Abstract

Reproductive performance in dairy cows and farm economic efficiency are related to uterine health status at the end of the voluntary waiting period (VWP). Uterine diseases affect about half of all dairy cows in the postpartum period, causing infertility by disrupting uterine and ovarian functions. The reproductive cycle of dairy cows has several critical checkpoints where interactions with the host immune response are necessary, and where deregulation can lead to reproductive failure. As immunity of the reproductive tract appears more and more as a major player in uterine health during the periparturient period in dairy cows, a better understanding of the complex immunological processes at play in the periparturient cow is essential to design animal and herd health management strategies to prevent postpartum uterine diseases in dairy cows and to reduce the carryover negative effect on reproductive performance. The objective of the present review is to focus on the immunological processes involved in pregnancy and the periparturient period in the dairy cow that could be associated with uterine diseases, as they relate to reproductive failure after the VWP.

Introduction

In dairy cows, the incidence of disease during the periparturient period is high. During the postpartum period, the most prevalent pathologies are metabolic, mammary and uterine diseases. Although these pathologies involve different organs, they are all linked to an impairment in immune function during the periparturient period. Of these pathologies, it is postpartum uterine diseases that have the greatest impact on the health and productivity of dairy cows and, consequently, on the financial sustainability of the industry. Both reproductive performance in dairy cows and farm economic efficiency depend on the uterine health status of cows at the end of the VWP.1-4

The reproductive cycle of dairy cows has several critical checkpoints where interactions with the host immune response are necessary, and where deregulation can lead to reproductive failure. Several inflammatory mediators have evolved alongside reproductive physiology and signaling reproductive events rather than acting exclusively as part of the inflammatory process. Some of these inflammatory mediators are associated with fertilization (e.g., in response to allogeneic sperm), pregnancy recognition, pregnancy maintenance in the presence of an immunologically distinct fetus, parturition, and uterine involution. Of course, immune defense also plays a critical role in infectious and inflammatory processes, especially those caused by sexually transmitted pathogens. In humans, more than twenty different pathogens can be transmitted through sexual intercourse.5 However in dairy cows, where artificial insemination has become the major mode of reproduction, sexually transmitted diseases are limited (trichomoniasis, campylobacteriosis, and leptospirosis).6 The postpartum period is by far the most vulnerable period for infection and inflammation of the reproductive tract in dairy cows.

Reproduction and immunity are very complex processes and interlaced through common mediators. Consequently, determining etiology, establishing a diagnosis, and achieving effective treatment for a reproductive pathology are often challenging. Clearly, understanding immunological processes in reproductive physiology is critical to improving the current management for high-yielding dairy cows. This review focuses primarily on the immunological processes involved in pregnancy and the periparturient period in the dairy cow, as they relate to reproductive failure after the VWP.

Innate versus adaptive immunity: a review

The immune system is divided into two major subsystems: innate and adaptive. When protecting the body against invading pathogens, the actions of these subsystems are different but complementary.
Innate immunity, which encompasses mechanical, chemical, and cellular components, is the first responder. It is on constant standby to respond promptly at the first signs of microbial invasion. The vulva, vagina, and cervix constitute mechanical barriers that prevent ascending invaders from reaching the uterus. In short, it is the mucosa of the vagina and the uterus that prevent pathogens from invading the reproductive tract. Mucus is a family of high-molecular-weight glycoproteins that are very effective at trapping microbes and inhibiting the growth of pathogens because of its acidic effect. Furthermore, epithelial cells produce antimicrobial peptides and glycoproteins that neutralize bacteria before they even reach the uterine cavity. Intact mucosal epithelial cells also play an active immunological role by sending signals to the underlying tissues immune cells, which then produces cytokines and chemokines. These substances act to destroy infected cells through necrosis, apoptosis, or phagocytosis, in addition to interacting with the adaptive immune response.

An important chemical component of the first line of immune defense is natural antimicrobial peptides (NAPs). These are produced by epithelial cells and neutrophils, and eliminate pathogens through abrogation of pH and ionic concentration gradients. Natural antimicrobial peptides possess additional functions in cell proliferation, cytokine induction, chemotaxis and modulating the innate and acquired immunity. The major NAPs are defensin, elafin, cathelicidin, secretory leukocyte protease inhibitor (SLPI), and lactoferrin.

As microbes evolved to become more efficient in breaking host defenses, the innate immune system was forced to develop other response mechanisms. The most rapid and active immune response to bacterial infections is provided by pattern recognition receptors (PRRs) which recognize pathogens based on pathogen-associated molecular patterns (PAMPs). Pattern recognition receptors can also recognize tissue and cellular damage in the host based on damage-associated molecular patterns (DAMPs) including nucleic acids released from damaged or dead cells. The most studied PRR is the Toll-like receptor (TLR) family and its nine members. Toll-like receptors are expressed at the surface of several innate immune cells, including neutrophils, macrophages, dendritic cells, dermal endothelial cells, and mucosal epithelial cells. This is the major sensing component of the innate immune system. Other classes of PRRs have also been identified: nucleotide oligomerization domain (NOD)-like receptors (NLRs); retinoic acid inducible gene I (RIG-I)-like receptors, or RLRs; and cytosolic DNA sensors.

Toll-like receptors are the most documented form of PRR in cows. These receptors detect and identify PAMPs, gather adapters to initiate intracellular signaling pathways to recruit immune cells, secret antimicrobial factors that eradicate pathogens, and facilitate interaction (crosstalk) with the adaptive immune system. Toll-like receptors are a fixed set of sensors programmed to respond the same way against all types of invaders and are highly conserved across species. Toll-like receptors signal transduction is mediated by the recruitment of different intracellular mediators like MyD88 and TRIF, which leads to the production of cytokines and chemokines, as well as prostaglandins, vasoactive mediators that manage the defense strategy and eventually cause the clinical signs associated with disease (e.g. swelling).

After TLRs have sensed and identified invading pathogens, the innate immune cellular effectors are called into play. These effectors include macrophages, neutrophils, eosinophils, basophils, and mast cells. After initiating phagocytosis, cellular effectors then release radicals, enzymes, and other molecules into the compartment in order to desactivate the contained invader and prevent the host from being exposed to dangerous elements. If the cellular effectors cannot eliminate the invader, molecular effectors like the protein complement system (e.g., C3) or mannose-binding lectin (MBL) proteins go to work in the extracellular space, although this process exposes host cells to toxic elements.

The cascade of events associated with the host response and triggered by the activation of inflammatory mediators of the innate immune system results in the cardinal signs of inflammation: fever, swelling, redness, and pain. Pus is a sign of infiltration by neutrophils and macrophages into a tissue that has been invaded by pathogens. Common inflammatory mediators in the reproductive tract include the cytokines IL-1β, IL-6, and TNF, along with chemokines such as IL-8, and the prostaglandin E2. Cytokines often produce secondary clinical effects like reduced appetite and activity.
Innate immunity is often triggered within hours of a microbial invasion; by contrast, the adaptive immunity response takes days. For example, it is not until seven days after first exposure, and two to three days after a second exposure, that the first antibody is measured in serum. In chronic situations the innate immune response remains similar in nature and efficiency over time, but in the case of the adaptive immunity, the response becomes more efficient at subsequent invasions.

The adaptive immune system functions in a very different way from the innate immune system. The primary difference lies in its ability to recognize many different unique molecular components of the invader and so block invasions in the future. The process is based on sampling and presenting pieces of the invader to adaptive immune cell responders called dendritic cells, which are differentiating monocytes that enter the invaded tissue. A molecular piece of the invader is anchored on the surface of the dendritic cells via major histocompatibility complex protein class I and class II molecules (MHC Is and MCH IIs). The dendritic cells then migrate to meet the lymphocytes in places like the lymph nodes and bone marrow. The adaptive immune system relies on two different families of lymphocytes: B cells derived from the bone marrow, and T cells derived from the thymus. All lymphocytes develop their specificity through gene rearrangement; in short, the antigen-binding domain of heavy and light chains is rearranged, enabling it to make antibodies of different classes. B cells recognize over 1,000 different antigens, some of which become antibody factories to produce a great number of antibodies for selected antigens. The more disulfide binding between chains, the more rigid and specific the antibody molecule is. The main classes of antibodies are: IgG, which exhibit the highest concentrations; IgM, the first antibody made after the activation of B cells; IgA, which is important for mucosal surface defense; and IgE, which is associated with fighting parasites and allergies.

In T cells, the different chains (alpha, beta, gamma, and delta) are re-arranged to provide different antigen receptors (TCRs) and different specificities to lymphocytes. Gamma and delta chains are the most common chains of T cells in cows. There are two types of T cells. The first is the helper T cell, which manages adaptive immunity by making the right combination of cytokines and surface proteins to provide enough B and T cells with killing capabilities at the right time. Killer T cells can recognize the right piece of antigen using the MHC protein on their cell surface and then destroy the invader. As with the B cell, the rearrangement of TCR genes enables recognition of more than 1,000 different antigens.

Due to the complexity of immune processes, specific tissues like lymph nodes and the spleen are organized as adaptive immunity screening and production facilities. The level of adaptive immune response is based on the number of lymphocytes able to recognize and respond to antigens. Thus, the larger the number of responding B and T cells, the faster and stronger the response to the invader.

Cytokines (e.g. TNF alpha, IL-1 and IL-6) are small pleiotropic glycoprotein mediators whose biological action is locally mediated by specific receptors. Chemokines (e.g., IL-8) are small chemotactic cytokines that act locally by recruiting leukocytes to the site of inflammation and activating them. Basically, chemokines attract immune cells to the tissue and then cytokines differentiate and activate them. Immune cells, including monocytes, macrophages, NK cells, and DCs, are sources of immunoregulatory cytokines and chemokines in the female reproductive tract. The concentration of cytokines and chemokines in the endometrium varies during both normal physiological processes and in the presence of pathological conditions of the reproductive tract. Both cytokines and chemokines have been shown to be critical for fertilization, implantation, pregnancy, and remodeling of the uterus during the menstrual cycle in women.

Modulation and suppression of immunity during pregnancy and the periparturient period

Immune modulation during pregnancy

The fertility rate for dairy cows is around 90% and does not differ between low-to-moderate and high-producing animals. However, the calving rate in lower producing animals is approximately 55%, compared to 35% in high-producing animals. Pregnancy losses are thought to occur primarily at the recognition or pre-implantation period. In fact, pregnancy is an active and highly regulated immunologic process in which the maternal immune system adjusts to the pregnancy and ensures support of the
developing alloantigenic conceptus without threatening the mother. This immune tolerance may be explained by the antigenic immaturity of the fetus because, as is the case in other mammalian species, the bovine trophoblast does not express MHC I protein in areas that are in contact with the maternal endometrium during early pregnancy. This phenomenon reduces exposure of the maternal system to paternal antigens. Chorionic tissue down-regulates MHC I expression throughout the pregnancy at the placental level, while it does so only during the first half of the pregnancy at the interplacentomal space. Interestingly, bovine embryos produced through somatic cell nuclear transfer express MHC I earlier during pregnancy and have a much lower conception rate than \textit{in vivo} embryos. Furthermore, the genes and pathways of innate and adaptive immunity involved in the maternal immune response to the embryo during the pre-implantation period are up-regulated.

Another immunological adjustment performed during pregnancy is the recruitment of macrophages. These cells play an important role in uterine remodeling before embryo implantation, immune tolerance toward fetal antigens, parturition, postpartum involution, immunomodulation of neighboring leukocytes, and uterine infection. During pregnancy, there is a massive accumulation of macrophages, mainly in the superficial uterine stroma in the interplacentomal region, in particular in the stroma of the maternal-villus tree of placentomes. A regional effect is also seen for MHC II expression on macrophages. In sheep, pregnancy is also associated with an increase in the number of macrophages in stroma. Some macrophages are pro-inflammatory (M1 type) and have the capacity of presenting antigens (cell-mediated immune response). Others are anti-inflammatory cells (M2 type) are produced during wound healing and tissue remodeling; their activity is immunosuppressive or promote an antibody-mediated immune response. The final effect of macrophages depends on their polarization status, which is determined by the surrounding milieu. Endometrial macrophages also produce platelet-derived growth factor beta, which plays a role in tissue remodeling and proliferation. In cattle, there is evidence that IFN-\(\tau\) alters peripheral and endometrial immune cell populations by increasing cells exhibiting T regulatory phenotypes (CD4+/CD25+) able to secrete IL-4, which can induce tolerance to paternal alloantigens. It should be noted that since there is no increased incidence of disease during pregnancy, alteration in maternal immune regulation during pregnancy does not seem to equate with generalized immunosuppression.

Inflammatory mediators have been recognized as a necessary component for the establishment, development, and maintenance of pregnancy. However, they may also be a significant impediment to a successful periparturient period in the dairy cow because they cause a deregulation of the immune system at the end of pregnancy when there is increased demands on the cow as the fetus completes its development and the mother prepares for lactation. The prolongation of this physiological and immunological processes may transform immunomodulation during pregnancy into immunosuppression in postpartum period.

Immune suppression during the periparturient period: the prepartum-postpartum nexus

The periparturient period covers the last two months of gestation and the first two months following delivery. It is particularly the transition period, the period three weeks before and three weeks after delivery, that is associated with an increased risk of disease and, more specifically, uterine disease. This is because this period is characterized by dramatic changes in the dairy cow’s metabolism and immune defense. In general, the nature of the response of uterine tissue to postpartum bacterial infection points to the important role played by the innate immune system.

There are a number of serious limiting stressors to the parturient’s innate immunity that eventually lead to a deregulated inflammatory response and an increased risk of uterine disease. These include a negative energy balance (NEB) associated with final fetal growth and the initiation of milk production; changes in the digestive tract associated with reduced dry matter intake; increased metabolic demands; changes in circulating hormones like progesterone, estrogen, cortisol, and prostaglandins associated with birth; and changes in the mission of the reproductive immune system as it passes from a controlled suppressive mode during gestation to a more active mode that attempts to control an overwhelming uterine infection during the postpartum period.
While bacterial infection is present in all cows in early postpartum, about 50% of them have compromised uterine health at the end of the VWP. What determines, then, whether or not the postpartum uterus go through a normal process of involution and returns to normal status, allowing for the establishment of a new pregnancy at the end of the VWP? Researchers hypothesize that high-producing dairy cows have a compromised systemic or local immune system to start with.

Parturition is a significant stressor on immunity in the dairy cow. The stress of parturition stimulates corticotropin-releasing hormone (CRH), causing the production of adrenocorticotropic hormone (ACTH), which then activates the hypothalamic-pituitary axis and increases plasma corticosteroids. During parturition, cows can exhibit a three-to-fourfold increase in baseline plasma cortisol concentrations. During metabolic disorders like hypocalcemia, a five-to sevenfold increase in the serum cortisol level can occur. Similarly, dystocia increases cortisol and can suppress the immune defense of dairy cows. Since glucocorticoids are elevated for only 24 hours at parturition and the immunosuppression seems to last for at least 21 days after calving, glucocorticoids are thought to be partly responsible for periparturient immunosuppression. In addition, changes in estradiol and progesterone just prior to calving may affect the immunocompetence of cows.

Immediately after calving, cows are poorly positioned to fight against postpartum infection and maintain control over the process of uterine involution. Loss of integrity of the endometrial lining during the early postpartum period removes an important physical barrier and neutralizes the action of mucins against bacterial invasion of the endometrial stroma. Antibacterial peptides that play a role in innate immunity may play an important role in uterine health. Intravaginal infusion of lactic acid bacteria decreased uterine infections and improved local and systemic immune responses in transitional dairy cows. The loss of uterine epithelium also means loss of potential expression of TLRs, a major component of the innate immune defense system in postpartum infectious uterine diseases. Finally, the deep abdominal location of the uterus in early postpartum is a mechanical impediment to uterine clearance. In the mare, differences between females in their ability to clear the uterus after breeding is related to susceptibility to postbreeding endometritis.

Reduced immune defense is observed not only around calving, but also during the whole transition periods. During the periparturient period, the proliferation of leukocytes (lymphocytes and neutrophils) is severely depressed, the ability of neutrophils to aggregate and phagocytose is reduced, and the cytotoxic activity of lymphocytes as well as the concentration of chemokines like IL-8 is decreased. Neutrophils are recognized as being the most important cell type for protecting the mammary gland and uterus from infection. Polymorphonuclear neutrophils (PMNs) in postpartum cows produce less reactive oxygen species (ROS) compared to PMNs in mid-lactation and prepartum cows. In addition, serum levels of IgG begin to decrease 8 weeks before calving, and serum levels of IgM fur weeks before calving. IgG levels recover by four weeks postpartum but IgM levels remain low. There is also a decrease in IgG1 levels during the peripartum period, most likely associated with the transport of immunoglobulins from the blood stream to the mammary gland. IgG1 is the immunoglobulin found in highest concentrations in the blood and milk of cows, and it plays an important role in antibody-mediated defense mechanisms.

Whereas the dry period in cows may be considered to be a resting phase between lactations, in reality considerable fetal growth, mammary tissue remodeling and high nutrition demands occur. The transition from late gestation to early postpartum results in dramatic metabolic disturbances in the lactation cycle of the dairy cow. The sudden increase in nutrient requirements for milk production at the time when dry matter intake and nutrient supply lags behind may be associated with inflammation and dysregulated immune responses and may represent the missing link in the pathobiology of disorders during that period. Metabolic status and levels of metabolites have an impact on the immune response of dairy cows and the risk of disease. During the transitional period, the cow’s intake of dry matter decreases, which further exacerbates the imbalance between energy needs and energy supply, and produces a NEB. In severe NEB cows, inflammatory immune genes are up-regulated and genes involved in the acquired immune responses are down-regulated. The NEB lowers glucose concentration, increases levels of ketones and fatty acids, and induces subclinical ruminal acidosis.
Glucose is the preferred nutrient of immune cells and has a stimulatory effect on the immune response. It is associated with increased proliferation and differentiation of leukocytes, and increased neutrophil chemotaxis and phagocytosis during inflammation. An increase of leukocyte activation is associated with hyperglycemia. Hypoglycemia is therefore associated with dysregulated immune cellular mediators. Insufficient blood glucose levels induce a decline of insulin and mobilization a triacylglycerol deposits as NEFAs which generates the metabolite acetyl coenzyme A (acetyl CoA) and energy via the Krebs cycle. In excess of acetyl CoA, ketones (acetoacetic acid, acetone, and B-hydroxybutyrate[BHB]) is produced. Ketone bodies negatively impact the immune response, causing a reduction in trap formation, chemotaxis and the phagocytosis of neutrophils, and reduced blastogenesis in lymphocytes. Cows with subclinical ketosis as measured by BHB concentrations are at higher risk of metritis during the first two weeks postpartum. Hyperketonemia has been shown to have multiple negative effects on different immune functions, even though immune cells do not use ketones as an energy source and that direct effect of ketones has not been measured in vitro. Depending on the level of saturation, non-esterified fatty acids (NEFAs) have both immunostimulatory and immunosuppressive effects on macrophage function by acting as ligands to TLRs. High concentrations of NEFAs suppress DNA synthesis, IgM secretion and IFN-γ production in monocytes. In general, saturated FAs decrease the phagocytic capacity of murine macrophages while unsaturated FAs increase it. In dairy cows, most studies have focused on metabolic status and disease and so the precise mode of action is unknown. Clinically, NEFA levels during the prepartum period are considered a better indicator of the risk of metritis, milk fever, and retained placenta than is plasma BHB, glucose concentration or calculated energy balance. Mid-lactating cows with dietary-induced NEB show a downregulation of neutrophil expression of genes associated with antigen presentation, respiratory burst, and pro-inflammatory response. High milk producing cows demand addition of concentrates into their diet composition. High content of starch in grains increases fermentability by rumen microbes and production of short-chain fatty acids reducing ruminal pH. The resulting ruminal lesions of this process allow penetration of bacteria and endotoxin with dissemination to the bloodstream. The presence of LPS in the bloodstream may challenge the immune system of the animal by binding to PRR, affecting leukocyte populations, triggering the production of proinflammatory cytokines and acute phase proteins. To trigger these processes, the period of ruminal acidosis must be long enough. Presence of LPS into the systemic circulation stimulates the release of proinflammatory cytokines (IL-1, IL-6 and TNFα) by mononuclear phagocytes.

Reproductive immunity and infertility

The periparturient period in dairy cows is characterized by an activation of the innate immune system that results in nearly 50% of all parturients showing signs of a uterine disease like metritis or endometritis. The recruitment of immune cells and inflammatory mediators coordinates the host immune response, whose task is to eliminate bacterial infection, and restore normal endometrial function and fertility at the end of the VWP. However, there is evidence to suggest that inflammation may persist long after the VWP and cause infertility. These long-term effects of the inflammatory process can impact endocrine signaling by the hypothalamic-pituitary-ovarian axis, uterine health, ovarian function, oocyte quality, and, ultimately, the establishment of pregnancy.

As previously mentioned, many factors produced by the oviducts and uterine endometrium are also immune mediators when there is any temporal or spatial deregulation causing an over- or under-expression of their production during infection. These immune mediators can then jeopardize embryo development either directly, or indirectly via its effects on the endocrine signaling system of the hypothalamic-pituitary-ovarian axis. For example, embryos cultured in fluid extracted from an inflamed uterus show a reduction in the number of blastomeres and their allocation. This would affect the embryo-mother interaction and potentially compromise pregnancy establishment. Proinflammatory mediators like IL1, IL6, TNF, and PGE are upregulated in endometrial cells in animals with endometritis compared to healthy animals. The induction of these mediators is TLR-dependent, depending on the bacteria.
components used.81, 82 Finally, LPSs, acting either directly or through inflammatory mediators, change the neuroendocrine signaling pathway. Intrauterine, systemic and intramammary LPS administration reduce gonadotropin releasing hormone (GnRH) secretion, luteinizing hormone (LH) pulses, and ovulation.83-85

Cows exhibiting clinical disease show a longer interval to estrus, irregular ovarian cycles, prolongation of the postpartum luteal phase, delayed onset to ovarian cyclicity, and, ultimately, failure to conceive.86 Ovarian function is perturbed both through this deregulation of the neuroendocrine axis previously described as well as directly. Although follicular fluid is free of immune cells, granulosa cells possess TLR, CD14, and MD-2 cells, which can recognize bacterial components87 and respond to invaders by increasing Il1b, IL6, and TNFa production.88-89 Lipopolysaccharide affects the estradiol production of granulosa cells and oocyte maturation by increasing germinal vesicle breakdown and changing spindle formation.90 Both antral and primordial follicle activation is increased because of the loss of specific proteins like PTEN/FOXo3a. This causes a depletion in the population of primordial follicles and eventually leads to infertility.

In general, then, the same immune mediators are involved in inflammation and ovarian function. As a result, when these immune mediators are perturbed due to uterine bacterial infection, they have a negative effect on fertility performance and this effect can last after the resolution of the uterine infection per se. The potential effect of postpartum uterine disease on folliculogenesis could explain the carryover effects of uterine disease on reproduction. Potentially, oocyte can grow and ovulate even though its developmental competence is disturbed.90

Take-home messages
1. The preferential energy partitioning in dairy cows toward milk production as a mono-focal goal fuels immunosuppression and leads to high rates of the reproductive tract infection and inflammation. It impacts the overall health of dairy cows, in particular reproductive efficiency.
2. Several inflammatory mediators have evolved alongside reproductive physiology in dairy cows. These mediators are used for signaling reproductive events like ovulation, fertilization, pregnancy recognition, and pregnancy maintenance. Thus, inflammatory processes are both a requirement and an impediment to uterine health and successful pregnancy.
3. Innate immunity encompasses mechanical, chemical, and cellular components. It is on constant standby to respond promptly to the first signs of microbial invasion.
4. Immunosuppression results in an increased incidence and severity of infections around the time of calving and in postpartum period of dairy cows.
5. The parturient period is the most challenging metabolic stage in the lactation cycle of dairy cows because it causes a physiological imbalance and inadequate adaptation to lactation. Various metabolites and nutrients (e.g. glucose, NEFA, and BHBA) influence the cow’s immune response and increase the risk of infectious diseases in the reproductive tract.
6. Understanding immunological processes in reproduction is critical to resolving reproductive problems in high-yielding dairy cows and improving the current management model.
7. Uterine bacterial infections affect immune mediators involved in both inflammation and reproduction at the neuroendocrine, ovarian, and uterine levels. This means that the infection’s negative effect on fertility performance may be carryover for a long period of time after the resolution of the uterine infection per se.

Practical implications
Starting at the drying period, all veterinary actions need to consolidate the immune strength of the dairy cow so that the parturient can meet the demand in postpartum period. Vaccination, stress control, well-being, comfort, nutrition, environment, management, genetic selection, calving care, early diagnosis of uterine infections are of equal importance toward a strong immunity, good fertility, and early establishment of a normal pregnancy.
Issues yet to be resolved

1. What imbalances tip the scale toward immunosuppression, and what are the cutoff points of these imbalances in order to negatively affect immunity and eventually, to cause infertility?
2. The importance of stress as a potent immunosuppressant in postpartum dairy cows.
3. The mechanism behind continued infertility following resolution of the uterine infection.
4. The mechanism of action by which toxins (LPS) and bacteria in the uterus and rumen during infection, affect hypothalamic-pituitary-ovarian function.
5. Characterization of cervicitis.
6. The global view of the cow immunity during the periparturient period in association with postpartum diseases.

Conclusion

There is growing evidence that the female reproductive tract is associated with a complex system of immune protection. It is becoming clear that several features (mucus, epithelial barrier, PAMPs, cytokines, chemokines by epithelial cells, and TLRs) have evolved to meet the challenges of the periparturient period. As the same mediators play a role in both immunity and female physiological reproductive function, fertility in dairy cows is intimately linked to immune system functioning. The tremendous metabolic burden that dairy cows experience during reproduction can disrupt the precarious balance achieved in the postpartum uterine defense in early postpartum, increasing the risk of disease and negatively impacting long term fertility. An understanding of the complex immunological processes at play in the periparturient cow is essential to design animal and herd health management strategies to prevent postpartum uterine diseases in dairy cows and to reduce the carryover negative effect on reproductive performance.

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