Artykuł przeglądowy *Review*

Immune system of the uterus in cows and its functions – selected issues

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Summary

Phagocytosis is the most important defense mechanism of uterus anti-infective response. This process involves specialized phagocytic cells, mainly polymorphonuclear neutrophils (PMN), monocytes and macrophages belonging to inborn mechanisms, which are constantly present in the uterus, or are transferred from an inflammation site as a specific response. The role of these cells is not only pathogens absorption and their intracellular killing, but also an elimination of dead tissues parts, which is especially important in the uterus in the postpartum period. Additionally, cytokines secreted by them after the contact with pathogens enhance further defense stages. The cells belonging to inborn defense mechanisms, recognize the microorganisms due to a specialized group of non-specific immunity receptors, referred to as pattern recognition receptors (PRRs). A few groups of these receptors have been recognized and described, and the classical and the best recognized example in uterus are toll-like receptors (TLR). These receptors have an ability of recognition of constant microorganisms components, so called group structures referred to as PAMPs (pathogen associated molecular patterns), which despite pathogens mutation stay unchanged, since they are essential for their survival (e.g. cellular membrane or nucleic acids parts). After pathogens penetration to uterus, they are recognized by the TLR system of the immunological system and uterine epithelium cells. Activated cells of non-specific immunity release proinflammatory cytokines, chemokines and defensins, which task is to support infection elimination, chemotaxis of active immune cells (neutrophils, macrophages, dendritic cells, mast cells) and to activate specific immunological response. Moreover, an activation of TLR receptors on the surface of macrophages leads both to an enhanced synthesis of proinflammatory cytokines, interleukin 1, 6, 8 and TNF-α, but they also increase their phagocytic ability and cause an increase in reactive oxygen species formation and nitrogen oxide synthesis. The kind of leucocytes sub-population contributing in immunological response seems to be of a key significance in infections elimination and protection of own organism's tissues. A significant role in this range has been recently attributed to regulatory cells. Recent studies have also shown that intrauterine administered substances can have a significant effect on local uterine immunity. Understanding the impact of these preparations may contribute to the development of more effective treatments for uterine inflammation.

Keywords: uterus, local immunity, cow, endometrium

The nature of dairy cattle production determines the need to sustain high lactation by inseminating cows and giving birth sequentially, after which uterine inflammation often occurs. Diseases affecting the uterus are a major problem in dairy cows breeding and generate large losses due to treatment costs and fertility issues (83). Sheldon et al. reports that up to 40% of dairy cows have signs of *metritis* within a week of parturition. At 3 weeks postpartum, 30% of cows have persistent uterine inflammation in the form of endometritis subclinica, and 15% to 20% have endometritis clinica (66). Weakened local uterine immunity is known to have a major impact on the development and persistence of endometrial inflammation (65). At the same time, regulation of the uterine immune system is important for fertilization and maintenance of pregnancy (49).

Mechanisms of local immunity in the uterus

All the mechanisms of local uterine immunity are not precisely described to date, especially the state of immunity during the inflammatory processes that occur. However, it is known that weakened local uterine

immunity has a decisive influence on the development and persistence of endometrial inflammation. It is recognised that efficient anti-infective immunity is of fundamental importance both in the elimination of the infectious agent and in the inhibition of inflammatory destructive changes in the uterus. The process of phagocytosis, which is the primary defence mechanism against pathogens, can be impaired in various pathological conditions. However, it is not known whether the development of inflammation can be directly related to dysfunctions of this immune mechanism. In a study by Mateus et al. (44) using flow cytometry, phagocytic cells were assessed, in the uterine washings of cows, during the postpartum period. The authors found that both phagocytic index and phagocytic cell count values were at a high level in the first 2 weeks after parturition and decreased 2.5 and 3 weeks postpartum. The more efficient phagocytosis in the first postpartum period, according to the authors, is explained by the presence of a large number of bacteria and particles that stimulate phagocytic cell activity. In the later period, with the decreasing amount of contaminants (antigens), phagocytic activity decreases. The use of flow cytometry to examine uterine washings in order to assess local immune mechanisms appears to be very important in clinical diagnosis. In this test, it is possible to assess the status of cells directly involved in local immunity present inside the uterus. Previous studies using flow cytometry have shown a significant decrease in the phagocytic activity of granulocytes and monocytes in uterine washings from cows with endometritis, which persisted from 5 days postpartum (DPP) throughout the observation period 22, 40 up to 60 DPP (3, 4). This was particularly true for the percentage of phagocytic cells and, in a recent study, also for the mean fluorescence intensity, an exponent of the intensity of phagocytosis of granulocytes and monocytes. Weakening of local anti-infective immune mechanisms in the uterus contributes to impaired elimination of microorganisms entering the uterus and may lead to the development of *endometritis* (21). This is confirmed by further studies showing significantly lower values for the percentage of leukocyte subpopulations with the phenotypes CD4, CD21, CD25, CD14 and CD4/CD25 and higher values for CD8 lymphocytes in uterine washings from cows with endometritis compared to cows without *endometritis* (4). Other studies conducted in cows with endometritis subclinica at day 65 postpartum also showed an increase in the percentage of TCD8 lymphocytes and a consequent change in the CD4 : CD8 ratio, which could also consequently lead to a weakening of local immunity and long-term persistence of *endometritis* (3). This indicates immunosuppression that coexisted with endometritis. The significant increase in the percentage of TCD8 suppressor lymphocytes and the anti-inflammatory IL-10 they produce in the uterine washings of cows with *endometritis* (5, 7) probably prevents endometrial damage through an inhibitory effect on immunocompetent effector cells, thereby attenuating autoimmune responses (65). Unfortunately, these studies also suggest that such effects may be associated with a weakening of local anti-infective immunity and a lack of complete elimination of microorganisms from the uterus. It is likely that the impaired biological function of granulocytes and monocytes and the described changes in leukocyte subpopulations in cows with endometritis resulted in a lack of complete ability to directly eliminate bacterial infection during the first phase of the postpartum period and a persistent inflammatory reaction, which had a significant impact on the development of endometritis (33, 44). At the same time, this leads us to believe that dysfunction in the cellular mechanisms of local uterine immunity in cows may be an important reason for the low efficacy of endometritis treatment.

In recent years, researchers have addressed the importance of Micro ribonucleic acid (miRNAs), which are small (~22 nt), noncoding and double-stranded RNA molecules in cases of endometritis, as a new marker of the disease and its potential for the development of new therapies (76). Studies in cows have shown that abnormal miRNAs expression can be linked to the occurrence of various diseases including mastitis, tuberculosis, fasciolosis, foot-and-mouth disease and metabolic disorders (52). Furthermore, researchers highlight the ability of micro RNAs to modify immune responses, such as the differentiation, survival and function of immune cells, as well as cytokine responses and intracellular signalling pathways. (12, 80). In the context of molecular biology, it is also worth mentioning the use of assessing the expression of pro-inflammatory genes, which can be used to assess the severity of inflammation based on reproductive tract swabs. A study by Fagundes et al. to compare the expression of CCL5, CXCL8, IL6 and IL1B genes in bovine endometrium showed that samples from animals with greater inflammation had higher gene expression than those with zero or moderate inflammation (19).

Another mechanism favouring the development of uterine inflammation may be the suppression of the immune response through a decrease in the percentage of regulatory T cells of CD4+CD25+ phenotype (Treg) and CD14 leukocytes (4). Treg lymphocytes and macrophages, with their immunoregulatory and effector functions, fundamentally influence the nature and intensity of the immune response (30, 31). Treg lymphocytes in cattle share many similarities with their human and rodent counterparts, while possessing some distinctive features, such as regulatory γδT cells (54). The γδT subpopulation, which in humans and mice accounts for only less than 5% of all circulating lymphocytes, in cattle make up 15 to 60% of mononuclear circulating lymphocytes (25). Such a large population suggests that they may play a key role in the formation and maintenance of immune tolerance

in this species. It is known that the action of Treg cells and γδ T cells makes the uterus an immunotolerant environment during pregnancy (42). A deficiency of these lymphocytes promotes autoimmune phenomena and its excess increases immune tolerance, which may favour the inhibition of anti-infective immunity (79). Regulatory lymphocytes are not a single cell subpopulation and may include lymphocytes with phenotypes of CD4+ (CD4+CD25+Foxp3+), CD8+ (CD8+CD25+Foxp3+,CD8+Foxp3+, CD8+CD122+, CD8+CD28–), γδ, NK and others (51). Although research into the function of regulatory cells in cattle has been carried out for many years, their functions are still only partially understood, with some diseases such as paratuberculosis (15) or in single organs e.g. in the udder (55). However, there is little literature data concerning regulatory cells in the uterus. Many aspects of local immunity in the uterus still need to be further understood, which could make a significant contribution to improving the prevention and treatment of uterine inflammation in the future.

Recognition of pathogens in the uterus

Most microorganisms can undergo mutations, which are associated with changes in their components and impair the ability of immune cells to detect pathogens, allowing pathogens to cause recurrent infections. However, there are molecules in the structure of microorganisms that must remain unchanged because they are essential for their survival, e.g. parts of the cell membrane or nucleic acids. These are group structures of microorganisms known as PAMPs (pathogen associated molecular patterns) (46). When the stimulus for the development of inflammation is a non-infectious factor, such as tissue damage or cellular stress, damage-associated molecular patterns (DAMPs) are released (57). New lines of research point to the hypothesis that the factor modulating the immune response is the balance of signals representing pathogens (PAMPs) and tissue damage (DAMPs). Acute inflammation can be triggered by both DAMP and PAMP, but it has been suggested that systemic inflammation is triggered by DAMP associated with metabolic dysfunction and more chronic tissue damage (39). PAMPs and DAMPs are recognised by a specialised group of non-specific immunity receptors known as pattern recognition receptors (PRRs). To date, several groups of these receptors have been described and the classic and best known example in the uterus are the Toll-like receptors (TLRs) (45, 73). The occurrence of TLR receptors is genetically determined and there are currently 10 receptors of this type known and described in cows, ranging from TLR1 to TLR10, each of which can recognise a different pathogen cell komponent (45, 73). TLR1, TLR2 and TLR6 recognise bacterial lipoproteins or glycolipids such as lipoteichoic acid, while TLR3, TLR7, TLR8 and TLR9 recognise nucleic acids, including those of viruses. Lipopolysaccharide from Gram-negative bacteria such as *Escherichia coli* combined with an LPS-binding protein is recognised by the TLR4 receptor. The TLR5 receptor recognises flagellin and TLR9 recognises unmethylated bacterial DNA sequences; the factor recognised by the TLR10 receptor is currently unknown. These receptors provide a link between non-specific and specific immunity, which enables an efficient response to pathogenic agents (66, 71). In addition, TLR receptors enable immune system cells to differentiate between self and foreign antigens. The innate immune cells of the uterus in cows, including endometrial epithelial cells, macrophages, dendritic cells and natural killer (NK) lymphocytes, express Toll-like receptors (TLRs). These receptors enable the rapid recognition of infectious agents and the activation of mechanisms that lead to their elimination (74). Activated non-specific immune cells release pro-inflammatory cytokines, chemokines and defensins to help fight infection, chemotaxis of activated immune cells (neutrophils, macrophages, dendritic cells, mast cells) and activation of the specific immune response. In addition, stimulation of TLR receptors on the surface of macrophages leads to both increased synthesis of the pro-inflammatory cytokines interleukin 1, 6, 8 and TNF-α, but also enhances their phagocytic capacity and results in increased production of reactive oxygen species and nitric oxide synthesis (66, 73, 89). Acquired immunity involves the expansion of different subpopulations of lymphocytes directed against pathogens. It is a highly efficient process with high specificity, but takes up to several days to fully develop. Presentation of the antigen to the lymphocytes, followed by their clonal selection, leads to an enhanced response and the production of specific antibodies. In the case of infection, all the characteristic symptoms of inflammation (congestion, swelling, pain, loss of normal function) are initiated by innate immunity. Cells of specific immunity can support and exacerbate these effects, but the essential signal that initiates and ultimately determines the response depends on the identification of the pathogen by components of the non-specific response (66, 73).

Local immune status of the uterus during pregnancy and in the postpartum period

Fertilisation, survival of the fertilised egg, implantation of the developing embryo and maintenance of the pregnancy all require regulation of the immune status. It is believed that all of the above-mentioned stages require a suppression of immunity, especially local uterine immunity. There is also emerging evidence that certain immune and inflammatory mechanisms are also crucial for implantation in mammals (48, 66). Specialised uterine NK cells, in the uterus of women and rodents, are not only the first line of defence, but also stimulate other cells of the immune system through the secretion of cytokines. In addition, they influence the development of blood vessels and the preparation

of the uterine endometrium for embryo implantation. There are few studies addressing this issue in cows, but there are papers available confirming increased levels of NK cells and CD8+ T lymphocytes in the uterus in cows during the early stages of pregnancy (78). It has also been confirmed that mast cells in the uterus not only play an important recognition and effector role during bacterial infections in mammals, but that the vasodilator chemokines they secrete can also support embryonic development (43). The number of lymphocytes and macrophages in the uterus has been found to decrease during the early stages of pregnancy, preventing immune rejection of the embryo. During middle and late pregnancy, lymphocytes and macrophages are found in the endometrium between the papillae, but not in the uterine papillae. Which indicates that both innate and specific immune responses reacting to incoming foreign antigens into the uterus in the area adjacent to the fetal membranes do not occur (66, 71, 77). Other authors' studies indicate that the endometrium of the uterus in cows during pregnancy is infiltrated with antigen-presenting lymphocytes and macrophages, which may be important for the recognition of foreign antigens, including pathogenic bacteria emerging in the uterus (40). Cells of the subepithelial layer of the endometrium contain high concentrations of Th lymphocytes (CD4+), B lymphocytes and antigen-presenting macrophages (CD14+), compared to other regions of the endometrium and myometrium (40). Bacterial antigens processed and presented by macrophages and major histocompatibility complex II (MHC II) cells stimulate Th lymphocytes to secrete cytokines. These then stimulate B lymphocytes to proliferate into plasma cells in the endometrium and produce specific antibodies (13). In addition, Th lymphocytes release cytokines that induce the proliferation of T and B lymphocytes in local and regional lymph nodes. These lymphocytes then migrate to the endometrium and act as effectors of the cellular and humoral immune response (71). The postpartum period is accompanied by changes in leukocyte counts, which can affect the immune response. For example, the percentage of T lymphocytes in the peripheral blood of cows changes from 45% in mid-lactation to 20% in the postpartum period, with a decrease in the percentage of TCD4+ lymphocytes and an increase in the percentage of TCD8+ suppressor lymphocytes (63, 64). More recent studies indicate that in cows the total number of leukocytes in the peripheral blood increases during the prepartum period and decreases during the first week after parturition to return to the pre-pregnancy state in the following 3 weeks (33, 44). According to Preisler et al. (56) the total number of leukocytes in the blood already decreases approximately 1 week before delivery and the lowest leukocyte levels occur from delivery to 24 hours after delivery. These authors also showed that the reason for the reduced leukocyte count is the high cortisol level during the above mentioned period. According to other authors, postpartum leukopenia is caused by the migration of leukocytes to the mammary gland, which is beginning to become active, and to the enlarged postpartum uterus (33, 88). In addition, the activity of phagocytic cells in the peripheral blood was also significantly reduced in the first week postpartum, compared to the prepartum period (33). According to Wathes et al. (81) and Galvão et al. (23), the immune status of postpartum cows is strongly influenced by energy, mineral and vitamin deficiencies, which always, but with varying intensity, occur at the onset of lactation in dairy cows. According to these authors, a negative energy balance (NEB) leads to a weakening of systemic and local uterine immunity. Due to the emerging negative energy balance and progressive deficiencies in many other nutrients, the animal body starts to use energy stored, among other things, in adipose tissue. This results in elevated serum levels of non-esterified fatty acids (NEFA) and ketone bodies, e.g. β-hydroxybutyric acid (BHBA).

In an *in vitro* study by Laceter et al. (35) it was shown that lymphocytes treated with NEFA at concentrations of 0.125 to 1 mmol/L, which is the concentration found in the serum of postpartum dairy cows, have a reduced ability to produce gamma interferon and immunoglobulins (IgM). Scalia et al. (60) believe that NEFA impairs phagocytosis and intracellular killing of polymorphonuclear cells and may even cause their death. In addition, during sustained energy deficiency, there is a reduction in the total number of leukocytes in the blood and a disruption in the production of cytokines and chemokines that regulate the immune response (23, 81). Neutrophils obtained from BHBA-treated cows in *in vitro* culture showed reduced pathogen recognition capacity, impaired phagocytic activity and intracellular killing (24). Existing immunosuppressive mechanisms associated with pregnancy and the postpartum period, may facilitate microbial proliferation and predispose to infectious diseases of the uterus.

Once the pathogen is recognized by the TLR system of cells of the immune system and uterine epithelium, there is a release of pro-inflammatory cytokines (TNF-α, IL-6, IL-8, IL-1), which regulate further immune response (22, 87). In addition, leukocytes recruited to the site of inflammation from the peripheral blood also release cytokines: among others, regulatory T lymphocytes and CD8 lymphocytes release interleukin 10. There are changes in the lymphocyte population: a decrease in the percentage of T_{reg} lymphocytes and CD21 and CD4 lymphocytes, and an increase in the percentage of CD8 and CD25 T lymphocytes, the latter of which are responsible for the release of antibodies. As a result of the processes occurring during uterine infection, there is a decrease in the phagocytic activity of phagocytic cells and also in their average fluorescence intensity.

Uterine response to infection

The uterine response to infection, shown in Figure 1, begins when pathogens enter the uterine lumen and are recognised by the TLR system of immune cells and the uterine epithelium. There is a release of pro-inflammatory cytokines, including tumour necrosis factor (TNF) and interleukins IL-6 and IL-8, which are synthesised locally in the uterus and regulate a further immune response to eradicate the infection (22, 87). Leukocytes that have been mobilised to the endometrium from the peripheral blood during delivery are also capable of synthesising pro-inflammatory cytokines (58, 67). This results in the recruitment and activation of additional leukocytes (59) and stimulates the secretion of acute phase proteins in the liver. The increase in serum IL-1 concentrations during the perinatal period, through vasodilation of the uterine blood vessels, results in an increase in the number of leukocytes in the endometrium. IL-1 also increases plasma calcium concentrations, which, by passing into the myometrium, stimulates uterine contractions and aids in the cleansing of the uterus post partum (71). Cytokines also stimulate prostaglandin synthesis, which accelerates uterine involution (16). IL-6 is a pro-inflammatory cytokine produced in the early phase of inflammation, activates mature neutrophils and accelerates granulocyte maturation, the transition of monocytes into mature macrophages and promotes NK cells differentiation (32). IL-6 also acts as a growth factor and induces the expression of oxytocin receptors in myometrial cells, which increases their responsiveness to oxytocin. IL-6 is present in the bovine uterus at high concentrations before birth and decreases to baseline values at 8 days postpartum (32). High levels of IL-6 were associated with a normal postpartum period, while low levels were observed during placental retention. Whether IL-6 is produced in the uterus of infected cows has not been proven, but it has been shown that the presence of IL-6 induces an increase in the inflow of neutrophils into the uterus of cows (20, 89). Pro-inflammatory cytokines, especially IL-6, are potent stimulators of the production of acute phase proteins (APPs) such as haptoglobin, acid glycoprotein, ceruloplasmin and serum amyloid A. Their function is to help eliminate the infection by, among other things, modulating other immune proteins, stimulating phagocytosis, but also very important is their protective function against the destructive effects of enzymes generated by the inflammatory reaction leading to organ damage. Acute-phase proteins are produced in the liver and their serum concentration in cows increases during the first few weeks after parturition, as a response to uterine infection caused by the *E. coli* (68, 84). Although the formation of acute-phase proteins in the uterus of cows has not yet been confirmed, there are studies confirming their presence in uterine washings in cases of inflammation. These studies may suggest the formation of APPs in the uterine lumen or their passage from the serum, which would be justified by the high serum APPs concentrations in cows with uterine inflammation in which APPs was also detected in the uterine washings (5, 6).

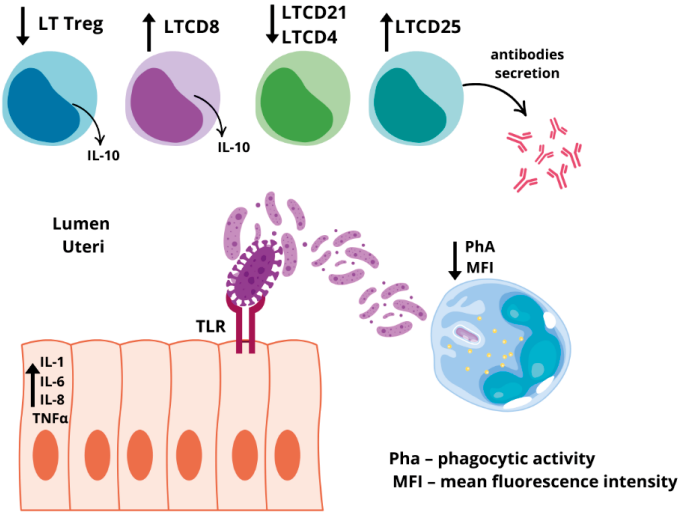

Fig. 1. Uterine response to infection

Phagocytosis

The first line of defence against pathogens in the bovine uterus, in addition to the endometrial epithelial cells, is provided by specialised phagocytic cells, mainly polymorphonuclear (PMN) neutrophils, monocytes and macrophages belonging to innate mechanisms, but also infiltrating later to the site of inflammation, as a specific response (66). The role of these cells is not only to engulf pathogens and kill them intracellularly, but also to eliminate dead tissue parts, which is particularly important in the uterus during the postpartum period. In addition, the cytokines they secrete after contact with the pathogen stimulate further defence stages. The process of phagocytosis in the uterus is also supported by proteins of the complement system and antibodies. Although the presence of all serum complement proteins in the uterine secretions of cows has not been documented, physiological bleeding from the uterine papillae at placental separation after parturition may supply cellular and serum complement components to the uterine lumen (34). In addition, substances released from mast cells cause the dilatation of fine blood vessels and an increase in their permeability, which also facilitates the infiltration of many serous components into the uterine lumen. And the degranulation of the mast cells of the uterus itself releases proteases that can activate certain complement components (34). Although antibody-producing cells are present in the uterus of cows, the local synthesis of immunoglobulins and their contribution to local immunity is not fully understood. There are studies showing an increase in antibodies in the secretions from the uterus, cervix and vagina of cows immunized previously with *Camphylobacter fetus* i *Histophilus somni* (10). Other authors have obtained an increase

in the amount of antibodies in the uterus after experimental intrauterine infusion of the *Arcanobacterium pyogenes* (in the current nomenclature *Trueperella pyogenes*) (82, 86). The above-mentioned works can indicate the active participation of specific antibodies in the neutralisation of bacterial infections. In the uterus of cows, the presence of immunoglobulins IgA, IgG, IgM with the exception of IgE has been confirmed and their presence is considered to reflect existing inflammatory processes (71). There are papers suggesting that the concentration of the different antibody classes may be different in different parts of the reproductive tract. IgA is synthesised locally in the vagina, where it is the predominant immunoglobulin, while IgG predominates inside the uterus but is only partially produced in its mucosa, as IgG1 the vast majority of this Ig comes from the peripheral circulation, as IgG2 (10, 47). It has also been established that the type of antibodies produced locally is largely dependent on the type of pathogen that causes the infection. *Campylobacter fetus* infection stimulates the synthesis of IgG1 (14), while *Brucela abortus* infection is associated with the presence of IgG2 (18, 53). IgA binds to bacteria to prevent their adhesion to endometrial epithelial cells and IgG opsonises bacteria to stimulate and facilitate phagocytosis. Antigen-antibody complexes further stimulate the classical pathway of the complement system (71).

The effect of sex hormones on uterine immune status

Hormonal activity associated with the ovarian cycle in dairy cows may play a major role in the functioning of immune mechanisms and influence the development of uterine infections or their elimination (41). As shown in Figure 2, the uterus of dairy cows is more susceptible to infection during the luteal phase of the cycle, when progesterone plays a dominant role, compared to the follicular phase, where there is a higher concentration of oestrogen (67). It was shown that experimental uterine infection with *E. coli* and *A. pyogenes* was much easier in the luteal phase of the ovarian cycle than in the follicular phase (62, 17). The negative effect of progesterone on local immunity has been linked by some authors to impaired synthesis of prostaglandins and leukotrienes. Increasing progesterone concentrations during corpus luteum development reduces prostaglandin F2α (PGF2α) and leukotriene B4 (LTB4) to basal levels and makes the uterus more susceptible to infections (28, 41). The negative effect of progesterone on lymphocyte proliferation is also known (41) and it is presumed that progesterone stimulates the synthesis of serpins in the uterus, which are serine proteinase inhibitors important for lymphocyte proliferation, adversely affecting uterine immunity (26). Progesterone stimulates prostaglandin synthase activity, resulting in an increase in prostaglandin E2 (PGE2), which is one of the pro-inflammatory factors and predisposes the uterus to develop inflammation (2, 61, 72). PGE2 controls the development of inflammation through specific receptors for prostaglandin E 2 and 4 (PTGER2 and PTGER4) located in the endometrial cells of the uterus (1, 27). If progesterone contributes to an increase in PGE2 and at the same time decreases PGF2α levels then it can be considered to inhibit its positive documented effects on the functioning of immune mechanisms. This prostaglandin stimulates chemotaxis of neutrophils and also improves their phagocytic capacity. It is also thought to stimulate the production of leukotrienes in the uterus, which also have chemotactic properties and stimulate antibody-independent cytotoxic cells (29, 41). Although PGF2α production in the endometrium and submucosa after parturition in cows with uterine infections is markedly increased (27, 75), its serum levels are lower in cows with uterine inflammation than in cows without inflammation (50, 61). While not fully understood, PGF2α has found use in the treatment of all types of uterine inflammation in cows (41). To date, the role of oestradiol during uterine infection has not yet been completely clarified. Studies have shown that intrauterine administration of oestradiol induced the growth of anaerobic bacteria (69). In the perinatal period in cows, when there are high levels of 17β-estradiol, impaired neutrophil function was observed (37, 82). Other studies have not shown neutrophil dysfunction

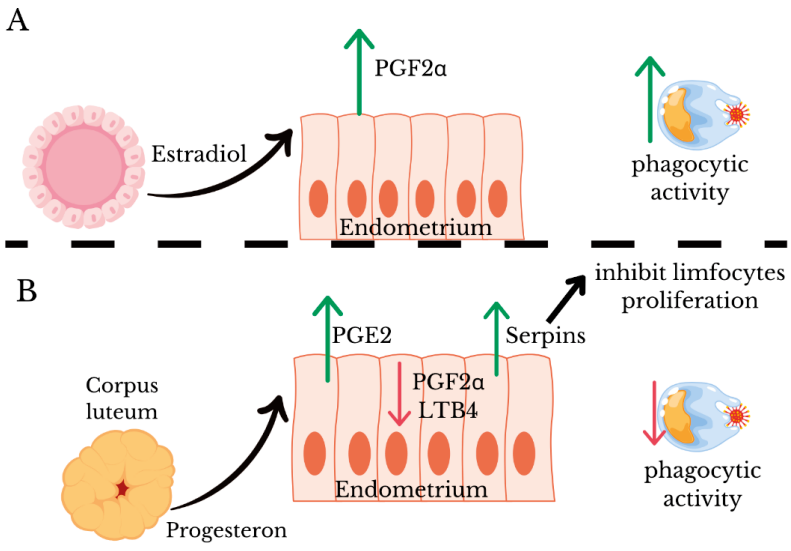

Fig. 2. The effect of sex hormones on uterine immune status
A. Estradiol released from the Graff follicle during the follicular phase of the oestrous cycle causes an increase in PGF2α release by the endometrium and an increase in phagocytic activity. This increases the local immunity of the uterus.
B. Progesterone secreted by the corpus luteum during the luteal phase of the estrous cycle causes a decrease in the release of PGF2α and LTB4 by the endometrium with a concomitant increase in the release of PGE2 and serpins, which inhibit lymphocytes proliferation. This leads to reduced phagocytic activity and reduced local uterine immunity.

during periods of high estrogen concentrations (38). *In vitro* studies have shown that 17 β-estradiol can adversely affect chemotaxis, phagocytosis and intracellular leukocyte PMN (29, 36). Chaveiro et al. (11), on the other hand, confirmed that 17β-estradiol improves neutrophil killing and only at very high doses has an adverse effect on neutrophil function.

Postpartum ovarian activity, in cases of uterine inflammation and its relation to uterine immunity

The high concentration of progesterone, which decreases during the last period of pregnancy and before delivery together with the high level of oestrogen, blocks the hypothalamic-pituitary hormonal axis as a result of the so-called negative feedback. This results in the ovarian cycle and cyclic ovarian function being blocked during and after pregnancy. The result of the activation of the endocrine system after parturition is the first ovulation usually without estrous symptoms, which occurs between 14 and 28 days postpartum (87). According to Herath et al. (28), in the normal postpartum period, the return of cyclic ovarian activity occurs quite quickly around 1 month after delivery. The first ovarian follicles producing oestrogens are formed, which is very important for keeping the local immunity of the uterus at an adequate level, according to the mentioned author this is of primary importance in preventing the development of inflammation of this organ. However, according to Sheldon et al. (70), in a large proportion of cows the first dominant follicles after parturition have very slow growth and a small diameter, so they produce too little oestradiol to prevent the development of uterine infections. Early ovulation and the production of an active corpus luteum increases the concentration of progesterone, which has an adverse effect on uterine immunity and also impairs uterine involution and keeps the cervix closed, facilitating the formation and development of inflammation and even predisposing to pyometra formation (41, 67). The developing endometritis leads to impaired prostaglandin production in the uterine endometrium. PGF2α synthesis is impaired while PGE2 production is increased. Insufficient concentration of luteolytic prostaglandin, keeps the corpus luteum producing progesterone and its adverse effects. In addition, the presence of PGE2 which has luteotropic and pro-inflammatory properties exacerbates uterine inflammation. Infection of the uterus with LPS-producing Gram-negative bacteria, e.g. *E. coli*, is critical to ovarian function. Heath et al. (28) found that during uterine inflammation, LPS appears in the fluid of the ovarian follicles and impairs the production of oestradiol in the granulosa cells of the follicles. This is evidence that inflammation of the uterus can directly affect the ovary and impair its function. In cows withendometritis clinica, the concentration of LPS in the follicular fluid was as high as 0.8 mg/ml. In cows without inflammation, the LPS content in the follicular fluid was unmeasurable, and in cows with endometritis sublinica, the LPS concentration had intermediate values. It was also established that LPS does not interfere with the mechanism of oestradiol synthesis, but causes apoptosis and death of granulosa cells of the Graff follicle, where the hormone is synthesised, with a subsequent reduction in oestradiol concentration. Other authors have demonstrated the negative effects of uterine inflammation on the higher levels of ovarian cycle regulation in cows. It has been established that LPS has an inhibitory effect on the production and release of gonadotropin-releasing hormone (GnRH) in the hypothalamus and on the pituitary gland by attenuating the secretion of luteinising hormone (LH). In contrast, it has no effect on the secretion of folliculotropic hormone (FSH) (70, 85). In the light of the studies presented here, the initial development of ovarian follicles is normal, but slower than normal, and lower oestradiol concentrations impair oestrous symptoms; moreover, cows with endometritis tend to have delayed or absent ovulation and even ovarian cyst formation. Furthermore, the inhibition of PGF2α synthesis as a result of endometritis, prolongs the activity of the corpus luteum, which also disrupts the ovarian cycle. The abnormalities mentioned above ultimately lead to the onset and persistence of infertility in dairy cows.

Effect of preparations administered intrauterine on the immune function of the uterus

Current treatment of uterine inflammation in dairy cows is based primarily on intrauterine administration of antimicrobial preparations. On the one hand, this treatment ensures rapid elimination of pathogens from the uterus, which accelerates the healing process. At the same time, however, antibiotics have a negative impact on local uterine immunity. They can weaken the phagocytic activity of the phagocytic cells in the uterus, which is of particular importance in low-severity inflammatory conditions – endometritis subclinica – because they further disrupt the already weakened local immunity mechanisms and, despite the elimination of pathogens, the complete elimination of the inflammation is prolonged. Preliminary studies (9) have shown that after intrauterine infusion of an antibiotic (Cefapirin), phagocytic activity and phagocytic cells killing are impaired. The results of immunological tests presented in Figure 3 showed that after administration of the preparation, the values of the assessed local immunity parameters were significantly reduced. Both the number of phagocytic cells (granulocytes and macrophages) and the mean fluorescence intensity (MFI), indicating the number of bacteria they engulfed, were significantly lower after cefapirin treatment. Similarly, in the oxidative burst after antibiotic administration, the number of phagocytic cells and the production of reactive oxygen forms, indicating the activation of intracellular enzymatic activity (lethality) of neutrophils, decreased.

It is therefore reasonable to assume that the impaired phagocytic activity of the phagocytic cells may be due to the effects of the administered intrauterine preparation. The mechanism of the negative effect of the applied preparation on the function of phagocytic cells in the uterus is unknown to date. After intrauterine application of an immunomodulatory preparation (methisoprinol), the evaluated parameters of phagocytic and killing activity of granulocytes and macrophages increased significantly. Simultaneous application of both preparations showed an attenuation of phagocytosis presumably due to the predominant inhibitory effect of the antibiotic, but also an increase in the enzymatic activity (MFI) of neutrophils, which may be due to the effect of methisoprinol. The results of the Brodzki et al. (9) study do not clearly confirm the stimulatory effect of methisoprinol on the activity of phagocytic cells in the peripheral blood, although after intrauterine administration of the preparation, a significant increase in the MFI of neutrophils was noted in both Phagotest and Bursttest after stimulation with *E. coli*. However, confirming whether intrauterine administered methisoprinol could be the cause of these changes requires further more detailed studies.

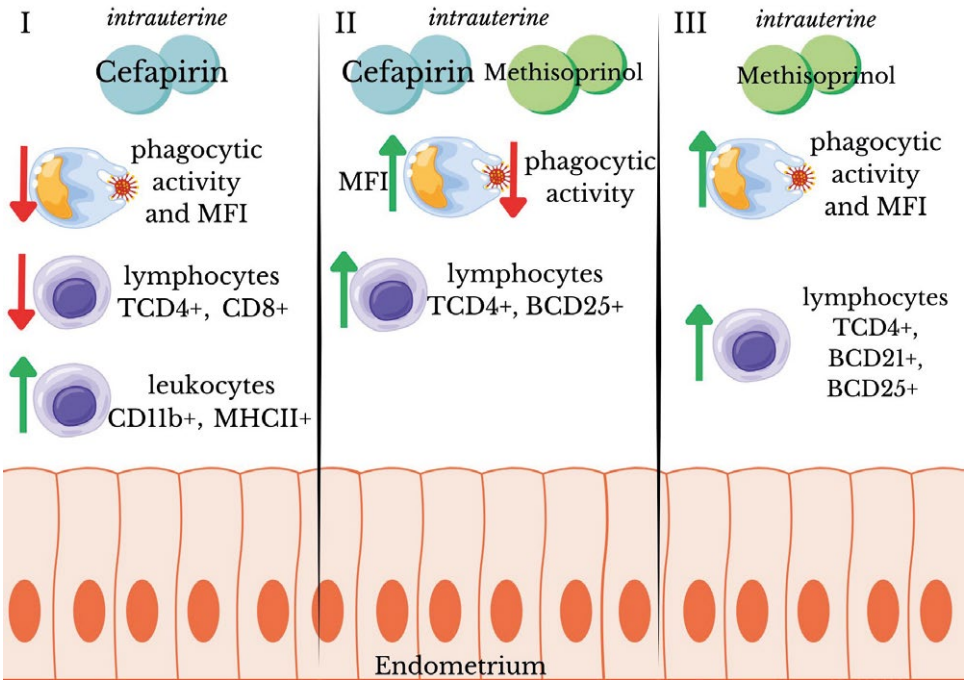

Fig. 3. Effect of intrauterine administration of an antibiotic (cefapirin) and an immunomodulatory agent (methisoprinol) on local immunity in endometritis (8, 9). I – Intrauterine administration of cefapirin is associated with a decrease in phagocytic activity and mean fluorescence intensity (MFI), which indicates the number of bacterial cells engulfed by phagocytes. There is also a decrease in the population of TCD4+ and CD8+ lymphocytes, alongside a concomitant increase in the percentage of CD11b+ and MHCII+ lymphocytes; II – intrauterine administration of both cefapirine and methisoprinol resulted in decreased in phagocytic activityand increased MFI and the percentage of TCD4+, BCD25+ lymphocytes; III – intrauterine administration of methisoprinol alone resulted in an increase in phagocytic activity and MFI, as well as in the percentage of TCD4+, BCD21+ and BCD25+ lymphocytes.

In addition, a later study (8) showed that intrauterine infusion of cephapirin attenuated the effector phase of the local uterine immune response manifested by a decrease in the percentage of TCD4+ and CD8+ lymphocytes on day 3 of the study, but enhanced leukocyte chemotaxis and antigen presentation by increasing the percentage of leukocytes with CD11b+ and MHCII+ surface particles, also on day 3 of the study. After intrauterine administration of methisoprinol, stimulation of mainly specific uterine immune mechanisms was observed (increase in the percentage of TCD4+, BCD21+ and CD25+ lymphocytes on days 3 and 10 of the study). Simultaneous application of both preparations showed an enhancement of specific uterine immune mechanisms presumably induced by methisoprinol, despite the inhibitory effect of the antibiotic an increase in the percentage of CD4+ helper T lymphocytes and activated CD25+ B lymphocytes observed on days 3 and 10 of the study. The described studies clearly indicate that intrauterine infusions have a clear effect on selected parameters of local uterine defence mechanisms in cows. However, these studies were only preliminary and need to be further extended both in terms of the quality of the intrauterine preparations used, the dose and the frequency of their administration (8, 9).

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