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The Consequence of Postpartum Uterine Disease on Dairy Cow Fertility[1]

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Introduction

After calving, all dairy cows have some bacterial contamination in the uterus. The persistence of pathogenic bacteria in the uterus is a major cause of uterine diseases in the dairy cow, including metritis and endometritis (Sheldon et al. 2009). Metritis is defined as a uterine infection occurring within 21 days of calving with a watery and extremely smelly vaginal discharge, while endometritis occurs after 21 days from calving and results in a pus-filled discharge from the vagina (Sheldon et al. 2006). Uterine disease affects 20 to 40% of dairy cows and has an approximate annual cost of $900 million to the US dairy industry, mostly due to a decline in fertility after the resolution of disease (Table 1) (Overton and Fetrow 2008). Risk factors for the development of uterine disease include retained placental membranes, birth of twins, difficult calving, and stillbirth (Potter et al. 2010). The immune response of the cow to the pathogenic bacteria in the uterus is likely to play a significant role in the establishment of disease.

Numerous bacterial species are associated with the development of uterine disease. The most commonly isolated uterine bacteria in diseased cows include *Escherichia coli*, *Trueperella pyogenes*, and anaerobic species such as *Fusobacterium necrophorum* (Bonnett et al. 1991). *E. coli* is known to infect the uterus within the first week after calving. Uterine *T. pyogenes* is related to greater damage of the uterine tissues and causes the most severe cases of uterine disease (Bonnett et al. 1991; Williams et al. 2005).

A cow's ability to become pregnant in an optimal period of time after calving is essential to milk production and economic success of a dairy farm. Uterine disease increases infertility in the dairy cow (Ribeiro et al. 2016). Cows with endometritis take longer to become pregnant compared to healthy cows (Dubuc et al. 2010). Metritis disrupts ovarian function and prolongs the period between ovulations when the cow can be bred (Opsomer et al. 2000). Cows with large quantities of bacteria in the uterus have reduced ovarian follicle size and estrogen production, which decrease fertility (Sheldon et al. 2002). Cows diagnosed with retained placental membranes and/or metritis show a reduced chance of becoming pregnant after breeding, and increased pregnancy loss (Ribeiro et al. 2016).

Uterine diseases usually take place early after calving and are resolved long before the first attempt to breed cows. It is still unknown why it is difficult for cows that have had uterine disease to become pregnant after the disease has been resolved and the cows are ready to be bred (Table 1).

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Uterine Response to Bacterial Infection

After calving, the uterus must recover quickly to be prepared for breeding following the voluntary waiting period, which is determined by the producer. This recovery involves a process called uterine involution, in which the uterus undergoes tissue repair, regeneration, and elimination of bacteria that may have colonized the uterus. The cow's immune system recognizes bacteria and attempts to eliminate them by activating a series of cellular receptors known as Toll-like receptors to combat infection. These Toll-like receptors are located on cells of the immune system and in the reproductive tract. Subsequently, the immune system of the cow is made aware of the bacteria and is activated in an attempt to eliminate the threat of infection (Herath et al. 2006). When Toll-like receptors of the uterus are activated, the cow's immune system produces molecules called cytokines that activate the immune system and aid in the killing of bacteria. Cytokines produced during uterine inflammation include interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNFα) (Cronin et al. 2012; Turner et al. 2014). These inflammatory cytokines attract specialized immune cells from the blood called neutrophils that kill and remove infectious bacteria. Additionally, other important inflammatory cytokines such as IL-10 reduce the immune response after the bacteria have been killed and return the uterus to a state in which pregnancy can be achieved (Sheldon et al. 2014). It is not yet known whether cows that fail to generate a robust immune response to bacteria develop uterine disease, or cows that "over-respond" to bacteria develop uterine disease due to their inability to resolve uterine inflammation.

The Ovarian Response to Bacterial Infection of the Uterus

Cytokines are important to both the immune response to bacteria and to normal physiological processes that regulate reproductive functions, such as ovulation, follicle growth, and corpus luteum formation. These processes contribute to the achievement of pregnancy (Richards et al. 2002). The dominant follicles of cows with uterine disease are smaller and slower growing, and they produce less estrogen than those from healthy herd mates (Sheldon et al. 2002). The infertility of cows with uterine disease may be a result of inappropriate immune response to uterine bacteria; however, bacteria also have direct negative effects on the egg and the granulosa cells of the ovary that support the egg's development. Certain parts of bacteria that are responsible for uterine infection are found inside the ovarian follicle along with the egg. The bacterial component called lipopolysaccharide can activate Toll-like receptors. Experiments show that lipopolysaccharide increases the production of immune cytokines and reduces estrogen production by the granulosa cells (Herath et al. 2007; Bromfield and Sheldon 2011). Lipopolysaccharide also reduces the likelihood that the egg will become an embryo after fertilization (Soto, Natzke, and Hansen 2003). It is not yet known how lipopolysaccharide from bacteria accumulates in the ovarian follicle; however, the impact it has on the cells of the ovary probably reduces the fertility of cows.

Treatments and Prevention Strategies for Uterine Disease

The use of antimicrobials is currently considered the best option for clinical treatment of uterine disease in the dairy cow. Interestingly, metritis has a self-cure rate of 30% (Haimerl and Heuwieser 2014). Ceftiofur is a broad-spectrum antimicrobial drug used largely for uterine disease. Due to its zero milk discard, it is the main antimicrobial applied to cows with severe uterine disease. Other antimicrobials such as ampicillin have been reported to have similar efficacy in resolving uterine disease after calving (Lima et al. 2014). Antimicrobial treatments are used to help alleviate the clinical symptoms of uterine disease in cows, but their use has no improvement on subsequent cow fertility (Galvao et al. 2009b). The use of the hormone prostaglandin F2α (a common component of estrous synchronization procedures) to return cows with uterine infection to a state of estrus for breeding and to help clear uterine infections has been tested. However, large studies now suggest this approach has little benefit as a treatment or as a way to improve fertility of cows with uterine disease (Galvao et al. 2009a).

Recently, experimental vaccines that target uterine disease-causing bacteria have been tested to prevent the establishment of disease and any subsequent effects on fertility. Results thus far have been contradictory. One study suggests vaccination reduces the disease severity and interval from calving to pregnancy (Machado et al. 2014), while a second study suggests vaccination has no effect on uterine disease incidence or fertility in dairy cows (Freick et al. 2017). Further work on the development of effective vaccines to prevent uterine disease and improve reproductive outcomes is needed.

Conclusion

Uterine disease is common in the dairy cow after calving and reduces fertility. The way in which fertility and uterine disease are linked is not yet fully understood, but it involves long-term effects on the uterus and ovary. Current treatment strategies alleviate the symptoms of uterine disease. However, it is unclear if these treatments prevent infertility of dairy cows caused by uterine disease.

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Table 1. Incidence and effects of uterine disease in dairy cows.

	Disease Presentation	Incidence	Reduction in Pregnancy Rate Compared to Healthy Cows
Healthy	Until pregnancy diagnosis	50 to 60%	-
Metritis	≤ 21 days after calving	36 to 50%	17.3%
Endometritis	≥ 21 days after calving	15 to 20%	27%
Adapted from Dubuc et al. (2010); LeBlanc et al. (2002); and Ribeiro et al. (2016).			