Physiology and Endocrinology Symposium: Maternal immunological adjustments to pregnancy and parturition in ruminants and possible implications for postpartum uterine health: Is there a prepartum–postpartum nexus?
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Establishment of microbial infections in the reproductive tract can have negative consequences for reproductive function of the postpartum female (Kasi-Manickam et al., 2004; Dobson et al., 2008; Gautam et al., 2009). In a large study involving 5719 postpartum

**ABSTRACT:** Establishment of microbial infections in the reproductive tract can have negative consequences for reproductive function of the postpartum female. Most periparturient cows experience bacterial contamination of the uterus after parturition, but only a fraction of these develop subclinical or clinical disease. It is not well understood why one female resolves uterine infections after parturition while another develops disease. Perhaps those that develop metritis or endometritis are exposed to a greater bacterial load at parturition than those that successfully restore the uterus to a healthy condition. A second possibility is that females that develop bacterial disease have compromised immune function, either systemically or in the reproductive tract and associated lymph nodes. Here, the possibility is raised that maternal immunological adjustments to the presence of the allogeneic conceptus may predispose some females to metritis or endometritis. Several regulatory processes ensure that adaptive immune responses against paternal antigens on the conceptus are downregulated during pregnancy. Among these are immunosuppressive effects of progesterone, local accumulation of immune cells that can inhibit inflammation and T cell responses, including M2 macrophages and γδ T cells, and differentiation of regulatory T cells to inhibit alloreactive lymphocytes. Some immunological adjustments to the conceptus also make the uterus more susceptible to bacterial infection. For example, progesterone not only depresses skin graft rejection but also reduces uterine capacity to eliminate bacterial infections. Macrophages of M2 phenotype can inhibit inflammation and facilitate persistence of some microbial infections. At parturition, immune defenses in the uterus may be further weakened by loss of the luminal epithelium of the endometrium, which is part of the innate immune system, as well as by disappearance of intraepithelial γδ T cells that produce the antibacterial proteins granulysin and perforin. It is currently not known whether molecules and cells that inhibit immune responses during pregnancy persist after parturition but, if so, they could contribute to compromised immune function in the uterus. It is hypothesized that individual variation in immune adjustments to pregnancy and parturition and the reversal of these changes in the postpartum period are important determinants of susceptibility of the uterus to infection.

**Key words:** endometritis, immunology, metritis, pregnancy, ruminants

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**INTRODUCTION**

Establishment of microbial infections in the reproductive tract can have negative consequences for reproductive function of the postpartum female (Kasi-Manickam et al., 2004; Dobson et al., 2008; Gautam et al., 2009). In a large study involving 5719 postpartum
dairy cows, first service pregnancy rate was 39.4% for cows diagnosed with metritis in the first 65 d postpartum, 38.7% for cows diagnosed with clinical endometritis and 51.4% for cows in which no disease was diagnosed during the first 65 d postpartum (Santos et al., 2011).

As has been highlighted by Sheldon et al. (2009), virtually all cows experience bacterial contamination of the uterus after calving (Fig. 1), but only a fraction of these develop subclinical or clinical disease. In the remainder of cases, immune defenses in the uterus are capable of eliminating the bacteria responsible for uterine infectious disease. In cattle, these most commonly are Escherichia coli and Trueperella (previously Arcanobacterium) pyogenes and, less commonly, anaerobic bacteria such as Prevotella and Fusobacterium species (Sheldon et al., 2009).

It is important for developing approaches to reduce incidence of bacterial diseases of the uterus to understand what determines whether or not a postpartum female successfully clears bacteria from the uterus after calving. One possibility is that females that develop metritis or endometritis are exposed to a greater bacterial load at parturition than those that successfully restore the uterus to a healthy condition. Perhaps microbial contamination of the reproductive tract is at a scale that overwhelms uterine defense mechanisms. A second possibility is that females that develop bacterial disease have compromised immune function, either systemically or in the reproductive tract and associated lymph nodes.

There is indeed evidence to implicate inadequate immune function as a cause of uterine disease. In one study, peripheral blood leukocytes of cows that developed endometritis were less capable of phagocytosis prepartum than those of cows that did not develop endometritis (Kim et al., 2005). Also, at calving, cows that subsequently developed metritis had reduced glycogen content in circulating neutrophils (Galvão et al., 2010a) and reduced expression of tumor necrosis factor α (TNFA) by E. coli-stimulated monocytes (Galvão et al., 2012). Moreover, the incidences of metritis and endometritis have sometimes been reduced by antioxidant treatments that improve neutrophil function (Hansen, 2012).

Initially, the postpartum female is poorly positioned to eliminate bacteria from the uterus. The loss of integrity of the epithelial lining of the endometrium during the early postpartum period (Moller, 1970) removes a physical barrier to bacterial attachment mediated by mucins (Davies et al., 2008) and allows ingress of bacteria into the endometrial stroma. Loss of the epithelium also removes an important source of antibacterial peptides (Davies et al., 2008) and proteins (Tekin and Hansen, 2003). The epithelium is also an important component of the innate immune system that expresses toll-like receptors (TLR) that trigger inflammation (Davies et al., 2008) and which can participate in antigen presentation, at least in humans (Wallace et al., 2001). In addition, physical clearance by discharge of products of inflammation through the cervix may be impeded by the position of the uterus in the body. In the mare, differences between females in ability for physical clearance are related to susceptibility to post-breeding endometritis (Troedsson and Liu, 1991).

The early postpartum female has also just completed a prolonged period when immune function in the uterus is suppressed because of the need to limit maternal immune responses against the allogeneic conceptus. Unless the sire and dam have identical major histocompatibility complex (MHC) genes, the conceptus is an allograft that can be recognized as foreign by the mother. Conceivably, an important determinant of whether a female develops metritis or endometritis after parturition is the degree of uterine immunosuppression before parturition and the rate at which immune function in the uterus is restored to a pregravid condition. The purpose of this review is to highlight the immunological adaptations of the female to the presence of the conceptus and to speculate how such adaptations could potentially compromise antimicrobial mechanisms in the reproductive tract after parturition. The focus is on ruminants, although concepts from other species will be introduced as appropriate.
Immunosuppressive Actions of Progesterone on the Uterus: Consequences for Survival of the Allogeneic Conceptus

Progesterone has been referred to as Nature’s Immunosuppressant (Siiteri et al., 1977). Such a designation is an exaggeration; direct effects of progesterone on lymphocyte function require large, usually pharmacological doses, and may involve destabilization of the plasma membrane rather than signaling through a specific receptor (Monterroso and Hansen, 1993). Nonetheless, progesterone does inhibit immune function in the uterus at physiologically-relevant concentrations. Most relevant for the success of pregnancy is the action of progesterone to inhibit tissue graft responses. Progesterone can prevent or delay rejection of tissue allografts in the uterus of the rat (Watnick and Russo, 1968) and sheep (Reimers and Dziuk, 1974; Hansen et al., 1986; Padua et al., 2005) and prolong survival of xenografts in the sheep uterus (Majewski and Hansen, 2002). An example of allograft survival in the uterus of an ewe treated with progesterone (P4) is shown in Fig. 2.

Graft rejection responses involve central effector and regulatory actions of T lymphocytes (Valujskikh and Li, 2007) and, in some cases, natural killer (NK) cells (Kroemer et al., 2008) and B-cells (Everly and Terasaki, 2012). Progesterone treatment in ewes causes a decline in endometrial lymphocyte numbers (Gottshall and Hansen, 1992). It has been proposed (Padua and Hansen, 2010) that the graft-promoting effect of progesterone in the sheep involves induction of an endometrial secretory product with immunoregulatory properties called SERPINA14 (previously termed uterine milk protein or uterine serpin). The SERPINA14 gene exists in a subset of mammals including cetartiodactyls, horses, pigs, and some carnivores (Padua et al., 2010). In the sheep, concentrations of SERPINA14 in uterine fluid reach milligram per milliliter concentrations (Moffatt et al., 1987). At this concentration, SERPINA14 can block T cell proliferative responses (Segerson et al., 1984; Peltier et al., 1999; Tekin et al., 2006), NK-cell activity (Liu and Hansen, 1993; Tekin and Hansen, 2002), and antibody production (Skopets et al., 1995). Coincidentally, prolonged exposure to progesterone (~30 d) is required both for its allograft-promoting actions (Reimer and Dziuk, 1974) and for the induction of large amounts of SERPINA14 (Leslie and Hansen, 1991).

The endometrium also produces SERPINA14 during pregnancy in the cow under the influence of progesterone (Leslie et al., 1990; Leslie and Hansen, 1991) but it is not known whether it is immunoregulatory in the cow or other species. Moreover, estrogen can also apparently regulate SERPINA14 production in the cow because amounts of SERPINA14 mRNA in endometrium are high at estrus (Ulbrich et al., 2009).

Immunosuppressive Actions of Progesterone on Uterine Antimicrobial Responses

In addition to affecting allograft survival, progesterone blunts antimicrobial responses in the uterus. Treatment of ovariectomized females with progesterone reduced the clearance of experimentally-introduced bacte-
ria in the uterus of cattle (Rowson et al., 1953) and sheep (Lewis, 2003; see Fig. 2) as well as of mares (Ganjam et al., 1982; Evans et al., 1986), rats (K aushic et al., 2000), and gilts (Wulster-Radcliffe et al., 2003). An indication of the importance of progesterone for regulating antibacterial responses in the uterus is the observation that delaying ovulation in postpartum dairy cows through administration of an implant containing the GnRH agonist Deslorelin improved uterine health (Silvestre et al., 2009). Interestingly, however, there is no evidence that cows that resume estrous cycles early after calving are more likely to develop uterine disease; the converse might be true (Galvão et al., 2010b).

Unlike for its graft-promoting effects, progesterone can compromise antibacterial responses after only a short exposure; for example, after 5 d in sheep (Lewis, 2003). Thus, there are differences in the mechanisms by which progesterone compromises allograft rejection versus those in which it reduces antimicrobial defenses. Some effects of progesterone may be mediated by inhibition of PGF$_2$α release from the uterus. Short-term treatment with progesterone reduces uterine secretion of PGF$_2$α (Silvia et al., 1991; Lewis, 2003) and administration of PGF$_2$α reduced severity of bacterial infection in ovariectomized ewes treated with progesterone (Lewis and Wulster-Radcliffe, 2006).

The mechanisms by which progesterone reduce competence of the reproductive tract to clear microorganisms is incompletely understood. In the mare, physical removal of material from the uterus through the cervix is reduced by progesterone (Evans et al., 1986). In sheep, progesterone inhibited leukocytic infiltration in response to bacterial inoculation (Brinsfield et al., 1964) but, in the cow, there was no effect of progesterone on the number of neutrophils recovered from the uterus of ovariectomized females after infusion of oyster glycogen or cell-free filtrate of a bacterial culture (Lander Chacin et al., 1990; Subandrio et al., 2000). In these same studies, progesterone did not affect functional capacity of uterine neutrophils, as determined in chemotaxis and phagocytosis assays.

There is also little indication that progesterone reduces humoral immunity in the uterus. In ovariectomized cows, progesterone had no significant effect on total IgG or IgA recovered from the uterus (Lander Chacin et al., 1990). Uterine content of IgG in the cow has been variously reported to be greater at estrus than during the luteal phase (Whitmore and Archbald, 1977) or vice versa (Brenner et al., 1995).

A key event in the activation of host defenses against microorganisms is recognition of the presence of the organisms by TLR and other pattern recognition receptors that bind to specific bacterial nucleic acids, lipids, and lipopolysaccharides (LPS) and activate local synthesis of antibacterial peptides and inflammatory chemokines and cytokines (Sheldon et al., 2009). The bovine endometrium expresses TLR on epithelial and stromal cells and produces an array of antibacterial peptides (Davies et al., 1908; Sheldon et al., 2009). This bacterial recognition system may be downregulated to some extent by progesterone. In vitro, treatment of epithelial or stromal cells isolated from bovine endometrium with progesterone reduced induction of secretion of PG caused by exposure to LPS (Herath et al., 2006). Also, analysis of bovine abattoir-derived material indicated that expression in the endometrial luminal epithelium of three genes involved in inflammation (CXCL5, IL1B, and IL8) is reduced during the luteal phase as compared with the periovulatory period (Fischer et al., 2010).

Role of Regulatory Immune Cells in Control of Uterine Immune Function during Pregnancy

Regulatory T Cells. Regulatory T cells (T$_{reg}$) are a class of CD4$^+$ T lymphocyte involved in suppression of autoimmune responses and inflammation caused by infection and tissue injury, metabolic disturbances, and other causes (Gobert and Lafaille, 2012). Differentiation is under control of the forkhead box P3 (FOXP3) transcription factor and takes place in 2 anatomical sites. One class of T$_{reg}$ cells is derived in the thymus (natural or tT$_{reg}$ cells) whereas another class, called pT$_{reg}$, is derived by differentiation of peripheral CD4$^+$ T cells (Littman and Rudensky, 2010).

The pT$_{reg}$ cells are particularly important for limiting inflammation at mucosal surfaces (Josefowicz et al., 2012). These cells are also critical to the survival of the allogeneic conceptus. Indeed, a major enhancer for FOXP3 necessary for differentiation of pT$_{reg}$ cells but not tT$_{reg}$ cells called conserved noncoding sequence 1 (CNS1) arose during evolution in placental mammals (Samstein et al., 2012). The relative number of T$_{reg}$ cells in blood, spleen, and lymph nodes increase during pregnancy in mice (Aluvihare et al., 2004) and in blood of humans (Somerset et al., 2004). A least a portion of the pT$_{reg}$ cells that differentiate during pregnancy are specific for paternal alloantigen (Samstein et al., 2012). In mice, antibody-mediated depletion of T$_{reg}$ cells decreased litter size in allogeneic pregnancies but not in syngeneic pregnancies (Aluvihare et al., 2004; Shima et al., 2010). Similarly, female mice deficient for CNS1 had reduced litter sizes in allogeneic pregnancies but not syngeneic pregnancies (Samstein et al., 2012).

Circulating T$_{reg}$ Cells have been identified in the cow (Gerner et al., 2010) and sheep (Rocchi et al., 2011), but it is not known whether or not numbers change during pregnancy. One characteristic of circulating T$_{reg}$ cells is high expression of another marker, CD25. The proportion of circulating CD4$^+$ T lymphocytes that were also...
positive for CD25 was greater for pregnant cows at d 33 to 34 of gestation and in the periparturient period than for nonpregnant cows (Fig. 3; Oliveira and Hansen, 2008).

**Macrophages.** Macrophages function not only in phagocytosis and antigen presentation, but also exert immunoregulatory roles. Differentiation of macrophages is dependent on the cytokine milieu. In the presence of inflammatory cytokines such as interferon-γ (IFNG) and TNFα or bacterial lipopolysaccharide, macrophages differentiate along the M1 activation pathway to promote inflammation. In contrast, differentiation in the presence of Th2 cytokines IL-4 and IL-13, leads to M2 activation to produce a macrophage that causes immunosuppression (Varin and Gordon, 2009). In the human, decidual macrophages exhibit an M2 phenotype (Gustafsson et al., 2008) and potentially limit immune responses directed against the conceptus.

Based on expression of the markers CD68 and CD14, cells characteristic of macrophages are very abundant in the stromal compartment of the endometrium of pregnant cows (Oliveira and Hansen, 2008; Oliveira and Hansen, 2009) and sheep (Tekin and Hansen, 2004). Moreover, endometrial CD14+ cells in the cow express a variety of genes characteristicly expressed by macrophages (Oliveira et al., 2010). At least a fraction of endometrial macrophages have differentiated along the M2 pathway. Twelve genes characteristic of M2-activated macrophages (SLCO2B1, GATM, MRC1, ALDH1A1, PTGS1, RNASE6, CLEC7A, DPEP2, CD163, CCL22, CCL24, and CDH1) were upregulated in CD14+ cells isolated from the endometrium of pregnant cows as compared with CD14+ cells from peripheral blood (Oliveira et al., 2010).

In unilaterally-pregnant ewes, in which pregnancy was confined surgically to 1 uterine horn, CD68+ cells accumulated in endometrium of both horns, although to a greater degree in the horn containing the conceptus (Tekin and Hansen, 2004). Thus, regulation of macrophage accumulation involves both systemic and local factors. Progesterone is not the systemic signal because treatment of ovariectomized ewes with progesterone did not result in an increase in numbers of CD68+ cells in the endometrium (Tekin and Hansen, 2004).

**γδ T cells.** The most abundant lymphocyte population in the endometrium of sheep during all but early pregnancy is the γδT cell (Fig. 4); as much as 13% of the cells in the luminal epithelium during pregnancy are γδT cells (Lee et al., 1992; Nasar et al., 2002). Accumulation of γδT cells in the endometrium is apparently due to a systemic signal because it occurs in both pregnant and nonpregnant uterine horns of unilaterally-pregnant ewes (Majewski et al., 2001). Presence of γδT cells in the endometrium of pregnant females is not a unique characteristic of sheep because a similar phenomenon has been reported in mice (Suzuki et al., 1995; Ack et al., 1999) and humans (Fan et al., 2011). To date, the presence of γδT cells in the endometrium of pregnant cows has not been reported.

The γδT cell is defined by the presence of a T cell receptor (TCR) formed by γ and δ subunits instead of the α and β subunits that characterize the more well-studied αβ T cell. The γδT cells have some features of the innate immune system and others of the adaptive immune system. The antigenic repertoire of the TCR is more limited than for αβ T cells and γδT cells do not require antigen presentation to recognize some antigens, particularly bacterial lipids and stress-induced proteins related to major histocompatibility Class I antigens (Wesch et al., 2011). The γδT cells can be cytotoxic to bacteria (Diehl et al., 2001), protozoa (Farouk et al., 2004), and tumor cells (Li et al., 2012). In addition, γδT cells can be involved in cellular regulation. Decidual γδT cells in mice have been reported to inhibit lymphocyte function through secretion of transforming growth factor-β.
(Suzuki et al., 1995). Decidual γδ T cells in humans can support trophoblast growth in vitro via proliferative and antiapoptotic actions caused by secretion of IL-10 (Fan et al., 2011). Experiments in the mouse using antibodies that deplete specific subtypes of γδ T cells indicate that there are separate abortogenic and fetoprotective subpopulations of γδ T cells, with the latter arising later in pregnancy than the former (Arck et al., 1999).

The main roles of endometrial γδ T cells in the sheep appear to be antibacterial and immunoregulatory. Intraepithelial γδ T cells in the luminal epithelium are highly granulated (Lee et al., 1992; Meeusen et al., 1993). The granules contain the antibacterial protein granulysin (Fox et al., 2010). In addition, mRNA for profilin, which is involved in destruction of intracellular pathogens (Stenger, 2001) can be identified (Fox and Meeusen, 1999). The capacity for immunoregulation is indicated by expression of IFNG, TNFA, TGFβ, and IL10 from γδ T cells isolated from endometrial epithelium of pregnant ewes (Fox et al., 1998).

**Natural Killer Cells.** Accumulation of NK cells in the uterine endometrium is one of the notable cellular changes in the uterus during pregnancy in a variety of species, including humans and rodents (Manaster and Mandelboim, 2010; Soares et al., 2012), pigs (Tayade et al., 2007), and horses (Noronha et al., 2012). Their function has been studied best in the mouse and human. Intraepithelial γδ T cells in the luminal epithelium are highly granulated (Lee et al., 1992; Meeusen et al., 1993). The granules contain the antibacterial protein granulysin (Fox et al., 2010). In addition, mRNA for profilin, which is involved in destruction of intracellular pathogens (Stenger, 2001) can be identified (Fox and Meeusen, 1999). The capacity for immunoregulation is indicated by expression of IFNG, TNFA, TGFβ, and IL10 from γδ T cells isolated from endometrial epithelium of pregnant ewes (Fox et al., 1998).

Changes in Systemic Immune Function during the Periparturient Period

Parturition is accompanied by coordinated changes in metabolism and function of the mammary gland, digestive tract, uterus, and cervix that is driven by changes in circulating hormones such as progesterone, estrogen, cortisol, and PG (Wood, 1999). Given the interaction between the immune system with the endocrine and metabolic systems (Stofkova, 2009; Pittman, 2011), changes in immune function in the periparturient period are to be expected. Indeed, there are extensive data that such changes occur in a way that could compromise competence of the female to clear microorganisms from the
reproductive tract. Alterations in the endocrine control of parturition could contribute to female susceptibility to uterine infection; circulating estradiol concentrations at calving were greater in cows that developed metritis than cows that did not (Galvão et al., 2010a). Among the changes reported in immune function in late gestation or the periparturient period in the systemic vasculature are a reduction in circulating IgG and IgM concentrations (Herr et al., 2011), reduced neutrophil function (Kehrli et al., 1992; Suzuki et al., 1995), and Treg cell (Aluvihare et al., 2004; Shima et al., 2010; Samstein et al., 2012), as well as differentiation of regulatory immune cells that can inhibit inflammation and T cell responses. These cells include the M2 macrophage (Gustafsson et al., 2008; Oliveira et al., 2010), γδ T cell (Lee et al., 1992; Suzuki et al., 1995), and T_{reg} cell (Aluvihare et al., 2004; Shima et al., 2010; Samstein et al., 2012). Some of the immunological adjustments to the presence of the conceptus also make the uterus more susceptible to bacterial infection. Progesterone not only alters allograft rejection responses, but also acts through some largely unknown mechanism independent of SERPIN14 to inhibit antimicrobial responses in the uterus (5). The M2 macrophages also inhibit inflammation (6), and SERPINA14 can inhibit B cell function (7). One cellular change associated with pregnancy, accumulation of γδ T cells in the luminal epithelium, may facilitate removal of bacteria through synthesis of proteins like granulysin and perforin (8). Note that the drawings for this figure and Fig. 6 are speculative: they combine concepts derived from sheep, cattle, and other species and not all of the pathways shown have been established in any one species. See online version to view figure in color.

Antibacterial Defenses in the Postpartum Uterus: Speculations About a Prepartum-Postpartum Nexus

As shown in Fig. 5, adaptive immune responses against paternal antigens on the conceptus are downregulated during pregnancy. Among the regulatory processes responsible for inhibition is an immunosuppressive role for progesterone (Reimers and Dziuk, 1974; Hansen et al., 1986; Majewski and Hansen, 2002; Padua et al., 2005), as well as differentiation of regulatory immune cells that can inhibit inflammation and T cell responses. These cells include the M2 macrophage (Gustafsson et al., 2008; Oliveira et al., 2010), γδ T cell (Lee et al., 1992; Suzuki et al., 1995), and T_{reg} cell (Aluvihare et al., 2004; Shima et al., 2010; Samstein et al., 2012). Some of the immunological adjustments to the presence of the conceptus also make the uterus more susceptible to bacterial infection. Thus, for example, progesterone not only depresses skin graft rejection, but also reduces uterine capacity to eliminate bacterial infections (Rowson et al., 1953; Lewis, 2003). The M2 macrophages can inhibit inflammation and facilitate persistence of some microbial infections (Varin and Gordon, 2009).
Nonetheless, many host defense mechanisms remain intact in the reproductive tract of the pregnant female, including an endometrial epithelium that produces perforin (Tekin and Hansen, 2003) and possibly other antimicrobial products. The endometrial epithelium presumably acts as a physical barrier to bacterial ingress even though luminal epithelium forms a syncytium with invading trophoblast (Wooding, 1992). Moreover, there is good reason to believe that intraepithelial γδ T cells in the uterine endometrium exert an antibacterial function (Fox and Meeusen, 1999; Fox et al., 2010).

As illustrated in Fig. 6, uterine susceptibility to bacterial infection increases in the immediate postpartum period. The loss of the luminal epithelium in the early postpartum period (Moller, 1970) removes an important physical barrier to bacteria, a source of antimicrobial molecules and, through synthesis of TLR and other pattern recognition receptors, a surveillance system to trigger inflammation in response to microbial infection. Furthermore, reduced functional activity of circulating neutrophils (Kehrli et al., 1989; Hoeben et al., 2000; Rinaldi et al., 2008) means that cells migrating into the uterus in response to inflammation have suboptimal capacity to phagocytose microbes. Finally, γδ T cells, which are probably antimicrobial during pregnancy (Fox and Meeusen, 1999; Fox et al., 2010), are rapidly eliminated from the ovine endometrium coincident with parturition (Lee et al., 1992; Nasar et al., 2002). The number of γδ T cells then begins to increase by day 3 postpartum (Nasar et al., 2002), but it is not known whether these new cells are differentially toward an antimicrobial phenotype.

**SUMMARY AND CONCLUSIONS**

What is not known is the extent to which molecules and cells that inhibit immune responses during pregnancy persist after parturition. Progesterone concentrations decline precipitously with parturition so the immunosuppressive actions of this hormone dissipate in the postpartum period. However, some of the products of progesterone action, such as SERPINA14, could conceivably persist in the uterus for some time after parturition. Similarly, kinetics of removal of endometrial M2 macrophages during the postpartum period is not known. Perhaps individual variation in immune adjustments to pregnancy and parturition and the reversal of these changes in the postpartum period are important determinants of susceptibility of the uterus to infection. The question is worthy of more investigation. A better understanding of the immunological adjustments in the reproductive tract to pregnancy and parturition could lead to strategies for reducing uterine infections in the postpartum period.

**LITERATURE CITED**


Prepartum determinants of postpartum uterine health


