

Reproductive losses caused by bovine viral diarrhea virus and leptospirosis

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Abstract

Bovine viral diarrhea virus and *Leptospira* spp. are two of the common pathogenic organisms responsible for reproductive losses in cattle worldwide. Both can be come endemic in herds resulting in chronic low-grade reproductive losses or they can be introduced into relatively naïve herds, resulting in substantial reproductive losses over a short period of time. Both organisms are a differential diagnoses for common reproductive losses that veterinarians investigate, including low conception rates and abortions.

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1. Introduction

Reproductive efficiency is a major contributing factor to the economic viability of the cattle industry [1,2]. Factors affecting reproduction have a substantial economic impact on producers whose enterprises require the production of viable and healthy offspring. Causes of reproductive inefficiency are numerous and range from simple management errors to complicated multifactorial disease complexes.

Worldwide, bovine viral diarrhea virus (BVDV) and *Leptospira* spp. are two of the most common infectious disease agents associated with reproductive losses [3–8]. Understanding their roles in causing reproductive losses is important in designing comprehensive and effective reproductive programs.

2. Bovine viral diarrhea virus

Reproductive losses associated with BVDV infection were described by Olafson et al. [9] in the first clinical description of bovine viral diarrhea (BVD). In this report, pregnant cows subclinically infected with BVDV often aborted 10–90 d later. Today, reproductive losses may be the most economically important consequence associated with BVDV infection and there are indications that the incidence of BVDV-related reproductive losses are increasing in the United States [3]. In addition to reduced reproductive efficiency, BVDV uses the reproductive system to maintain and spread itself in the cattle population by inducing immunotolerance following fetal infection, resulting in birth of calves persistently infected with the virus. Cattle persistently infected with BVDV are the major source of virus spread both within and between farms.

Reproductive losses from BVDV can have numerous clinical manifestations, ranging from an insidious reduction in reproductive performance at the herd level to devastating abortion storms [10]. Understanding the

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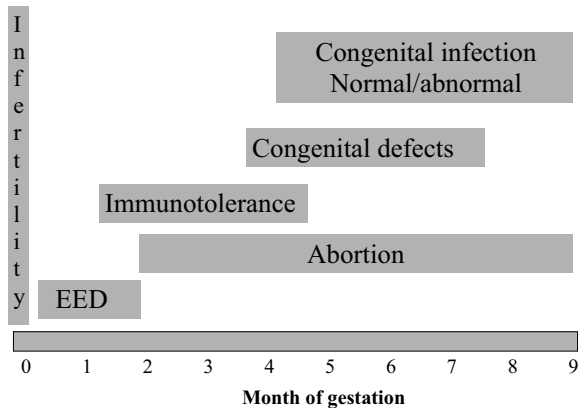


Fig. 1. Potential clinical reproductive outcomes following infection with bovine viral diarrhea virus. EED: early embryonic death.

various clinical consequences is critical in both diagnosing BVDV related problems and developing effective control programs (Fig. 1).

Field and epidemiological studies suggest that BVDV can have an important impact on early reproductive performance in the form of infertility and early embryonic deaths [11–13]. Early reproductive losses may occur as a result of ovarian dysfunction [14–16], uterine inflammation [17] and direct damage to the embryo [18,19].

Following implantation, transplacental infection can occur and outcome of the infection is largely dependent on the timing of the infection, the immunocompetence of the developing fetus, the virus biotype involved, and the virulence of the virus. Fetal death following BVDV infection of susceptible dams can occur throughout gestation, although they are most common during the first trimester [20,21]. However, BVDV should not be ruled out in cases where late-term abortions predominate. Depending on the time of infection, fetal reabsorption, mummification or expulsion can occur [22,23]. In diagnostic lab surveys in the United States, BVDV has been isolated from 0.1% [24], 1.5% [25], 4.54% [26], and 27.2% [27] of submitted abortion cases. Fetal death usually follows 10–27 d post-exposure, with expulsion of the fetus occurring up to 50 d later. Because of the delay between fetal death and subsequent diagnosis of abortion, fetal and placental lesions seen are usually non-diagnostic and BVDV virus isolation is not always successful.

Fetuses that survive infection with noncytopathic BVDV between 18 and 125 d of gestation invariably develop immunotolerance to the virus and subsequently become persistently infected with BVDV. Although the exact mechanism of immunotolerance is unclear, it is generally felt that circulation of virus during the period of

gestation when immunocompetence is developing (90–120 d) is a prerequisite for persistence. Viral proteins are recognized as self-antigens with resulting negative selection of BVDV-specific B and T lymphocytes during their ontogeny. Persistent BVDV infection in cattle appears to arise from specific B- and T-lymphocyte immunotolerance [28,29], that results in an absence of neutralizing and non-neutralizing antibodies to the persistent virus [30]. Persistent infections have been reported following BVDV infection as early as 18 d [31] and as late as 125 d of gestation [32]. Noncytopathic BVDV is the only biotype that has been observed or been able to experimentally produce persistence. Experimental infections with cytopathic BVDV have failed to produce persistently infected calves [22].

Fetal infection between 100 and 150 d of gestation, also referred to as congenital infection (CI), often results in the development of a variety of congenital defects. During this stage of gestation, organogenesis is being completed and the immune system is becoming fully functional. Although not clear, the combination of direct cellular damage by virus and inflammatory responses to virus have been proposed as pathogenic mechanisms [33]. Congenital anomalies involving the central nervous system are most common following fetal infection with BVDV; these include microencephalopathy, hydrocephalus, hydranencephaly, porencephaly, cerebella hypoplasia, and hypomyelination. Other teratogenic effects that have been associated with BVDV infection include cataracts, microphthalmia, optic neuritis, retinal degeneration, thymic hypoplasia, hypotrichosis/alopecia, curly hair coat, hyena disease, deranged osteogenesis, mandibular brachygnathism, and growth retardation. In the later stages of gestation, immunocompetence and organogenesis are usually complete. Although abortions and the birth of weak calves have been attributed to infection with BVDV late in gestation, fetuses infected during this time period are usually able to mount an effective immune response to BVDV and effectively clear the virus. These calves are usually normal at birth and have precolostral neutralizing antibodies to BVDV [34]. However, calves congenitally infected with BVDV may be at more risk for experiencing a serious postnatal health event. In studies attempting to define the impact of congenital BVDV infections on large dairy farms, Munoz-Zanzi et al. showed that calves born with BVDV neutralizing titers were twice as likely to experience a severe illness during their first 10 months of life [35] and were at increased risk for failing to conceive as breeding heifers [36] compared to calves born free of BVDV neutralizing titers. Further studies are needed to

determine if detrimental effects continue for an extended interval.

3. Leptospirosis

Leptospirosis is an economically important bacterial infection of livestock that causes reproductive losses due to abortions, stillbirths and infertility and non-reproductive losses due to septicemia and nephritis. In addition, leptospirosis is presumed to be the most widespread zoonotic disease in the world [37].

The disease is caused by infection with the spirochete *Leptospira*. *Leptospira* have been classified into genomospecies based on genetic sequences. There are currently more than 15 recognized genomospecies of *Leptospira*, seven of which contain organisms pathogenic to cattle [37]. *Leptospira* serovars are recognized and approximately 200 different serovars of pathogenic *Leptospira* have been identified throughout the world. In particular regions, different *Leptospira* serovars are prevalent and are associated with one or more maintenance host(s), which serve as reservoirs of infection. Maintenance hosts are often wildlife species and, sometimes, domestic animals and livestock. For example, common maintenance hosts for the serovars bratislava, canicola, and icterohaemorrhagiae are pigs, dogs and rats, respectively.

The most common cause of leptospirosis among cattle is infection with *Leptospira* belonging to serovar hardjo. Cattle appear to be the primary maintenance host of this serovar. Other common causes of leptospirosis in cattle include the serovars pomona and grippityphosa. Two serologically indistinguishable but genetically distinct types of serovar hardjo have been identified: *Leptospira interrogans* serovar hardjo (type hardjoprajitno) and *Leptospira borgpetersenii* serovar hardjo (type hardjo-bovis). Serovar hardjo type hardjo-bovis is common in cattle populations throughout the world; type hardjoprajitno is isolated primarily from cattle in the United Kingdom.

Reliable estimates of the prevalence of serovar hardjo infections are lacking. Recent estimates of the prevalence of *Leptospira* infection in a sample of US dairies and beef cow-calf operations indicated that the overall herd prevalence infection was approximately 35–50%, with most of those infections likely due to serovar hardjo [38]. Accurate data for the frequency of abortion attributable to leptospirosis are limited. In Northern Ireland, where both types of serovar hardjo are present, hardjo was recognized as responsible for nearly half of all bovine abortions in one study [39]. In one large study in Canada, where type hardjo-bovis is

prevalent, serovar hardjo caused about 6% of abortions [40] whereas a smaller US study implicated leptospirosis in 10% of abortions [41].

Leptospirosis typically occurs through bacterial exposure to mucous membranes and generally results in no or relatively mild acute clinical signs. Abortions, stillbirths, or birth of weak calves occur as a result of serovar hardjo infection but generally are only seen when a cow is infected for the first time when she is pregnant. Abortions may occur many weeks after infection of the dam and are usually not associated with any obvious illness in the cow. Infected, but apparently healthy calves also may be born and retention of fetal membranes may follow hardjo abortion. Abortions due to serovar hardjo infection tend to occur sporadically as opposed to abortion ‘storms’ which may occur as a result of infection with serovars pomona or grippityphosa.

Following primary bacteremia, the *Leptospira* localize and persist primarily in the kidneys and the genital tract. *Leptospira* located in the kidneys are voided in the urine and serve as a source of infection for other animals. Persistent infection of the male and female bovine genital tract is a prominent feature of serovar hardjo infections and may last >12 months [42]. The precise location of the persistent infection in the female genital tract is not known, but the bacteria has been isolated from multiple locations [43]. Other non-host maintained serovars (i.e. pomona) persist for shorter intervals.

Persistent infection of the reproductive tract may be the most economically important manifestation of serovar hardjo infection. Infertility, manifest as increased services per conception and prolonged calving intervals, is associated with this infection [44–46]. The pathogenesis of these events is not clearly understood; presumably the presence of *Leptospira* in the uterus and oviducts of infected cows interferes with implantation of the embryo or other early pregnancy events.

4. Control

Control of BVDV and leptospirosis generally involve a multi-pronged attack. The first step is to reduce exposure to the pathogens themselves. In the case of BVDV, this primarily involves identifying and eliminating persistently infected cattle and installing biosecurity measures to prevent the reintroduction of the virus. Antibiotic treatment of cattle infected with leptospirosis may eliminate the carrier stage of this disease. In addition, controlling exposure to other

serovar maintenance hosts and contaminated environments is necessary. The second step is to institute an appropriate vaccination program that is designed to reduce the risk of reproductive pathology. Vaccines and timing of vaccine administration must be chosen with full knowledge of the disease pathogenesis and the limitations of the vaccines used. Vaccines for either BVDV or *Leptospira* spp. are not fully effective; therefore, they must be used in conjunction with other control methods.

5. Conclusion

Leptospirosis and BVDV are well known causes of reproductive losses and should be considered when investigating any bovine reproductive problems where an infectious cause is suspected. Industry professionals should fully understand these diseases before recommending control programs for them.

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