Pathogenesis of Fetal Infection in Ruminants

B. I. Osburn, *D.V.M., Ph.D.*
Department of Pathology
School of Veterinary Medicine
University of California
Davis, California 95616

Introduction

Fetal infections resulting in malformation and/or abortion cause considerable economic loss. Unfortunately, understanding the basic factors leading to either abortion or malformation is minimal. Information obtained during the last 10 to 15 years provides a basis for a working hypothesis which can be of potential benefit for understanding the nature of disease processes. A review of fetal infection, factors associated with fetal susceptibility to infection, the abortion phenomenon and the recommended steps for diagnoses of infected fetuses will be emphasized.

Routes of Fetal Infection

There are four potential routes by which the fetus can become infected, namely, 1) placental, 2) cervical, 3) Fallopian tubes, and 4) transovarian. The most important route by which many of the more damaging infectious agents reach the fetus is through the placentome. The intimate attachment of the placentome between the mother and fetus represents a likely place for primary placental infection to occur. In the latter one half of pregnancy in the bovine, hematomas caused by maternal vascular leakage occur in the placentome (1). These structures undoubtedly facilitate exposure of placental cotyledons to bacteria, viruses and/or fungi which may on occasion be found in the blood of cattle. Various factors may favor a mild subclinical infection in the cow leading to localization of a microorganism in the placentome. For instance, many infectious agents become systemic at the time of the initial infection. Latent viruses (*i.e*, infectious bovine rhinotracheitis [IBR]), or bacteria such as *Brucella sp.*, may be localized in certain organs until circumstances such as stress or pregnancy result in viremia or bacteremia with subsequent localization in the placentome (2,3,4,5,6).

Infectious agents may enter through the cervix. Most often this occurs at the time of breeding or around the time of birth (perinatal period). Infection early in pregnancy often leads to early embryonic death such as that observed in vibriosis. Perinatal infections may or may not be harmful to the newborn animal. The fate is dependent upon the immune status of the newborn animal and the pathogenicity of the microorganism.

Transovarian infection probably occurs in the bovine since evidence suggests that it occurs in a number of other species. However, at this time there are no known transovarial agents of cattle which cause fetal infection. Rarely, infectious agents associated with peritonitis may reach the placenta through the Fallopian ducts. Sporadic cases may occur; however, it is usually associated with more serious complications in the cow and consequently is of little or no significance on a herd basis.

Factors Favoring Fetal Infection

Once invasion of the placenta by microorganisms occurs, fetal infection has been accomplished. A set of unique circumstances then renders the bovine fetus highly susceptible to infection. First of all, the bovine placenta is incapable of transporting maternal antibodies to the fetus, thereby leaving the calf with no passive resistance. Second, the fetal calf has an immature immunological system with limited capabilities of responding to antigens. Third, there appear to be limited numbers of granulocytes available for responding to invasion by microorganisms and fourth, there may be special factors or undifferentiated cell populations which provide a favorable site for the replication of bacteria, viruses or fungi.

Passive transfer of antibodies from mother to the fetus or newborn provides an immediate form of protection for the calf (7). In cattle, nearly all of the passive transfer of antibodies occurs in the colostrum thereby making this form of resistance available only to the newborn. The agammaglobulinemic fetal calf is highly susceptible to infection (8,9,10).

In addition, the fetus is often further compromised by an immature immune system which in a deliberate sequential fashion matures during gestation (11). Lymphoid organs, including the thymus, lymph nodes and spleen, do not acquire lymphocytes until the later part of the second month of gestation (12). These organs serve the important function of providing a home for cells to localize and interact with antigens associated with microorganisms. Although these organs and lymphocytes are present early in fetal life, the calf lacks the ability to respond to most antigens associated with microorganisms

before the third month of gestation (12,13). For instance, the fetal calf may be capable of making antibodies to one microorganism at 130 days of gestation while it may be around 200 days before it makes antibodies to another agent (12,13). The exact reason for this is not known, however it may be associated with genetic regulatory mechanisms.

An example of the consequence of infection occurring before and after the development of immunological competence is as follows:

Campylobacter (Vibrio) *fetus* on occasion can be associated with mid and late term abortions. Inoculation of live organisms into the cow or fetal calf before 200 days of pregnancy will kill the fetus in two to three days with subsequent abortion of a dead calf (14,15). Inoculation after 200 days of gestation results in premature delivery of a live calf. The late term calves often appear normal and have antibodies (14,15). These observations suggest that the agammaglobulinemic, immunologically immature calf of less than 200 days gestation is highly susceptible and easily killed by the pathogenic factors associated with *Campylobacter fetus* infection. However, once immunologic competence to this agent is acquired, the fetal calf appears capable of defending itself to some degree from the pathogenic factors of *Campylobacter fetus*. Interestingly, infection of adults with this agent does not cause systemic disease.

Another factor which appears to favor microorganisms in the fetus include the presence of metabolic by-products which stimulate growth of some bacteria (16). Erythritol, a metabolic by-product of the bovine placenta and fetus stimulates the growth of *Brucella sp.* Substances such as this may allow some bacteria to localize and establish infection in the fetus.

Certain viruses have a predilection for undifferentiated cells in the immunologically immature fetus (17,18,19). Organs such as the brain undergo considerable differentiation and development during later fetal life. Viruses such as bluetongue, bovine virus diarrhea (BVD), and border disease have affinity for the undifferentiate neural tissue and cause extensive necrosis (17,18,19,20). As a consequence, cerebral malformations such as hydranencephaly, porencephaly (cerebral cysts), and cerebellar hypoplasia occur. The clinical manifestations associated with these infections include a dummy syndrome, incoordination, blindness, ataxia, etc. In most cases, virus cannot be isolated from newborn calves. In fact, the best means of determining the infectious cause of the disease is to examine serum for antibodies in precolostral calves (21).

Infection with these viruses early in gestation allows the virus to become well established with little or no immunological resistance on the part of the calf (18,22). Virus can be readily recovered from tissues with no evidence of specific serum antibodies directed to the agent. The virus seems to persist until the calf acquires immunologic maturity to the agent. In the case of BVD infection, neutralizing antibodies do not appear until about 200 days gestation (22). After the fetus is capable of making antibodies, the chance of isolating virus from tissues is greatly reduced (18,22). Infection with BVD virus after 200 days gestation appears to result in a rapid clearance of virus and the appearance of neutralizing antibodies in the serum (22). The only way that the infection can be determined in these instances is by testing serum for neutralizing activity (21,22).

Recently, a phenomenon of transient immune suppression has been postulated to occur in the perinatal period (23). Transient immune suppression has been associated with sudden release of large amounts of corticosteroids from the fetal adrenal gland. Corticosteroids suppress the immune system by causing a lymphopenia affecting lymphocytes primarily associated with cellular immunity. Evidence of the susceptibility of the newborn animal to infection during this period was recently demonstrated in newborn lambs (24). Infection of fetal lambs during the last 1/3 of gestation resulted in clearance of bluetongue virus and the appearance of neutralizing antibodies in the serum 10-14 days postinoculation. In contrast, inoculation of lambs at birth results in a persistent viral infection which lasts for six weeks. Serum neutralizing antibodies were not detectable until six weeks of age. These studies indicate that physiological events associated with the birth process lead to a transient immunosuppression, thereby rendering the newborn animal highly susceptible to infection (24).

Factors Associated with Abortion

Many aborted calves appear autolyzed. Autolytic changes at the time of abortion seem to be associated most often with calves under 200 days' gestation. In contrast, many calves aborted or delivered prematurely after seven months' gestation may be alive at the time the birth process starts. The explanation for the difference in the physical condition of the calves has been attributed to the hormonal milieu in the cow and the calf.

In the cow, pregnancy during the first trimester is controlled by progesterone secreted by the corpus luteum. During the second and third trimesters the placenta and corpus luteum provide most of the progesterone needed to maintain pregnancy (22,25). As mentioned earlier, pregnancy appears to be terminated when the fetal calf releases large amounts of corticosterone from its adrenals (23,27). This hormone appears to suppress progesterone production by the placenta. A release of prostaglandins by the endometrial cells causes a sudden regression of the corpus luteum leading to a dramatic decline in plasma progesterone (28,29). Once this occurs, uterine contractions and relaxation of the cervix result in expulsion of the calf.

Fetal infections during the first or second trimester of pregnancy do not appear to cause a stress syndrome leading to the release of corticosteroids with

subsequent abortion. Instead, calves killed by infectious agents are retained for two or three days before expulsion occurs (26). Apparently, it requires this long for the appropriate set of events to occur leading to a decline in plasma progesterone levels and a release of the uterus from the control mechanism.

Abortion or premature delivery during the last trimester of pregnancy is often associated with the delivery of a live calf. Exceptions to the rule occur in infections such as that associated with bovine rhinotracheitis virus (30). In many third trimester infections the disease process appears to stress the fetus. Once this occurs the release of corticosteroids from adrenal cortex may be of sufficient magnitude to lead a similar set of events to those observed in normal delivery (31). That is, the premature release of corticosterone from the fetal adrenals starts the chain of events leading to decreased placental progesterone production, release of prostaglandins, decreased progesterone production from the corpus luteum and the subsequent uterine contractions leading to expulsion. Often, calves near birth may appear normal or as small weak calves.

Diagnosis of Fetal Infection

The diagnosis of fetal disease is one of the most perplexing problems facing veterinary diagnosticians today. Most diagnostic laboratories report that successful diagnoses are made in 18 to 30% of the submitted aborted fetal material. In order to improve on the low percentage of correct diagnoses, it is important to understand that laboratories receive as much information and material as possible. The following represent a list of recommended procedures to follow when submitting material to a laboratory.

1. Complete history including vaccinations, breeding history, age of affected cows, etc.
2. Either the whole fetus and placenta, or representative tissues need to be submitted for histopathological evaluation.
3. Tissues such as brain, lungs, liver, abomasum and placenta need to be submitted for culturing.
4. Serum from the fetus should be collected if possible and submitted for serological analyses.
5. Paired serum samples collected at the time of abortion and two weeks later should be submitted from the affected cow.

It is important that as much as possible be submitted to the laboratory in order to assist in the diagnosis.

Summary

Although a considerable amount of information about fetal infection has occurred in the last 15 years, criteria necessary for making a diagnosis have not been clearly established. Some explanations for the types of processes involved in fetal infections have been reviewed in this article. It is imperative that research be continued and expanded on this important problem. Additional information will make it possible for developing better criteria for understanding and diagnosing fetal infections.

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