et al., 2014). The reported incidence of PVD varies between 10% and 20% (LeBlanc et al., 2002; Dubuc et al., 2010). The incidence of subclinical endometritis is dependent on the cut-off for diagnosis and the time after parturition varies from 37 to 74% of animals (Gilbert et al., 2005). The incidence of pyometra is about 4% of dairy cows in each lactation (Akordor et al., 1986), but its rate may increase up to 13 % through routine use of GnRH in the early postpartum period (Etherington et al., 1984).

▪ Why are RFM and Uterine Diseases so Detrimental to Dairy Cows?

The impact of RFM ranges from impaired reproductive performance to the development of severe metritis, resulting in loss of milk production, reduced reproductive performance, increased risk of culling, and other uterine diseases and mastitis (reviewed by McNaughton and Murray, 2009). The economic losses caused by metritis are striking, calculated at $380 per affected cow due to reduced milk production, delayed conception, treatment and increased culling (Drillich et al., 2001). Clinical and subclinical endometritis have been associated with reduced P/AI at first service, increased pregnancy loss, and prolonged time to pregnancy (reviewed by Gilbert, 2016). Cows diagnosed with both clinical and subclinical endometritis had an extended interval from calving to pregnancy compared with those diagnosed with only one of the two diseases or with cows having no diagnosis of uterine diseases (Dubuc.et al., 2011). Subclinical endometritis leads to reduced fertilization and compromises early embryo development and survival (Cerri et al., 2009; Hill and Gilbert, 2008).

▪ What are the Risk Factors for RFM and the Development of Uterine Diseases?

The risk factors for RFM include induced parturition, shortened gestation, abortion, dystocia, fetotomy, cesarean section, twins, and deficiencies of vitamin E, selenium, beta-carotene, and calcium (reviewed by Lima, 2013). The risk factors for metritis include primiparity, dystocia, male offspring, twins, stillbirth, abortion, prolapsed uterus, RFM, ketosis, reduced feed intake 2 to 3 weeks before calving, increased levels of BHBA, NEFA, haptoglobin, and hypocalcemia (reviewed by Lima, 2013). Risk factors for PVD include dystocia, male offspring, twins, stillbirth, abortion, RFM, metritis, vulval conformation, and ketosis (reviewed by Lima, 2013). Risk factors for subclinical endometritis include body condition score, ketosis, haptoglobin, negative energy balance (reviewed by Gilbert, 2016). Risk factors for pyometra include the use of GnRH early postpartum and exposure to Tritrichomonas fetus positive bulls (reviewed by Gilbert, 2016).

▪ Metabolic Stress, Immune Response and Uterine Diseases

A common denominator across uterine diseases is the disruption of the immune response. Dairy cows seem to be prompt to the development of metabolic stress, which in turn compromise the ability of the immune system to recognize fetal membranes and pathogens, that when not eliminated will cause the development of uterine diseases. During the peripartum, stressors such as dietary changes, hind-gut acidosis, systemic inflammation, heat stress, psychological stress, feed restriction, and compromised gastrointestinal integrity can disrupt energy homeostasis (tendency of body biological systems to maintain stability while adjusting to conditions that are optimal for survival) and homeorhesis (tendency of body biological systems to return to a particular state) and immune competence (Sheldon et al., 2017).

Also, calcium deficiency can lead to an impaired immune response and increased odds of developing uterine diseases (Martinez et al., 2012).

The immune system recognizes and eliminates pathogens through the identification of pathogen components called major pathogen-associated molecular pattern (PAMPs). Professional immune cells, endometrial cells, and granulosa cells have a series of receptors – named pathogen recognition receptor (PRR) – that can identify the PAMPs. A major PRR is toll-like receptor TLR4 that when bound by a PAMPs will activate a molecular cascade that leads to the production of proinflammatory cytokines (IL-1β, IL-6, and TNFα) and chemokines (CXCL1, CCL20, and IL-8) that can elicit an effective immune response (Sheldon and Bromfield, 2011).

Recent work by Sheldon and colleagues (2017) discussed how metabolic stress hampers the inflammatory response to pathogens. They showed that glucose and glutamine, the primary energy sources for cells, have their abundance reduced in postpartum dairy cows. They also showed that inflammatory responses aggravate metabolic stress, with cows and tissues using glucose in more significant quantities when challenged by PAMPs. They also showed that perturbing glycolysis or AMP-activated protein kinase activity decreased IL-1β, IL-6, and IL-8 in the endometrium.

▪ How Pathogens Get Access to the Uterus of Dairy Cows?

It is widely believed that uterine bacteria ascend from the vagina or through the vagina from the environment or feces when the cervix, which serves as an anatomical and immunological barrier, opens during parturition (Sheldon and Dobson, 2004). However, pathogens associated with the development of metritis such as Bacteroides, Fusobacterium, and Porphyromonas are part of the natural flora of the rumen in cows and are shed in feces. Thus, ascending uterine contamination from the environment could contribute to the development of metritis. Furthermore, a specific uterine pathogen, Fusobacterium necrophorum, is known to gain access to the circulation, probably during episodes of rumen acidosis, and cause liver abscesses in cows (Tadepalli et al., 2009).

A recent study, considering the scenarios described above, investigated the possibility of hematogenous (through the blood) contamination of the uterus (Jeon et al., 2017). The investigation revealed that significant uterine pathogens such as Bacteroides, Porphyromonas, and Fusobacterium were part of the core genera in blood, feces, and vagina. However, other uterine pathogens such as Prevotella and Helcococcus were not part of the core genera in vaginal samples. Moreover, uterine pathogens showed a significant and robust interaction with each other in the network of blood microbiota, but not in feces or vagina, suggesting that hematogenous uterine contamination might be necessary for the etiology of uterine diseases.

▪ How Can RFM and Uterine Diseases be Treated?

Retained Fetal Membranes

Although manual removal remains a common practice, many studies failed to show any benefit of this approach on reproductive performance or milk production, and more severe uterine infections occurred when compared with more conservative treatment (Bolinder et al.,1988). Therapy of RFM with GnRH, oxytocin, and $PGF_{2\alpha}$ is not beneficial to placental release or future reproductive performance (reviewed by Gilbert, 2016). A study suggested that collagenase, an enzyme capable of breakdown collagen, might aid detachment of the caruncle-cotyledon bond in cows with RFM (Eiler and Hopkins, 1993). The umbilical arteries of cows with RFM were injected with 200,000 IU of collagenase leading to earlier placental release than untreated herd mates. Although collagenase therapy was promising, the high cost (~US$75.00) and lack of studies evaluating effects on milk production and reproduction made its use an unfeasible alternative.

The results of antimicrobial use to treat RFM are controversial. Cows diagnosed with RFM are more likely to develop metritis. Thus, the claim behind using antibiotics to treat RFM is to prevent or mitigate the possible severity of metritis and its subsequent adverse effects on fertility. Intrauterine antimicrobials however were unable to reduce the incidence of metritis or improve fertility (reviewed by Lima, 2013). Oxytetracycline, which is often used for intrauterine treatment in cattle with RFM and metritis, inhibits metalloproteinase (MMPs) essential for endometrial repair in other species, which may interfere with the normal placental detachment mechanisms. The use of systemic antibiotics are believed to be beneficial in RFM cases with concurrent metritis and fever (reviewed by Lima, 2013). A study revealed that treating only cows with RFM and fever can reduce unnecessary antimicrobial use (Drillich et al., 2006). Treatment of cows with RFM for five days with 2.2 mg/kg of ceftiofur hydrochloride was beneficial in preventing metritis when compared with estradiol cypionate or no treatment; however, no significant subsequent improvements in reproductive performance were identified (Risco and Hernandez, 2003).

Metritis

Cows diagnosed with metritis develop moderate to severe illness. There is, therefore, a consensus that most of the metritis cases require systemic antibiotic treatment (LeBlanc, 2008). Currently, the most common treatments of choice for metritis are ceftiofur (2.2 mg/kg IM once a day); procaine penicillin (21,000 IU/kg IM once or twice a day for 3 to 5 days); or ceftiofur crystalline free acid sterile suspension (6.6 mg/kg s.c twice each 72 hours) (reviewed by Lima, 2013). Other alternative treatments reported with similar efficacy to ceftiofur or penicillin include the systemic use of tetracycline at a dosage of 10 mg/kg, systemic use of ampicillin at a dosage of 11 mg/kg, and intrauterine treatments with oxytetracycline and ampicillin (reviewed by Lima, 2013). The addition of one dose of flunixin meglumine does not improve outcomes over the use of systemic antibiotics alone (Drillich et al., 2007). Carprofen decreased the use of antibiotic for metritis from 3.63 to 1.63 doses per cow without altering the incidence of endometritis, reproductive performance, or milk production (Pohl et al., 2016).

Endometritis and Pyometra

Endometritis treatments reported include systemic or intrauterine administered antibiotics, intrauterine substances and systemic use of $PGF_{2\alpha}$. Except for cephapirin and hypertonic dextrose (reviewed by Lima, 2013), all other studies had negligible to no benefits on reproductive performance. Many studies suffered from issues such as a lack of negative controls and statistical power, diagnostic criteria for endometritis that were not validated as having an impact on reproductive performance, and no label approval for intrauterine use with no published information on withdrawal times. Several studies investigated the use of $PGF_{2\alpha}$. However, the majority showed no benefits for reproductive performance (reviewed by Lima, 2013). A meta-analysis evaluated the benefits of $PGF_{2\alpha}$ in cows with endometritis and confirmed a lack of improvement in reproductive performance (Haimerl et al., 2013). Although $PGF_{2\alpha}$ (in cows with a function corpus luteum) induce luteolysis, open the cervix, stimulate uterine contractility and potentially release inflammatory content, these benefits are not sufficient to restore the fertility of cows with endometritis.

Pyometra

Pyometra, on the other hand, can be treated with $PGF_{2\alpha}$ and its analogs (reviewed by Gilbert, 2016). Treatment results in bacteriologic clearance of the uterus in about 90% of treated cases. Recurrence of pyometra after a single treatment occurs in 9% to 13% of cases, and first service conception rate of approximately 30% or more follows treatment; however 80% of animals may be expected to conceive within 3 to 4 inseminations (reviewed by Gilbert, 2016).

▪ Novel Therapies and Strategies to Mitigate the Detrimental Impacts of Uterine Disease in Dairy Cows

Lately, the threat of antimicrobial resistance provided reasons and funds to support a plethora of new studies focused on the development of preventives or novel treatments to reduce the incidence and the negative impact of uterine disease and use of antibiotics.

Mannose and Bacteriophage

Machado et al. (2012) evaluated the effects of intrauterine administration of mannose or a bacteriophage cocktail and the presence of E. coli and T. pyogenes in the uterine lumen on uterine diseases and reproductive performance of dairy cows. Unfortunately, the results of their study revealed no effects on uterine health, reproduction performance, or responses in cultures for E. coli and T. pyogenes.

Essential Oils

A study compared the efficacy of using an intrauterine solution containing a certified organic product – an essential oil based on carvacrol (Optimum UterFlush, Van Beek Natural Science, Orange City, IA) – against a intrauterine use of iodine povidone (control) in organic dairy farms (Pinedo et al., 2015). Cows treated with essential oil had a lower incidence of fetid discharge at days 6 and 14 after the first treatment and increased odds of pregnancy at the first AI, 150 days postpartum, and 300 days postpartum.

Metritis Vaccines

Two vaccines for metritis have been tested (Machado et al., 2014; Freick et al., 2017). The first vaccine contained different combinations of proteins

(FimH; leukotoxin, LKT; and pyolysin, PLO) and/or inactivated whole cells (Escherichia coli, Fusobacterium necrophorum, and Trueperella pyogenes). This formulation, when used subcutaneously, reduced the incidence of metritis from 27.6% in control cows to 11.1% (Machado et al., 2014). The second vaccine was a herd-specific vaccine containing inactivated whole bacterial cells of Trueperella pyogenes, Escherichia coli, Streptococcus uberis, Bacteroides, and Peptostreptococcus species obtained from uterine swabs of primiparous cows diagnosed with metritis. This second formulation was unable to reduce the incidence of metritis (Freick et al., 2017).

Probiotics

A study evaluated the effects of an intravaginal infusion of a cocktail of lactic acid bacteria (LAB) composed of Lactobacillus Sakei FUA3089, Pediococcus Acidilactici, FUA3138, and Pediococcus Acidilactici FUA3140 on the incidence of metritis (Deng et al., 2015). Treatment with LAB at 1 and two weeks before calving reduced incidence of metritis from 38.0% to 15.0 and 6.0%, respectively. Moreover, authors reported lowered incidence rates of metritis and total uterine infections of postpartum dairy cows were associated with enhanced vaginal mucus secretory immunoglublin A. Cows administered intravaginally with LAB had lower systemic inflammation, as denoted by lower concentrations of lipolisaccharide-binding protein (LBP), and a tendency of lower serum amyloid A (SAA) in the serum of the treated cows. Authors suggested that intravaginal administration of LAB might be a key strategy to improve immune status and lower the risk of uterine infections of transition dairy cows.

Chitosan Microparticles

A study evaluated the intrauterine use of chitosan microparticles (CM) a day after calving to prevent metritis (Daetz et al., 2016). Treatment with CM decreased the incidence of metritis up to 7 DIM when compared with CON (46.2 vs. 65.4%). But, differences in the rate of metritis were not present at day 4 (11.5% vs. 17.3%), 10 (61.5% vs. 73.1%), and 14 postpartum (63.5% vs. 73.1%). An ongoing study (presented by Dr. Klibs Galvao at the DCRC webinar) is evaluating the effects of CM as treatment for cows with metritis, and according to his presentation, the results are not encouraging for CM as a treatment for metritis.

Chromium Propionate

A recent study evaluating the use of chromium propionate 21 d before expected calving through 63 d postpartum administered by daily topdress at a rate of 8 mg/d revealed a reduction on the incidence of purulent vaginal discharge and a tendency to reduce the influx PMNL to the uterus between 40 to 60 days postpartum (Yasui et al., 2014). The cows treated with chromium propionate also had an increased infiltration of PMNL at day 7 postpartum, a sign of effective uterine immune response early postpartum, and one that authors suggested was the major driving factor behind the reduced incidence of cows with purulent vaginal discharge between days 40-60 postpartum.

Recombinant IL-8

A recombinant chemokines (rIL-8) developed by Dr. Rodrigo Bicalho's laboratory was used intrauterine within 12 hours of calving to prevent RFM and metritis. The rIL-8 was able to reduce the incidence of RFM from 7.7% to 2.9% and the rate of metritis from 19.2% to 6.8% (Bicalho, 2016). No results on incidence of endometritis were reported.

Automated Health Monitoring System

Stangaferro et al. (2016) demonstrated that the use of health index – an arbitrary numerical value generated according to the postpartum recovery of rumination, activity and days in milk of the cow – produced by Data Flow II software (SCR Ltd., Netanya, Israel) and used as a diagnostic tool resulted in sensitivities (percentage of cows diagnosed as sick) of 49 to 78% for metritis. The specificity of using the health index (percentage of cows diagnosed as healthy) as a diagnostic tool for postpartum disease (e.g., displaced abomasum, ketosis, indigestion, mastitis, and metritis) was 98% (Stangaferro et al., 2016). These are promising results and suggest that herds that have sub-par transition cow monitoring by herd personnel or no other means of evaluating performance (e.g., individual daily milk yield, milk yield deviation, etc.) could benefit significantly from automated rumination-activity monitoring systems.

Although a series of these new preventives and therapies hold promise to overhaul how uterine diseases can be managed, more studies are needed to replicate current successful outcomes and to clarify what is the cost-benefit of using these new technologies to reduce the incidence of uterine diseases.

▪ Management Strategies to Prevent RFM and Uterine Diseases

A common denominator across uterine diseases is a disrupted immune function derived from metabolic stress. Therefore, it is reasonable to surmise that management strategies to prevent uterine disease should focus on optimizing cow comfort, adequate intake of energy, calcium, and antioxidants to maintain homeostasis and a fully functional immune system during the periparturient period. Additionally, adequate immunizations to prevent infectious diseases, the use of sexed semen and calving ease selection to favor the birth of female and smaller calves, and proper techniques to assist cows to calve can help prevent the occurrence of uterine diseases. Dry matter intake is the principal factor of dairy production, and its effects on uterine health have been demonstrated. Thus, several management strategies have been suggested (LeBlanc, 2015) to reduce the odds of uterine disease development:

1. Feed daily for 3 to 5% left over
2. Provide ≥75 cm (30”) bunk space per cow or 4 cows per 5 headlocks
3. Offer ≤85% stall stocking density
4. Provide >11m^2 (120 ft^2) of bedded pack/cow
5. Build a maternity pen that supports 130 to 140% of the average number of monthly calvings with comfort stalls
6. Have an adaptation of <24 h in calving pen
7. House heifers in pens separate from mature cows
8. Minimize group changes
9. Have heat abatement (sprinklers and fans) on when THI > 68
10. Manage nutrition, so cows calve with BCS = 3.0 to 3.5
11. Offer 3 to 4 weeks on close-up diet or 6 weeks as one dry group
12. Meet but do not exceed energy requirements 8 to 3 weeks prepartum
13. Offer water ad libitum with at least 10 cm (4”) linear trough space per cow and two sources per pen
14. Feed 1000 IU vitamin E/d; up to 2000 IU/d for RP; 0.3 ppm selenium (ideally approx. 6 mg/d).
15. Provide anionic salts during the prepartum for multiparous to prevent hypocalcemia.
16. Monitor health for early diagnosis of disease and treatment.

▪ Conclusions

An important factor related to the treatment of uterine diseases is the cost-benefit to dairy producers. For cases of RFM with fever and puerperal metritis, treatment is justified to improve the cow’s welfare and to the reduce odds of death. However, improvements in reproductive performance, the incidence of other diseases, and milk production are not always present (Chenault et al., 2004; McLaughlin et al., 2012). For endometritis, the treatment with intrauterine cephapirin does lead to improved reproductive performance and seems a reasonable choice. However, optimization of cost-benefit is undoubtedly a function of prevention rather than treatment. A fair case can be made that uterine diseases have metabolic stress as a common denominator and strategies that minimize its risks are pivotal to prevent uterine disorders. Moreover, the worldwide threat of antimicrobial resistance has led to the development of an arsenal of surrogate therapies that can aid in the prevention of uterine diseases. Nevertheless, more studies are needed to refine the novel therapeutics, which can consistently lead to improved cost-benefits for dairy producers. Therefore, it is reasonable to surmise that soon a program incorporating the novel preventives and strict management practices to reduce metabolic stress will be available to optimize dairy producers' strategies and mitigate the negative impact of uterine diseases in dairy cows.

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