

Immunology of Bovine Pregnancy: Vulnerability to Infectious Diseases

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"The fetoplacental unit behaves like other successful parasites in actively engineering the mechanism(s) responsible for its success"

D.A. Clark, 1990

Abstract

Pregnancy results in a period of immunosuppression as the fetus develops. The extent of this immunosuppression has been the subject of active investigation as it relates to conception, maintenance of early pregnancy, and fetal survival to term. The immunosuppression that allows for fetal survival may, in some circumstances, allow for infectious microorganisms to cause a systemic infection in the pregnant cow, and may even invade the fetus, resulting in abortion, stillbirth or calves born with congenital defects. The purposes of this paper are to focus in on answering three questions pertaining to the immune response during bovine pregnancy and during the perinatal period. The questions are: why is the pregnant cow more susceptible to infectious diseases; why do pregnant cows shed more infectious microorganisms than nonpregnant cows; and, how can we realistically manage against increased vulnerability to infectious diseases during pregnancy and increased shedding of infectious microorganisms in the environment?

Introduction

The dilemma facing bovine practitioners is how far to pursue making a diagnosis of reproductive failure to differentiate infectious from noninfectious.^{7,10,29,36,37,42}

There are several factors to consider when making this decision such as management conditions in regards to sanitation, herd size, number of animals aborting within the past 90 days, and vaccination program.^{7,50,53,54}

There is a growing concern that infectious agents may not be the sole cause of reproductive failure and that those agents known to be associated with abortion may do so even in the face of adequate vaccination programs when one exists.^{15,16,42} Dealing with noninfectious causes of abortion is complex and will require more in-depth studies on the immune response of the pregnant animal. Nutrition has been directly correlated with conception, maintenance of early pregnancy, fetal survival to term, and even neonatal calf survival.^{1,16,22,34,54} The junction between nutrition and immunity is vital to our understanding of pregnancy and conversely our understanding of vulnerability to infectious microorganisms.

This paper will focus in on answering several questions pertaining to the immune response during bovine pregnancy and during the prenatal period. The questions are: why is the pregnant cow more susceptible to infectious diseases than the nonpregnant age matched control cow; why do pregnant animals shed more infectious agents than nonpregnant animals; and how can we realistically manage against increased vulnerability to infectious diseases during pregnancy and increased shedding of infectious microorganisms in the environment?

Why is the pregnant cow more susceptible to infectious diseases than the nonpregnant age matched control cow?

Answering this questions requires information derived in part from other species such as human, sheep and mice.^{6,9,11,31,40,48,49,52,55} Although generalizations are oftentimes made regarding the immune compromised state of the pregnant cow, definitive studies to define this are lacking and in need of immediate investigation.³³ For the purposes of our discussion, I will make several assumptions and draw conclusions whenever I can. The assumptions are as follows: cattle are exposed to the majority of infectious pathogens by 6 to 8 months of age. Their exposure dose is dependent upon the stocking density, pregnant/peripartuant cattle in the vicinity, and weather. Pregnant cattle are unique to the population for two reasons, they are selectively immunosuppressed and they shed progressively more infectious agents toward parturition and postpartum.¹⁵

The selective immunosuppression of the pregnant cow is designed to allow survival of the fetal graft.¹⁶ The true mechanisms whereby this occurs are still the subject of intensive investigation. At this time, we can summarize the proposed immune parameters occurring during bovine pregnancy (Figure 1). The T-cell population is affected by progesterone, prostaglandin E₂ and fetoprotein resulting in a decrease in T-cytotoxic cells and an increase in T-suppressor cells. The B-cell function is also modulated during pregnancy with a decrease in T-cell dependent antibody (probably due to decreased or ineffective T-helper cells) and an increase in blocking or enhancing antibodies. There are also decreases in

Interleukin 2, α interferon and colony stimulating factor, all of which play vital roles in maintaining T-cytotoxic and macrophage functions.^{15,19,21,23,28,39,41,44,51}

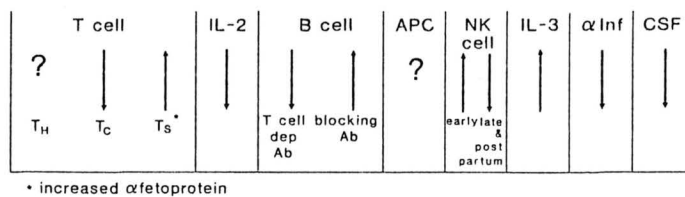


Figure 1. Proposed immune parameters during pregnancy. Abbreviations: T-cells, Thymus derived helper, cytotoxic, suppressor cells; IL-2,3 Interleukins; B-cell, bone marrow derived; APC, antigen presenting cells (macrophages), NK cells, natural killer cells α Inf, alpha interferon; and CSF, colony stimulating factors.

With this selective immunosuppression, T-cell dependent defenses become compromised.^{15,16,23,52} These include all viral infections, especially the herpesviruses, such as IBR virus and bovine herpesvirus type 4.^{15,18,39,47} Also intracellular bacterial infections, such as *Brucella abortus* become more aggressive during pregnancy.^{12,13} Macrophage function becomes temporarily compromised allowing opportunistic bacteria and chlamydia, which are usually confined to the external mucosal surfaces of the body, to become systemic resulting in bacteriemia, placentitis and fetal invasion. With altered macrophage function and impaired humoral immune response, primary infection with protozoal agents such as *Neospora* spp. have become well recognized in locations throughout the United States.^{2,3}

Why do pregnant cattle shed more infectious agents than nonpregnant animals?

This question oftentimes gets overlooked in the course of a disease investigation because the pregnant cow appears clinically normal. She, nonetheless, is temporarily immunosuppressed, which indirectly affects virus shedding as well as bacteria and gastrointestinal parasites.^{15,33,56} It has been speculated that the combination of immunosuppression and parturition result in a 1 to 4 week period of time during which the pregnant cow and her calf are in a vulnerable position.¹⁶ The pre- and post parturient cow are shedding increased microorganisms in their immediate environment via fecal matter, saliva, nasal secretions, urine, and placental tissues.

The newborn calf is essentially born in a microorganism-rich environment, and is totally dependent upon colostral antibodies for lactogenic (gut) and systemic passive protection.^{7,16,34,50,54}

Since there is an increased shedding of infectious microorganism during pregnancy, especially the last

trimester and 3 to 4 weeks postpartum, the question also arises regarding the line between an asymptomatic shedder and the cow which shows clinical signs of disease such as late stage abortion, postpartum metritis and mastitis. The predominant microbial infections during this period are bacterial and are due in part to decreased neutrophil function and continued decreased macrophage function.^{20,28,51,55} The line between asymptomatic shedder and clinical diseases during late stages of pregnancy and the periparturient period is no doubt related to nutritional factors. These factors, such as selenium and copper deficiency, have been reported to result in increased susceptibility to *H. somnus* and chlamydial-induced diseases, respectively.^{15,16}

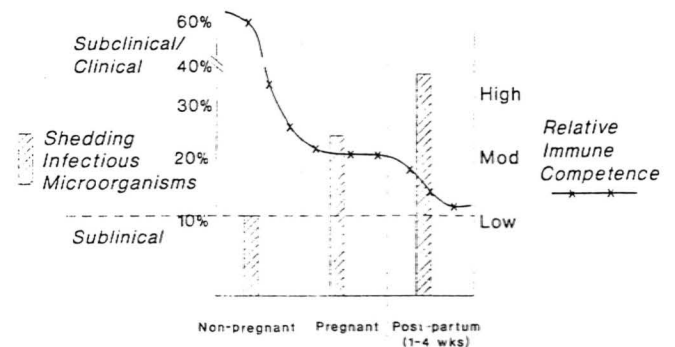


Figure 2. Proposed relationship between clinical and subclinical shedding of infectious microorganisms and relative immune competence during pregnancy and postpartum.

Management via vaccines/segregation

Attempting to understand the pregnancy-associated immunosuppression and increased shedding of microorganisms is one thing, but to figure out how to manage these biological problems poses the biggest questions of all.¹⁵ For many years, we have focused on identifying causal agents of abortion, postpartum metritis and mastitis in hopes of preparing vaccines to properly immunize the pregnant cow against these disease organisms.^{2,5,10,14,16,17,25,27,30,38} What we have come to realize is that vaccines may only stimulate partial immunity, if any at all, since the same mechanisms that control the immune response to natural infections are mobilized against potential vaccine-induced immunity. This poses several questions that relate to microbial shedding by the pre- and postparturient cow, as well as when are the most appropriate times to vaccinate for optimal immunization during pregnancy.^{5,16,25,50}

Knowledge that microbial agents are being shed in high quantity from the pre- and postpartum cow places her in a shedder category, and for this reason, pregnant cattle in their last week of parturition should be segre-

gated from other cattle that are due to calve, or just recently calved. If this is not feasible, provide a stocking density to allow for plenty of space for calving and minimize transmission of infectious agents to susceptible cattle. Vaccination before breeding is essential in order for the maximum immune response to function against challenge with the wide array of infectious microorganisms.^{16,25,50} In order to maximize the immune response, attenuated, modified live viral/bacterial preparations are ideal since they stimulate both T- and B-cell functions of the immune system. Vaccination during pregnancy poses several risks, including abortion due to trauma, modified live virus induction of abortion, contamination of vaccine with abortigenic-tolerogenic pathogen, e.g., BVD virus or bluetongue virus^{8,26,35,43,46}

Possible solutions to the use of modified live antigens and the suppressed immune response during pregnancy may be the use of immunomodulations (interleukins/cytokines), and nutritional supplementation with microelements such as Se and Cu.^{4,24,32,45,56}

The more we begin to understand the selective immune suppression during pregnancy, the better we can use external modulation to selectively boost the immune system, or the immune response of other cattle at risk to acquire infection from pregnant cattle that are shedding.

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