

Inflammation in the Bovine Female Reproductive Tract

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ABSTRACT

Inflammation of the reproductive tract of a cow occurs when the physical and functional barriers to contamination are breached or specific infection occurs. Commonly, contamination occurs at parturition and to a lesser extent at estrus. Uterine contamination following calving is common, but most healthy cows are able to clear the uterus of bacteria in the first 2 to 3 wk after calving. Persistent infections are more likely to be caused by *Actinomyces pyogenes*. Specific venereal infections tend to be more host-adapted and produce a lower grade inflammation. Nonspecific bacterial contamination of the endometrium generally induces a neutrophilic influx into the stratum compactum and uterine lumen. Neutrophils phagocytize bacteria with the aid of opsonins in the uterine fluid. Mast cells and eosinophils may also contribute to the inflammatory reaction, which may damage the surface epithelium and release vasoactive substances that allow leakage of serum antibodies into the uterine secretions. Specific antibodies of immunoglobulin (Ig) isotype A, M, G₁, and G₂ in uterine secretions have been described. In model species, the immune capability of the uterus is influenced by steroid hormones, especially estradiol, which increases secretory component and both IgA and IgG content in uterine secretions and increases the activity of antigen-presenting cells in the uterus. Similar cyclic fluctuations in immune components have been described for cows, including changes in the population of subsurface cytotoxic and helper T cells and changes in the expression of major histocompatibility II antigen on surface cells.

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(**Key words:** inflammation, uterus, immunity, estradiol)

Abbreviation key: CL = corpus luteum, E₂ = estradiol, LTB₄ = leukotriene B₄, MHC = major

histocompatibility complex, P₄ = progesterone, pIgR = polymeric Ig receptor, ROS = reactive oxygen species, TNF = tumor necrosis factor.

INTRODUCTION

Inflammation is the specific or nonspecific immune response of higher organisms to tissue injury or to the invasion of that tissue by foreign or perceived-as-foreign organisms (59). When it occurs in the uterus of the dairy cow, the clinical consequences include a reduction in fertility as measured by calving-to-conception intervals, first service conception rates, and other performance indices (7, 9, 28, 40, 54, 70). A generally conventional series of cellular and chemical responses constitute the inflammatory reaction. And, for the enormous surface area that is exposed to environmental flora at the mucosal surfaces of the respiratory tract, gastrointestinal tract, and to a lesser extent the reproductive tract, an effective system of mucosal defense, including mucosal inflammation, has developed at this interface. Immune protection of the reproductive tract requires most of the same cellular and chemical strategies as do other mucosal surfaces. However, some unique influences of the endocrine environment that mediate reproductive events also significantly affect this mucosal immune system and will be discussed in the context of their influence on protection from microbial attack.

Anatomical and Physical Protective Mechanisms

Effective defense against reproductive tract invasion by environmental organisms is mediated by anatomical and functional barriers as well as nonspecific and specific immune responses. The major anatomical barriers between the contaminated world and the relatively sterile environment of the uterus include the vulva, the vestibule (guarded by a muscular sphincter), and the cervix. In the cow the cervix is a formidable barrier composed of a series of mucosa-lined collagenous rings. In addition, the cervico-

vaginal mucus (especially the scant, tenacious mucus of the luteal phase) can function as a physical barrier for organisms that would otherwise ascend the reproductive tract. The circular and longitudinal muscular layers of the uterus provide physical propulsion of particulate material, including microbes. As with nearly every other aspect of the reproductive tract, the properties of these structures are dynamic and change with the hormonal environment.

Endocrine Dynamics

Any discussion of the hormonal influences on the reproductive tract risks being either too superficial or too detailed. This discussion will lean towards the former and will assume some fundamental knowledge of reproductive physiology. For details, the reader is referred to the review by Stevenson (54). Briefly, in the cycling female, the hypothalamic "pulse generator" releases bursts of GnRH, which in turn stimulate the pulsatile release of gonadotrophins (FSH and LH) from the adenohypophysis. These pulses of gonadotrophins induce growth in a cohort of small ovarian follicles, and the growing follicles produce estrogens, predominantly estradiol (E_2). This E_2 production is transient, and follicles that do not ovulate become atretic via apoptosis of follicular granulosa cells (58). Two to three waves of such follicular growth occur in a typical 21-d estrous cycle, producing two or three very small surges of E_2 secretion, but ovulation will not occur as long as a functional [i.e., progesterone (P_4)-secreting] corpus luteum (CL) is present on either ovary (54). The endometrium ultimately causes rapid lysis of that CL via the pulsatile release of the eicosanoid $PGF_{2\alpha}$ on or about the 17th d after ovulation. Within about 48 h of the complete lysis of the CL, and the consequent cessation of P_4 production by the ovary, E_2 from the dominant follicle induces a major surge of LH, which will induce the dominant follicle to ovulate. This ovulated follicle forms a new CL, which secretes P_4 as its major steroid product. Peripheral blood levels of P_4 tend to rise beginning about 2 to 3 d after ovulation and peak at about 8 to 10 d and remain elevated until the next episodic release of endometrial $PGF_{2\alpha}$ (54).

Estradiol and P_4 have both opposing and complementary effects on the female genital tract with E_2 stimulating epithelialization (especially of the vaginal lining and endometrial glands) and vascularization of the endometrium (22) and increased production of cervical mucus and oviductal secretions (54), enhancement of uterine contractility (1, 49), initiation of sexual receptivity (54), and several specific

effects on the secretory immune system (22, 67, 68, 69). Progesterone aids in endometrial gland differentiation (22) and enhances uterine gland secretion, reduces cervical mucus production, prevents uterine contractility (49), and acts as a counter-influence to E_2 in immune protective responses of the reproductive tract (67, 69).

In the cycling cow, the uterus is usually under P_4 influence. That is, the nonpregnant uterus is in the luteal phase (under the influence of P_4) for about 14 to 15 d of its 21-d cycle (i.e., from about d 3 to 17 after estrus and ovulation) (54). It is under its most significant E_2 influence, with no P_4 to counter its effects, for about 1 d (immediately preceding standing estrus) (54). The pregnant uterus, however, is under constant P_4 influence for nearly all of its 280-d gestation (62). In addition to the overall P_4 background influence during pregnancy, during the last 6 to 8 wk of gestation the placenta contributes an increasing amount of estrogen with a steep burst of estrogen production 1 to 3 d before calving (62).

Uterine Inflammation—Definitions

Veterinary clinicians have loosely applied the term metritis to any and all inflammatory processes that involve the uterus. To improve communication among clinicians and researchers, the inflammatory conditions of the bovine uterus discussed in this review will adhere to definitions used by pathologists (30, 38) and theriogenologists (41, 43, 48) as follows.

Endometritis. This condition is a superficial inflammation of the endometrium only, extending no deeper than the stratum spongiosum. Histologically, endometritis is characterized by some disruption of surface epithelium, infiltration with inflammatory cells, vascular congestion, and stromal edema and by varying degrees of lymphocyte and plasma cell accumulation in the superficial layers (20, 38). Microbes associated with endometritis usually arrive by the ascending route, either following natural service, artificial insemination, or—more commonly—parturition or abortion (47). Note that these are conditions that occur when the cow is not under the influence of P_4 . Usually a small amount of purulent exudate exists, although this may not be noticed in the standing animal (47, 55). The cow or heifer is rarely systemically ill as a direct result of endometritis, although endometritis has been epidemiologically associated with other illnesses [(23), reviewed in (24)], which can have overt manifestations.

Pyometra. This condition is a purulent inflammation of the endometrium associated with significant fluid accumulation in the uterine lumen. In contrast

to endometritis, this condition is most frequently associated with the luteal phase, (i.e., when the cow or heifer is under P₄ influence) (30, 43, 48). Indeed, the condition is thought to be the result of a failure of the damaged endometrium to terminate the luteal phase (i.e., a failure to release appropriate bursts of PGF_{2α}) (43). Pyometra is most common in postpartum cows that have ovulated at least once following calving. It can also occur in naturally serviced cows or heifers as a postcoital phenomenon when venereal organisms are involved [reviewed in (5)]. As with endometritis, there are few if any overt signs of illness in a cow with pyometra (47).

Metritis or perimetritis. This condition is a severe inflammatory reaction and involves all layers of the uterus (endometrial mucosa and submucosa, muscularis, and serosa). It generally occurs soon after a difficult calving and is often associated with trauma to the uterus or gross contamination or a metabolically compromised animal (30). Animals with metritis or perimetritis are usually septicemic with overt signs of illness (fever, depression, weakness, and inappetence) (47). The inflammatory process is not well delimited, as with endometritis or even pyometra, but can extend to the serosal surfaces of other peritoneal viscera as well.

Of the three manifestations of uterine inflammation, endometritis is by far the most common (47). In fact, several studies suggest that some measure of inflammatory reaction in the postpartum endometrium is common rather than being an exception [(28, 55); reviewed in (9)]. Because endometritis is typically a postpartum process, to describe normal events that occur in the postpartum, involuting uterus seems appropriate.

Natural History of the Postpartum Uterus

Within about 30 d of calving, the uterus that delivers up to 65 kg of calf, fetal membranes, and fluids returns to its prepregnancy size. The uterine weight diminishes by over 90% during this period (48). This remarkable change involves the release of the fetal membranes, ischemic necrosis and sloughing of several layers of the caruncular epithelium, recovering of surface defects with a new epithelium, and shortening of the muscle fibers of the myometrium. Most of these changes occur early in the postpartum period (first 2 wk) before the pituitary-ovarian axis has induced a return to cycling. Most dairy cows will have their first postpartum ovulation by about 17 to 27 d after calving (54). Periparturient insults, including dystocia, uterine prolapse, and re-

tained fetal membranes may delay normal involution [reviewed in (9, 24, 48, 54)].

Because the physical barriers to contamination are compromised during normal parturition, and because the normal involution process produces a large volume of necrotic tissue in a fluid medium (lochia), significant bacterial contamination of the postpartum uterine cavity is common. Over 90% of uteri are contaminated in the first 15 d after calving with a diminishing percentage yielding positive bacterial cultures over the next 2 to 4 wk, until by 45 d postpartum, only 9% or less have positive cultures (21, 44, 54). The flora cultured in the early postpartum period represent a broad spectrum of environmental contaminants (e.g., *Escherichia coli*, *Actinomyces pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus* spp., *Streptococcus* spp., and *Pasteurella multocida*) and include some anaerobic species (e.g., *Clostridium* spp., *Bacterioides* spp., and *Fusobacterium* spp.) (9, 28, 42, 43). However, as involution proceeds, most bacteria are eliminated such that, by 2 to 4 wk, many uterine cultures are bacteriologically negative (9, 29). Persistent infections (beyond 21 d postpartum) are more likely to be associated with *A. pyogenes* and with anaerobic agents, especially *Bacterioides* (43), which apparently reduces chemotactic and phagocytic activity of neutrophils and allows both itself and *A. pyogenes* to persist [(64); reviewed in (70)]. Table 1 lists the results of bacterial isolation from cases of bovine endometritis occurring from 3 to 6 wk postpartum as were reported in three representative studies over the past 25 yr (7, 40, 55). Of the agents recovered from the postpartum uterus, *A. pyogenes* is most consistently associated with inflammatory damage to the endometrium, and several studies (7, 8, 21, 40) suggest that fertility is impaired in cows that maintain an *A. pyogenes* infection (with or without concurrent anaerobic infection) beyond the first 3 to 4 wk postpartum. Because many cows have begun cycling by this time, it is possible that some cows with persistent *A. pyogenes* infections are increasingly under P₄ influence, a factor that may impair their ability to clear the infection. Thus, if the cow does not clear the *A. pyogenes* infection before ovulating again, she may have more difficulty clearing the infection in the subsequent luteal phase (43). The suggested reasons are discussed later.

Postcoital Infection

In the case of a venereal rather than postpartum infection, the two classical pathogens—one a motile gram-negative bacterium, *Campylobacter fetus* var.

TABLE 1. Bacterial isolates associated with postpartum endometritis in dairy cows (listed in order of frequency of isolation, by authors).

Bacterial isolate	Correlated with inflammation or infertility (Y/N)	Authors
<i>Escherichia coli</i> , <i>Aerobacter</i> spp.	Y	
<i>Streptococcus</i> spp.	N	
<i>Actinomyces pyogenes</i>	Y	
<i>Staphylococcus epidermidis</i> , <i>Staphylococcus aureus</i>	N	
<i>Micrococcus</i> spp.	N	Studer and Morrow (55)
<i>Corynebacterium renale</i> , <i>Cornebacterium equi</i> , and <i>Cornebacterium pseudo-TB</i>	N	
<i>Proteus</i> spp.	N	
<i>Pasteurella multocida</i> , <i>Hemophilus</i> spp.	N	
<i>Fusobacterium necrophorum</i> , <i>Clostridium septicum</i>	N	
<i>A. pyogenes</i>	Y	
<i>Streptococcus</i> spp.	N	
<i>Pasteurella hemolytica</i>	Y	Miller et al. (40)
<i>E. coli</i>	N	
<i>Staph. aureus</i>	N	
<i>P. multocida</i>	N	
α hemolytic <i>Streptococcus</i> spp.	N	
<i>A. pyogenes</i>	Y	
<i>E. coli</i>	N	
<i>Bacillus</i> spp.	+/- ¹	
<i>Staph. epidermidis</i>	N	Bonnett et al. (7)
<i>Proteus</i> spp.	N	
Diphtheroids (<i>Corynebacterium</i> spp.)	N	
<i>P. multocida</i>	N	
<i>Hemophilus somnus</i>	N	
<i>Pasteurella hemolytica</i>	N	

¹+/- = significant correlation not established.

venerealis, and the other a flagellated protozoan, *Tritrichomonas foetus*—are well adapted to the female genital tract and can persist for months after infection at coitus (51, 52). Both agents are noninvasive, (i.e., they are uterine lumen dwellers existing in the extracellular compartment). Both can cause mild to moderate inflammation of the mucosae of the vagina, uterus, and uterine tube (oviduct) (2, 18, 50). Interestingly, pregnancy frequently is established in the face of infection, although many such pregnancies fail in the first 1 to 3 mo of gestation [(45); reviewed in (48)]. Because these are sexually-transmitted agents that affect the pregnant uterus, they gain access to the reproductive tract under E₂ influence (i.e., at estrus) and exert their pathological effects (embryonic death or abortion) in a P₄-dominated environment.

Cellular and Molecular Events in Uterine Inflammation

Once the physical defenses are breached, the next line of defense in the endometrium is the innate immune system, which includes neutrophils, macrophages, and serum complement. The presence of all

serum complement proteins in bovine uterine secretions is not thoroughly documented, but mechanisms for its delivery into the uterine lumen probably exist. For example, in the cycling cow, there is frequently a small amount of physiological hemorrhage from the caruncular endometrium shortly after ovulation (48). This hemorrhage would bring cellular and serum components, including complement, to the uterine lumen. In addition, vasoactive substances released from mucosal mast cells (32, 59) would be expected to increase permeability of small vessels such that serum may leak into the superficial endometrial tissue space and, perhaps, into the lumen. Activation of mast cells and damage to basement membranes can be accomplished by the action of neutrophil lysosomes (15). In cycling heifers at diestrus, mast cells were noted immediately beneath the uterine epithelium (25). In cows, endometrial mast cell numbers were highest around estrus and lowest at midcycle (57).

Neutrophilic influx into the superficial endometrium and then into the lumen characterizes the early response of the uterus to surface infection. Experimental reproduction of this influx has been attempted by several researchers (12, 14, 37, 56, 71). Their approaches were varied and included intrauter-

ine infusion of oyster glycogen (14, 56) or killed bacteria (12). Klucinski et al. (37) sensitized the host by vaccination with *Mycobacterium tuberculosis* or *C. fetus venerealis* and then challenged the endometrium by intrauterine instillation of purified antigen from *M. tuberculosis* or *C. fetus venerealis*, respectively. Animals so sensitized and challenged were presumed to have developed a cell-mediated response in the first case and an Arthus-like reaction in the latter (34). In either instance, challenge induced a significant influx of neutrophils into the uterine lumen. Intracellular killing activity by these sequestered neutrophils was significantly greater than for circulating neutrophils from the same cows. Recruitment and activation of neutrophils was presumed to be the result of cytokine release from lymphocytes induced by the prior immunization (33). However, when nonspecific inflammation was induced in the endometrium by instillation of lipopolysaccharide, intracellular killing by uterine neutrophils was reduced relative to circulating neutrophils (33, 36).

In an effort to develop a more physiological approach, Zerbe and others (71) showed that leukotriene B₄ (LTB₄), a potent chemotactic molecule that is increased in inflamed uteri (3), could induce a significant influx of neutrophils following infusion into the uterine lumen at estrus. It is important to note that estrus alone is associated with a mild influx of neutrophils into the superficial endometrium (20). Others (33) have noted that the maximum number of cells in the normal uterine lumen occurs shortly after estrus and ovulation (i.e., from d 2 to 8 of the cycle). The overwhelming majority of these cells are neutrophils.

Neutrophils infiltrate tissue spaces and cavities and phagocytize and kill microbes by several mechanisms. They can be directly attracted to microbial products (e.g., *N*-formylated peptides of low molecular weight) (59, 60). Other complement-independent chemotactic stimuli include the previously mentioned LTB₄, which has been shown by immunohistochemical techniques to be present in greater quantity in tissues identified as endometritic by conventional histological examination (3). In addition, complement component C5a is a powerful chemotactic agent for neutrophils (59). Once neutrophils are in the lumen, phagocytosis is enhanced by opsonization of microbes or other particulate material (63). Opsonins include the complement component C3b and specific antibody; the neutrophil surface has receptors for C3b and receptors for the Fc component of the antibody, such that binding and engulfing of opsonized microbes is greatly enhanced (35, 59, 63, 64).

Phagocytized organisms can be killed by oxygen-dependent (respiratory burst) and oxygen-independent (lysozymes and proteolytic enzymes) mechanisms (33, 59, 60). The ability of circulating neutrophils to phagocytize and kill bacteria by generation of superoxide anions [reactive oxygen species (ROS)] is apparently diminished as parity of the cow increases (27). In addition, cyclic fluctuations in opsonin-mediated phagocytosis and killing also apparently occur. Watson (63) showed that uterine flushings from follicular-phase cows had enhanced phagocytosis and killing by neutrophils over that produced by flushings from luteal phase uteri.

Several researchers have shown that cows with naturally occurring persistent endometritis have altered neutrophil function. In addition, both phagocytic activity and bactericidal activity were apparently reduced in cows with experimental endometritis (13, 33, 34, 37, 71). Neutrophils flushed from normal uteri on postestrus d 2 to 6 had a greater degree of expression of Fc receptors (as detected by rosette formation) for IgG₁ and IgG₂ antibodies than did peripheral blood neutrophils. Neutrophils from cows with experimental endometritis showed a decrease in the expression of Fc receptors for IgG antibodies and a lower index of Fc-mediated phagocytosis (34, 35). However, the neutrophils were apparently able to at least partially compensate by increasing phagocytic activity mediated by nonimmunological receptors (36), the nature of which was not described. In the LTB₄-induced endometritis model, Zerbe et al. (71) reported a similar decrease in phagocytic activity of uterine versus blood neutrophils with or without complement opsonization, but uterine neutrophils retained their ability to generate ROS after stimulation. They (71) also noted that other surface molecules on uterine neutrophils, including class I major histocompatibility complex (MHC) I and the integrin LFA-1, showed diminished expression relative to circulating neutrophils, but also that CD11b and another uncharacterized surface antigen were upregulated in endometritic cows. It is interesting to note that the upregulation of CD11b, an important component of the C3b-binding integrin, CR3, did not appear to increase opsonin-aided phagocytosis. Zerbe et al. (71) suggested that Fc receptors or other complement receptors [e.g., CR1 (CD35)] may be more important mediators of phagocytosis than is CR3.

When nonspecific endometritis was induced by the infusion of lipopolysaccharide from gram-negative bacteria, the ability of uterine neutrophils to kill phagocytized bacteria via the oxygen-dependent system (i.e., via the generation of ROS) was weakened

(33). Given the environment of the early postpartum uterus where gram-negative bacterial contamination is likely, it would seem that the first line of defense can quickly become compromised.

In addition to neutrophil migration, other cellular components that are eventually activated include macrophages, lymphocytes, eosinophils, and mast cells. The latter two cell types typically patrol beneath the surface of skin and mucous membranes (59). Both eosinophils and mast cells have high affinity FcεRI receptors that bind IgE antibodies. Subsequent binding of antigen by these receptor-bound antibodies causes sudden degranulation of mast cells. Inflammatory mediators are then released, such as tissue necrosis factor (TNF) α, histamine and prostaglandins, interleukins, and chemotactic factors for neutrophils and eosinophils, including LTB₄ and eosinophil chemotactic factor A (ECF-A) (39, 59, 60). The eosinophils also release inflammatory mediators and microbe-destroying chemicals such as superoxides and lytic enzymes. Uterine mast cell degranulation releases tryptase (32) and other proteases that can activate complement components C3 and C5 to generate anaphylatoxins. They also release kallikreins that generate kinins (59). The latter are potent vasoactive agents that increase vascular permeability. Such leakage may allow circulating IgG access to the microbial antigen in the stratum spongiosum, assuming that the antigen can traverse the epithelial layer. Surface epithelial damage from mast cell and eosinophil inflammatory mediators may allow serum immunoglobulin access to the uterine lumen. Recently, with toluidine blue staining, we have shown that the population of mast cells in the endometrium of *T. foetus*-infected heifers declines dramatically at about the 9th week following infection (R. H. BonDurant, L. B. Corbeil, C. Campero, and M. L. Anderson, unpublished observations, 1998). If this decline was due to a degranulation of mast cells, then the timing was coincident with the peak levels of trichomonad-specific IgG₁ in the uterine lumen and with a peak in embryonic or fetal loss (45). Eosinophils were abundant in the stratum compactum of the endometrium of heifers we observed.

Intraepithelial lymphocytes are generally present in the stratum compactum of the endometrium. Their numbers fluctuate with the stage of the estrous cycle, being highest in the periestrus period and lowest at mid-diestrus (61). One study (16) of endometrial T cell subsets reported that these periestrus accumulations of intraepithelial lymphocytes are predominantly of the CD8 type in the normal uterus, and that CD4 cells are more prevalent in the deeper stratum spongiosum in late diestrus.

Antibody-Mediated Protection and Damage

With the exception of IgE, all the major isotypes of bovine Ig have been identified in secretions of the bovine uterus, although the transport of these molecules to the uterine lumen is less understood. Clearly, the uterine mucosa is capable of secreting IgA, and numerous studies (19, 26, 53, 65) have shown high levels of pathogen-specific IgA in the reproductive tract without a concurrent rise in the peripheral serum after experimental or natural infection. In the case of *C. fetus venerealis* or *T. foetus* infection, uterine secretions tend to have greater responses in IgG than IgA, and vaginal secretions tend to have more IgA activity (17, 19, 53). Similarly, clearance of these organisms starts in the uterus first, and the vagina usually clears the infection later (19, 52). Whereas IgA can only bind the agent (and perhaps prevent microbial adhesion to mucosal surfaces), IgG can opsonize and activate complement (10, 59). Complement, in turn, could arrive in the uterine lumen via the leakage of serum induced by mast cell degranulation or eosinophil activation. Cows immunized intramuscularly with purified outer membrane antigen from *Hemophilus somnus* and then exposed by intrauterine instillation of killed homologous organisms showed antigen-specific IgG₁ and IgG₂, but not IgA, in estrous uterine secretions (11). Based on ratios of specific antibodies to Ig and Ig to serum albumen Butt et al. (11) estimated that most of the uterine IgG₂ and half of the uterine IgG₁ originated from the serum.

In animals with long-term venereal infections (>8 wk) or persistent postpartum infections, we and others (2, 8, 38) have noted the presence of lymphoid aggregates in the stratum spongiosum. Some of the aggregates appeared to have primary and secondary follicles, which suggested inductive sites for local immune responses. One study (7) found that the presence of such lymphoid aggregates had a sparing effect on infertility caused by *A. pyogenes*. Such a protective response would require that antigen be taken up through the intact uterine epithelium (10) because, at least in the case of the venereal agents, the pathogens are not invasive, and surface epithelium is not extensively eroded (2). Because an equivalent of the gastrointestinal M cell in the uterus does not seem apparent (2), it is possible that the uterine epithelium itself may absorb and process antigen, a phenomenon that has been described in the rat uterus (see later) (68). By use of immunohistochemical techniques, we have seen that surface antigen of the noninvasive *T. foetus* was present within uterine

epithelial cells and appeared to be in the mononuclear cells below the basement membrane of the superficial and glandular epithelium (6).

There is evidence that antibodies can be protective against inflammatory damage caused by infection. In studies in which immunization boosted pathogen-specific IgG₁ or IgA in the reproductive tract, inflammatory lesions were noticeably milder after challenge of vaccination versus control groups (2). However, as with many inflammatory responses, it is possible that the host response to the agent may cause significant harm to the host or, in the case of *T. foetus* infection, to the pregnancy. Recently, with in vitro methods, BonDurant et al. (6) reported that target cells were more likely to be destroyed by *T. foetus* if those target cells were first coated with an antigen shed from the surface of the parasite and then incubated with antiserum to that shed antigen (6). Target cells coated with antigen, but without antibody, were destroyed less frequently than were target cells coated with antigen and antibody. Blockage of the Fc portion of the bound antibody with F(ab)₂ fragments of anti-bovine Fc partially reduced the cytotoxicity of the trichomonad (6). In this instance, the parasite was apparently acting as a neutrophil or natural killer (NK) cell in that it appeared to bind the Fc portion of a specific antibody and to be activated by that binding.

Hormonal Influences on Inflammation and Protective Mechanisms

With laboratory animal models, Wira and Kaushic (67) have shown a distinct influence of the sex steroid environment on immune function in the female reproductive tract. These authors, citing their own work and that of others, concluded that both the spectrum of immune cells and their relative concentrations in the endometrium change with the stage of the female cycle. In addition, antibody concentrations and isotypes vary with the stage of the cycle and by anatomical location. In rats, the secretory component [or polymeric Ig receptor (**pIgR**)] responsible for transporting IgA antibody to luminal surfaces of the reproductive tract and other mucosae was found to be regulated by female sex steroid levels with E₂ increasing both mRNA and pIgR protein in endometrial tissues (31). When rats were immunized in the intraperitoneal space or intra-Peyers' patches, E₂ appeared to enhance the secretion of specific antibodies of both IgA and IgG isotypes into the uterine lumen but lowered the amount secreted by the vaginal mucosa (67).

Other estrogen effects include the regulation of antigen presentation by uterine or vaginal epithelium. As mentioned, the uterine epithelium is apparently able to act as antigen-presenting tissue; so, apparently, are underlying stromal cells, although hormonal influences for these two cell types are contradictory. With tritiated thymidine incorporation by sensitized T cells in the presence of uterine stromal or epithelial cells with or without the sensitizing antigen, Wira and Rossol (69) showed that uterine epithelial cells from late diestrous rats (when E₂ levels are higher) were better able to present antigens to T cells than were uterine epithelial cells from early to mid-diestrous rats (lower estrogen levels). The antigen-presenting efficiency of uterine stromal cells, however, was lowest at late diestrus (69). It would appear that E₂ upregulates antigen presentation by uterine epithelial cells, at least in the rat.

In the vagina, both macrophages and dendritic cells have been described as candidate antigen-presenting cells (67). As with uterine stromal cells, vaginal cells were less efficient at antigen presentation when under the influence of rising E₂ levels (late diestrus). Interestingly, the addition of P₄ to the E₂ environment counteracted the E₂-mediated inhibition of antigen presentation. Because antigen presentation is generally MHC class II-restricted, one proposed mechanism for the dynamics of antigen presenting cell efficiency is a hormonal regulation of MHC II expression (67). In the normal bovine uterus, the dynamics of immune cell populations capable of presenting antigen have been related to the stage of the estrous cycle (16). Specifically, MHC II expression increased as estrus approached.

The Uterus as Inductive Site for Local Immune Responses

From Wira and colleagues (67, 69) and from others (2, 16, 17, 66), it seems clear that both afferent and efferent arms of local immune response exist in the female reproductive tract. On the afferent side, macrophages, keratinocytes and dendritic cells act as antigen-presenting cells in the vagina (69), at least in the rat model; those antigens that ascend to the uterus may be processed and presented by endometrial epithelial or stromal cells (17, 69). At proestrus or estrus, the uterus may be exposed to sperm and seminal plasma antigens and to microbial antigens. The high E₂ levels that prevail at this time may induce an increase in antigen-presenting efficiency in uterine cells (16, 67, 69). The uterine cells

could then present antigens to T cells, many of which lie beneath the glandular epithelium of the stratum spongiosum (16). Cytokines released by T cells induce proliferation of local and regional (lymph nodes) T and B cells (66, 67, 68). If the T helper (Th) cell response is predominantly of the Th₁, type interferon α and TNF α and TNF β are the major cytokines produced (59); luminal interferon α increases endometrial pIgR, independent of E₂ levels (46). This response results in more tissue IgA transport into the lumen (46) and perhaps an increase in IgG₂ production (59). A Th₂ response, with interleukins 3, 4, 5, 10, and 13, is associated with enhanced B cell production of IgG₁, IgA, and IgE (59). Lymphocytes from local and regional lymphatic tissue, and probably from the spleen, gut, and respiratory tract, may migrate to the endometrium where they would affect cell-mediated and antibody-mediated immune responses against the antigen(s) (67). Ovarian steroids influence the migration of leukocytes into the reproductive tract. In addition, E₂ induces an increase in the production of pIgR (68), which transports more IgA across the uterine epithelium. The means by which IgG arrives in the uterine lumen during E₂ peaks is less certain. An IgG Fc receptor has been shown to exist in the bovine mammary gland (4), which may account for the high IgG levels in bovine colostrum. To determine whether a similar receptor exists on uterine epithelial cells would be interesting. In the absence of specific transport, IgG may arrive in the uterine lumen by leakage from small venules following nonspecific inflammation mediated by neutrophils, mast cells, and eosinophils and associated chemokines and cytokines.

In the cycling cow, all of the necessary immunological components are apparently present and seem to be finely tuned by ovarian steroids so as to be at peak performance during times of exposure to environmental antigens. If the rat model holds for the cow, the bovine uterus should be more able to clear infections of *E. coli*, *Staphylococcus*, *Pseudomonas*, and *A. pyogenes* during estrus than at any other time. However, in the early postpartum period, after placental estrogens have waned and before ovarian activity has resumed, the low estrogen milieu may predispose the uterus to bacterial colonization by disarming specific responses and by leaving only nonspecific responses available (e.g., neutrophilic infiltration). Even this response is apparently compromised under the influence of endotoxins as a result of opportunistic infection by Gram-negative bacteria in the early postpartum period. Interestingly, bacterial flora of the postpartum uterus begin to diminish at about the

same time that the pituitary becomes sensitive to GnRH again (i.e., around d 14 postpartum) with resultant small pulses of E₂ production by the ovary (54). For postcoital infection with venereal agents, the organism is introduced at estrus when E₂ levels are rapidly declining from peak level. The pathogen survives long enough to establish itself in the uterus and oviducts and apparently causes insufficient inflammation to induce either immediate death of the preimplantation conceptus or premature release of a luteolytic burst of endometrial PGF_{2 α} (2, 5, 45). The pregnancy commonly survives for 60 d or more, a condition that maintains the local environment under influence of P₄ influence. If the reproductive system of the cow responds as does that of the rat, then a pregnant heifer infected with *T. foetus* or *C. fetus venerealis* would have diminished ability to present antigen from the uterine lumen and to transmit specific IgA back into the lumen. Vaginal responses would not be expected to change. Although we have not been able to test the former hypotheses because of the difficulty of repeated sampling from the pregnant uterus, we do know that the pregnant heifer with infection continues to secrete high levels of antigen-specific IgA into the vaginal lumen (R. BonDurant, L. Corbeil, C. Campero, M. Anderson, unpublished observations, 1998).

In summary, the most common forms of uterine inflammation occur as the result of postpartum ascending contamination by nonspecific environmental organisms or by specific venereal infection with host-adapted agents at estrus. The initial response is a neutrophilic influx, which may induce further inflammatory responses. These include mast cell activation, eosinophil chemotaxis, and serum extravasation with subsequent complement activation. For nonspecific infection and inflammation, some uterine neutrophil function is apparently compromised relative to circulating neutrophils. Evidence from the rat model and from cow studies suggest that in addition to the nonspecific responses, the reproductive tract appears to contain all the elements necessary for induction of a specific local immune response. This response may include antigen-presenting cells (uterine epithelium, vaginal keratinocytes, dendritic cells, and macrophages), subepithelial T helper cells, intraepithelial cytotoxic T cells, and perhaps B cells. Although most of these same immune components have been at least partially described for the bovine uterus, their functions need to be specifically demonstrated before the rat model can be entirely translated to a cow model.

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