Pregnancy loss in cattle

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Abstract

Pregnancy loss in cattle has a major economic impact on livestock producers. Additionally, some agents are zoonotic and therefore are also a public health concern. Determining the cause of pregnancy loss in cattle is often unsuccessful. In only ~ 30% of mid- and late-term pregnancy losses is a specific cause identified. Pregnancy loss is higher during the embryonic period compared to the fetal period, and causes are noninfectious or infectious. Noninfectious causes include genetic defects (arthrogryposis multiplex, bovine arachnomelia syndrome, bovine citrullinemia, and chromosomal abnormalities), toxic plants and toxins (lupine, hemlock, locoweed, pine needles, ergot alkaloids, certain molds, and nitrates), nutritional deficiencies (vitamin A and E, selenium, and thyroid hormones), environmental factors (heat stress), and medications (prostaglandin $F_{2\alpha}$ and glucocorticoids). Infectious causes include bacterial (brucellosis, chlamydiosis, coxiellosis, foothill abortion, leptospirosis, listeriosis, and *Ureaplasma diversum*), fungal (*Aspergillus fumigatus*), viral (bluetongue virus, bovine viral diarrhea, Cache valley virus, and infectious bovine rhinotracheitis), and protozoal (neosporosis and trichomoniasis).

Keywords: Cattle, abortion diseases, pregnancy loss, embryonic mortality

Introduction

Pregnancy loss reduces reproductive efficiency in cattle.[1-3] Implications of this loss are not only technical but also economical.[4,5] Additionally, some agents are zoonotic and hence a public health concern. The estimated annual cost of pregnancy loss was ~ $1.4B in the US[6] and ~ £250M in the UK.[7] The cost of each case of abortion in the US was $640,[8] averaging $600 in the US. Average calving rate in dairy cows for each insemination is ~ 50%, and in large commercial dairy operations in the US it is frequently 30 - 40% or lower.[10,11] Since fertility rate in dairy cattle has declined considerably, each pregnancy is now even more valuable.[11] Every factor that affects the wellbeing of a pregnant female is a potential cause of pregnancy loss, acting either directly or indirectly on the conceptus. Pregnancy status is a clinically dynamic condition, with an inherent risk of pregnancy loss. Multiple risk factors are associated with pregnancy loss (time of pregnancy, twin pregnancy, body condition score change, lameness, mastitis, medications during pregnancy, and vaccinations). The objective of this paper is to review the common causes of pregnancy loss in cattle, with an emphasis on infectious causes and to supplement information provided in the proceedings.[12-14]

Prevalence

In 2 US studies,[15,16] a cause for abortion was detected in 23.3 and 35.3% of cases out of a total of 3,812 and 2,544 cases, respectively. From 1983 to 2001, 1618 aborted fetuses from Northcentral US farms were examined and a specific cause was reported in 592 cases (36.59%).[17] In Australia, the cause of pregnancy loss was detected in 37% of 265 case submissions[18] and in Canada the cause was detected in 23% of 227 cases.[19] In England, the cause of abortion remained unknown in several cases.[20] Two aspects are noteworthy; only aborted fetuses of a recognizable size are submitted to laboratories; hence most of the fetuses are > 4 - 5 months of age. Consequently, reports are biased toward the latter half or third of pregnancy.[23] Secondly, the organism isolated may not have been the cause of abortion; especially, if the sample was highly contaminated as is often the case with fecal contamination and the consequent isolation of coliform bacteria.

Noninfectious causes of pregnancy loss

Noninfectious causes of pregnancy loss include genetic defects (arthrogryposis multiplex, bovine arachnomelia syndrome, bovine citrullinemia, and chromosomal abnormalities), toxic plants and toxins (lupine, hemlock, locoweed, pine needles, ergot alkaloids, certain molds, and nitrates), nutritional deficiencies (vitamin A and E, selenium, and thyroid hormones), environmental factors (heat stress), and medications (prostaglandin $F_{2\alpha}$ and glucocorticoids).

Infectious causes of pregnancy loss

Infectious causes of pregnancy loss include bacterial (brucellosis, chlamydiosis, coxiellosis, foothill abortion, leptospirosis, listeriosis, and *Ureaplasma diversum*), fungal (*Aspergillus fumigatus*), viral (bluetongue virus, bovine viral diarrhea, Cache valley virus, and infectious bovine rhinotracheitis), and protozoal (neosporosis and trichomoniasis) causes. Some viral agents (Schmallenberg virus, Akabane virus, and Aino virus) are exotic to North America.[24]

Risk factors associated with noninfectious causes

Period of pregnancy

Pregnancy loss decreased as the interval between breeding and pregnancy diagnosis increased.[25,26] In general, 4 of 5 lactating dairy females diagnosed pregnant at ~ day 30 had a viable fetus at the end of first trimester.[25,27,28] Herd size influenced both frequency of veterinary visits and the timing of pregnancy diagnosis with larger herds generally having more frequent assessments of reproductive performance. As frequency of farm visits increased, the average days pregnant at diagnosis decreased,[29] therefore, the likelihood of finding pregnancy loss is higher in larger herds compared to smaller herds. Cows first diagnosed pregnant at day < 41 were less likely to have a calf than cows diagnosed later.[30] Pregnancy loss was higher when pregnancy diagnosis was performed before day 48 of pregnancy.[29] Recent studies, involving only lactating cows reported an increase in pregnancy loss when transrectal ultrasonography was used for pregnancy diagnosis. This could be due to earlier and perhaps more accurate pregnancy diagnosis compared to transrectal palpation. In California, embryo/fetal mortality was 19% when diagnosed between days 28 - 90.[28] In Texas dairy farms, embryo/fetal mortality was 19.2% when diagnosed at ~ days 30 -120.[25] Herds from central Utah and California that used fixed time artificial insemination had 24% pregnancy loss between days 28 - 98.[27] Risk of pregnancy loss is higher during the embryonic period compared to the fetal period. Therefore, every female diagnosed pregnant during the embryonic period should have a follow-up examination during the fetal period to verify pregnancy status.

Lactation

Pregnancy loss was lower in heifers than cows[25,31-32] However, age of cow was not a risk factor for pregnancy loss.[8] A gradual increase in pregnancy loss, as estimated by progesterone profiles, was observed, particularly beyond the fourth lactation.[34] In lactating cows, the risk of pregnancy loss was similar among parities.[32] Higher rates of late embryo/fetus mortality in older compared to younger females have been reported in many species.[34-37] Cited reason include reduced oocyte fertilization capability, and the inability of the uterus to provide adequate gestational support.[35,36]

Number of embryos

The number of embryos increased the risk of pregnancy loss.[25,33,38] Twin pregnancies had 2.5 - 3 times higher possibility of pregnancy loss compared to a singleton.[25,33] The majority of embryo/fetal mortality observed in twins was Type I characterized by positive fetal membrane slip, embryo/fetal degeneration, a functional corpus luteum, and prolonged uterine clearance.[25,39] Reasons for the risk of higher pregnancy loss in twin pregnancy is unknown. However, competition between embryos or fetuses for nutrition, space, or both could account for some embryo/fetal losses. In singleton pregnancies, higher pregnancy loss occurred during the embryonic period compared to the fetal period.[25] However, for twin pregnancies, pregnancy loss during the first 4 months of pregnancy was similar at each evaluation.[25]

Body condition score

A 1-point reduction in body condition score from calving to 30 days postpartum increased pregnancy loss in a subsequent pregnancy by 2.4-fold.[40] In dairy cows, under pasture-based milk production systems, cows that lost body condition during days 28 - 56 of pregnancy had a higher rate (11.6%) of embryonic loss compared to cows that either maintained (4.7%) or gained (5.7%) body condition during this period.[41] Furthermore, cattle with lower body condition scores (< 2.5; scale 1 - 5) at pregnancy diagnosis had higher chances of pregnancy loss than those with higher body condition scores (Romano, unpublished observations).

Bull

Sire had a substantial effect on the rate of embryonic death.[42] A higher incidence of pregnancy loss was observed in cows inseminated with semen from 1 of 6 bulls. This particular bull increased the rate of pregnancy loss by 3.4 times.[40] Increased risks of abortion were associated with 8 sires out of 233 (odds ratios of mates to abortion ranged from 1.9 to 3.9).[32] Sire affected pregnancy loss and therefore selection of bulls according to this criterion might result in higher calving rates in lactating Holstein cows.[43]

Artificial insemination

Insemination of pregnant cows resulted in pregnancy loss. Two factors might be associated with this circumstance; observation of primary signs of estrus (standing to be mounted) in pregnant cows and incorrect estrus detection. Fifteen percent of pregnant females had signs of estrus during the first half of pregnancy.[44-47]Accuracy of estrus detection ranged from 3 to 26% in females (had higher concentrations of P_4 at AI),[48-54] and 60% farms faced this problem.[49,50] Confirmed pregnant females after insemination had conceptus death and consequent pregnancy loss[55-59] with abortion some weeks later.[60]

Transrectal palpation

Transrectal palpation continues to be the most frequent method for pregnancy diagnosis.[61-64] Although 100 years have passed from the first report,[65] its impact on safety and accuracy of conceptus detection are still not clearly established.[62-64] Besides pregnancy diagnosis, this technique was also used to rupture the amniotic sac or crush the embryo or fetus in unwanted pregnancies prior to the availability of prostaglandin $F_{2\alpha}$.[37,60,66]

Safety of the conceptus remains controversial;[64] pregnancy loss was not reported by some[4,67,68] whereas others[30,69-73] suggested increases. Palpation of the allantochorion or amniotic sac during the embryonic period did not increase pregnancy loss as confirmed by subsequent transrectal ultrasonography in the fetal period.[64,74,75] However, calving rates or clinical status of newborn calves were not reported. Amniotic sac palpation during the embryonic period (until day 45) for pregnancy diagnosis,[76] especially between 36 and 42 days, increased the risk of atresia coli/jejuni in newborn calves.[77-82] In atresia coli/jejuni, a section of the large bowel or jejunum is absent, resulting in a blind-ending intestine. This congenital condition is lethal, and surgical correction is the only effective treatment.[83-87] Late embryonic or early fetal period palpation of the allantochorion membrane or amniotic sac did not increase pregnancy loss nor affected calving rates or incidence of calves with congenital abnormalities.[25,26,88]

False-negative diagnoses of pregnancy increased the probability of culling or submission to an immediate or delayed estrus synchronization (protocols use at least 1 dose of prostaglandin $F_{2\alpha}$ or its analogs) treatment protocol.[89,90] Prostaglandin $F_{2\alpha}$ is a potent luteolytic agent that induces immediate abortion during early stages of pregnancy.[91,92] Iatrogenic abortion will most often go undetected[25] yet will still have a negative effect on herd economics.[9,93] A false-positive diagnosis resulted in an animal coming into estrus or not calving at the expected time, ultimately, increasing the probability of culling.

Mastitis

Mastitis increased the risk of pregnancy loss.[94-96] Exposure to clinical mastitis during the first 45 days of pregnancy was associated with loss of pregnancy during the next 90 days.[97] Pregnancy loss was higher (9.7 - 11.8%) in cows that were affected with clinical mastitis compared to unaffected cows (5.8%).[95] Defining a clear risk period for pregnancy loss in clinical mastitis is critical to determine the true impact.[98] After controlling for breeding type and lameness, the odds ratio for pregnancy loss was 2.21 times higher (95% CI = 1.01 - 4.83) in cows that had clinical mastitis.[99] Higher rates of pregnancy loss were associated with the occurrence of clinical mastitis (hazard ratio =1.57) in pasture-fed dairy cattle.[100] Furthermore, subclinical mastitis prior to artificial insemination was associated with subsequent pregnancy loss during the late embryonic period.[96] Odds ratio for pregnancy loss was 20% higher in cows affected with subclinical mastitis. The impact of mastitis on pregnancy loss was higher in older cows (parity ≥ 3).[101] Cows with a linear somatic cell count (score > 4.5 before AI) were twice more likely to lose the embryo from 28 to 41 days.[96]

Inbreeding

Pregnancy loss was higher in inbred systems in heifers (2.5%) and cows (13.0%).[98] At 150 days, inbred dams had a higher pregnancy loss (28.4 versus 19.2%).[42] Inbreeding increased the risk of deleterious lethal disorders (e.g. bovine leukocyte adhesion deficiency),[103] or uridine monophosphate synthase deficiency,[104] recessive deleterious haplotypes,[105] and accumulation or interaction of genes with small negative effects on fertility.[106]

Noninfectious causes of pregnancy loss

Genetic diseases

With increased use of artificial insemination and reproductive techniques a growing concern worldwide is the emergence and widespread dissemination of hereditary diseases. A nonsense mutation in the APAF1 gene created a lethal effect (Holstein Haplotype1) responsible for 525,000 spontaneous abortions worldwide over the past 35 years, accounting for ~ $420M in losses. This disease-associated haplotype was traced to the ancestor Holstein sire Pawnee Farm Arlinda Chief born in 1962, a bull considered the second most influential sire in the Holstein breed history.[107]

Arthrogryposis multiplex congenita (commonly known as curly calf syndrome) is a lethal autosomal recessive genetic disorder of Aberdeen Angus, originating in the bull Rito 9J9 of B156 7T26 and distributed widely through the bull GAR Precision 1680. The condition was characterized by fetal musculoskeletal malformations including severe muscular atrophy, arthogryposis, scoliosis, and torticollis.[108]

Arachnomelia syndrome is an autosomal recessive inherited disease in cattle. Affected calves have skeletal malformations mainly affecting legs, spinal column and skull, and die around birth. The disease has been reported in Holstein Friesian, Red Holstein, and Simmental cattle.[109] Although a description of bovine congenital abnormalities is beyond the scope of this paper, heritable bovine fetal abnormalities were reviewed.[110.]

Toxic plants and toxins

Pregnancy loss and teratogenesis were attributed to numerous plants and toxins. However, with only limited studies, and with methodological limitations and small sample sizes, results must be interpreted with caution.

Some toxic plants contain compounds that might cause death, reproductive problems, teratogenesis, and neurological or digestive disorders. Late-term abortion and fetal membrane

retention were attributed to consumption of juniper (*Juniperus communis*). Chronic ingestion of some species of locoweed (*Oxytropis* and *Astragalus*) during pregnancy resulted in joint malformation and abortion. Consumption of *Pinus ponderosa* needles caused third trimester abortion and fetal membrane retention. Perennial broomweed (*Gutierrezia microcephala*) consumption caused abortion, premature delivery, birth of weak offspring, and fetal membrane retention.[111]

As the amount of nitrate needed to cause abortion is close to the lethal dose, it is uncommon to have abortions without some fatalities. Nitrate toxicity occurs when high nitrate concentrations in the feed overwhelm the capacity of the animal's digestive system to the extent that the rate of conversion of nitrate to nitrite is faster than the conversion of nitrite to ammonia that is incorporated into amino acids and proteins.[112]

Mycotoxins are secondary metabolites of fungi that contaminate feed and have substantial negative impacts on animal health and productivity. Feed contamination of zearalenone, an important mycotoxin produced by fungi of *Fusarium* genera, caused hepatotoxicity, hematotoxicity, immunotoxicity, and genotoxicity. Zearalenone and its major metabolites α-zearalenol and β-zearalenol, mimic17$_{\beta}$-estradiol and elicit substantial estrogenic activity. Although cattle are resistant, increased consumption of zearalenone was associated with infertility, enlargement of the mammary gland, reduced milk production, vaginitis, and early pregnancy loss.[112]

Vitamin E and selenium deficiency

Congenital nutritional muscular dystrophy caused by vitamin E and selenium deficiency is uncommon but has been reported in beef cattle.[114] Affected calves were in lateral recumbency, unable to move at birth, and with no suckling reflex. Serum creatine kinase and aspartate aminotransferase were elevated with lower vitamin E and selenium concentrations. Affected calves responded adequately to supportive therapy and with vitamin E and selenium treatment. Animals that died had pale to white skeletal muscles. Histological examination revealed swollen skeletal muscle fibers with fragmented sarcoplasm and mineralization.

Vitamin A deficiency

Deficiency during pregnancy was suspected in cases of perinatal calf mortalities.[115] Birth of hypovitaminosis A calves to animals fed a deficient ration is less well documented; calves delivered were dead or weak, lacked coordination and were blind.[116]

Medications

Prostaglandin F$_{2\alpha}$ treatment during the first 4 - 5 months of pregnancy caused luteolysis, resulting in immediate abortion.[91,92] Therefore, an accurate diagnosis of nonpregnancy is essential, if the female is submitted to an estrus synchronization protocol that used prostaglandin F$_{2\alpha}$. Glucocorticoids use during pregnancy have an inherent possibility to provoke abortion. Use of corticosteroids, depending on the dose, duration, and specified steroid, might result in inhibition of endogenous steroid production following drug withdrawal. Use of glucocorticoids in smaller pregnant females was associated with cleft palate. Use of sodium iodine and pregnancy loss was inconclusive;[117,118] therefore, further investigation is necessary.[119]

Environmental

Heat stress had major effects on fertility and embryonic survival in lactating dairy cows.[120,121] Compromised endometrial function and secretory activity, smaller follicles, and suppressed dominance of large follicle were noticed.[122] Decreased serum estradiol concentrations, decreased plasma concentrations of LH, and decreased progesterone secretion were documented. Furthermore, oocyte quality, embryo development, and embryo survival were impaired by heat stress. Oocyte and earlier stage embryos were highly sensitive, whereas day-3 or older embryos appeared resistant.[120,123] Absence of heat stress had similar results for artificial insemination and embryotransfer.[124] Higher pregnancy loss was observed in dairy cattle if heat stress was experienced at artificial insemination.[125] Day 7 embryos without heat stress were more capable of establishing pregnancy.

Infectious causes of pregnancy loss

Brucellosis

Brucellosis is a zoonotic disease (notifiable in US) caused by several *Brucella* species. Brucellosis in cattle is caused by *Brucella abortus* and could result in abortion, birth of weak calves, retention of fetal membranes and decreased milk production. Abortion generally occurred in the last trimester of pregnancy.[126] Bison and cervids also are susceptible.[127]

Currently in the US, individual states are designated brucellosis free when none of their cattle are infected for 12 consecutive months under an active surveillance program.[128] As of August 1, 2020, all states are considered free of cattle brucellosis (aphis.usda.gov); however, presence of infected free-ranging bison and elk in the greater Yellowstone area, Yellowstone national park and Grand Teton national park threatens surrounding states' brucellosis status.

Brucellosis is transmitted to susceptible animals mainly by direct contact with infected animals or by fomites. Fluids and fetal membranes from infected fetuses and vaginal discharges from cows that have aborted contain large numbers of organisms, an important source of infection. Infected wildlife could transmit the disease to domestic livestock.

Fetal membranes might have macroscopic evidence of inflammation, hard to distinguish from inflammation caused by other bacteria or fungi. Gross lesions are not uniform throughout

the fetal membranes. Some cotyledons are swollen and necrotic and others might have mild lesions or appear normal. Intercotyledonary spaces might have extensive ill-defined thick areas of yellow discoloration. Histologically, there is sloughing of chorionic epithelial cells in the intercotyledonary spaces and infiltration of large numbers of mononuclear leukocytes and some neutrophils in stroma. Large numbers of bacteria are observed in the cytoplasm of chorionic epithelial cells and in the exudate. Aborted fetuses generally exhibit advanced autolysis characterized by extensive blood-tinged subcutaneous edema and blood-tinged fluid in the thoracic and abdominal cavities. Fetal lung might have microscopic evidence of bronchopneumonia characterized by infiltration of mononuclear leukocytes and some mature and immature neutrophils. Interlobular septae are expanded with edema and leukocytes. Organisms can be demonstrated in tissues, secretions, and exudates using modified Ziehl-Neelsen staining.[130]

Diagnosis of brucellosis is by isolation of the organism from fetal membranes, fetal tissues, and stomach content. *Brucella* polymerase chain reaction is generally used to identify the organism in cultures and less often directly from tissue of infected fetuses. *Brucella* antigen tests (rose Bengal test and buffered plate agglutination test), complement fixation, indirect or competitive enzyme-linked immunosorbent assay (ELISA) and the fluorescence polarization assay are the most common serological tests that demonstrate the presence of antibodies in maternal serum. Antibodies in milk are detected by ELISA test and the *Brucella* milk ring test.[127]

Bovine brucellosis can be prevented by vaccination with RB51 vaccine, a live vaccine that should not be used in pregnant animals. Heifers should be vaccinated between 4 and 12 months of age. Adult cattle might be vaccinated in selected high-risk situations.[131] The vaccine is not 100% effective and usually protects between 70 - 80% of vaccinated animals. *B. abortus* strain RB51, is a rough rifampicin-resistant strain that lacks the expression of lipopolysaccharide o-side chain and does not induce antibodies against this chain detectable by routine serological tests, therefore, allowing vaccination and test-and-slaughter policies to be performed at any age.[132]

Campylobacteriosis

Campylobacter spp. are important animal pathogens and opportunistic human pathogens. Several species and subspecies of *Campylobacter* cause pregnancy loss and infertility in ruminants.[133] Mammal-associated *Campylobacter fetus* is comprised of 2 subspecies: *C. fetus* subsp. *venerealis* and *C. fetus* subsp. *fetus*, with both being well-known causes of reproductive failure in ruminants.[134] *C. fetus* subsp. *venerealis* causes bovine genital campylobacteriosis, characterized by infertility and abortion.

Chlamydiosis

Chlamydia abortus, formerly known as *Chlamydophila abortus* or *Chlamydia psittaci* serovar 1, is an obligate intracellular organism that causes abortions in sheep, goats, and occasionally in deer, cattle or llamas. Subclinical infection with *C. abortus* might severely affect bovine herd health and production.[135]

Coxiellosis

Coxiellosis, often referred to as Q (Query) fever, is a highly infectious zoonotic disease caused by the intracellular bacterium *Coxiella burnetii* that primarily affects goats and sheep, and less often cattle.[136-138] Other species less commonly affected include dogs, cats, rabbits, a variety of wild and domestic mammals, and birds. In cattle, abortion by *C. burnetti* is generally sporadic and only rarely occurs in clusters. Fetal membranes might have diffuse reddening of the cotyledons and loss of translucency of the intercotyledonary areas; however, in some cases, there are no gross lesions. Microscopically, there is fibrinonecrotic placentitis with large numbers of intratrophoblastic gram-negative coccobacilli.[139]

Foothill abortion

Foothill abortion, also known as epizootic bovine abortion, is a tick-borne disease caused by the bacterium *Pajaroellobacter abortibovis*, transmitted by the bite of the Pajaroello tick. It is a substantial problem for beef producers in the foothills and mountainous regions of California, Northern Nevada and Southern Oregon. Abortion or birth of weak offspring occurs only in pregnant naive heifers or cows that are introduced to endemic areas 100 - 145 days before calving. Abortion occurs in the last trimester of pregnancy. It is common for affected fetuses to induce their own delivery, but often die during calving or shortly after birth.[140]

Some of the aborted fetuses have severe abdominal distention caused by ascites. There is severe, generalized fetal lymphadenomegaly and splenomegaly. Numerous petechial hemorrhages are present in mucous membranes; the thymus is generally small with areas of severe hemorrhage and edema; and the liver is swollen and nodular. Multifocal, areas of pale discoloration are observed in many organs but especially in the heart and kidney. The most characteristic microscopic lesion is inflammation of the thymus with attenuation of the cortex, loss of thymocytes and diffuse infiltration of macrophages in the medulla and septae. Microscopic lesions in the liver consist of distention of the central veins and attenuation of the hepatic plates. There are large areas of hepatic granulomatous inflammation. Alveolar walls of the lung are distended with histiocytes. In the brain, there is histiocytic inflammation of the meninges and multifocal areas of vasculitis.[141,142]

Leptospirosis

Leptospirosis is a global zoonosis that causes significant economic losses for cattle production. Leptospirosis is an important cause of abortion in cattle, as well as septicemia, hepatitis, nephritis,

and meningitis, particularly, in young animals. Leptospirosis is caused by > 260 antigenically distinct serovars belonging to 25 serogroups grouped in 9 pathogenic species, 5 intermediate and 6 saprophytic species of leptospira, and a gram-negative bacterium belonging to the Spirochaetales order.[143]

Transmission most commonly occurs by contact with urine of infected animals, postabortion discharges, milk, and contaminated water. Infected bulls may transmit during coitus and pregnant cows may transmit organisms transplacentally to their fetus. *Leptospira* serovars *hardjo* and *pomona* cause endemic reproductive problems in cattle manifested as abortions, fetal mummification, stillbirth, retained fetal membranes, premature births and the birth of weak and/or low-weight calves. In addition, the disease has been associated with a subtler syndrome characterized by early embryonic death and subfertility.[144]

The majority of abortions occur in the last trimester of pregnancy, but some serovars cause second trimester abortion, fetal mummification or embryonic mortality. Abortion rate vary from 3 - 10% with *L. hardjo* to 50% with *L. pomona*. Fetuses are generally autolyzed and do not have specific gross lesions. Histologically, some cases have mild inflammation of fetal membranes and the presence of the organism might be identified (not in all cases) by special silver stains. Some fetuses have renal tubular necrosis and interstitial nephritis.[130]

Demonstration of leptospira DNA by reverse transcription polymerase chain reaction (RT-PCR) in the kidney of aborted fetuses is the preferred diagnostic test. On a herd basis, serologic diagnosis of leptospirosis could be challenging in vaccinated animals. Microscopic agglutination tests, used commonly, measures the antibody titer in maternal serum at abortion and again 2 - 3 weeks later. A 4-fold increase in paired samples is considered diagnostic. In some serovars such as pomona, grippotyphosa, Icterohaemorrhagiae and canicola, maternal serum antibody titers ≥ 1600 appear to correlate with abortion. However, maternal antibodies in cases of abortion caused by serovar hardjo often are low or negative at the time of abortion; therefore, a low antibody titer does not rule out leptospirosis as the cause.[145]

Salmonellosis

Salmonella enterica subsp. *enterica* serovar Dublin might, in the course of a systemic infection, colonize the placenta and fetus and cause placentitis, abortion, and stillbirth.[146] The organism could be isolated from fetal membranes and fetal abomasal contents.

Ureaplasma diversum

Ureaplasma diversum is a common inhabitant of vagina and prepuce of clinically normal cattle, associated with infertility, endometritis, salpingitis, and abortions. Abortions are usually sporadic; however, severe outbreaks, involving multiple animals, occur occasionally in the second and third trimester of pregnancy.[147]

Mycotic abortion

Mycotic abortion in cattle is most often caused by *Aspergillus fumigatus* infection. Other causes of mycotic abortion include other fungi of the genera *Absidia* spp., *Mucor* spp., *Rhizopus* spp., *Mortierella wolfii*, *Candida* spp., and *Torulopsis*.[148] In cattle, fetal infection generally occurs through the hematogenous route to the placentomes by extension from maternal fore stomachs or respiratory infections. Mycotic infections of the fetus often result in sporadic, late-term abortions - between the 6th and 8th month of pregnancy. Fetal infection is characterized by severe fetal membrane inflammation and fetal dermatitis, the latter characterized by raised circular epidermal plaques. Histologically, mycotic fetal membrane inflammation is characterized by severe necrotizing and suppurative inflammation with thrombosis. Presence of fungal hyphae in the lesions could be apparent in H&E-stained sections or with Gomori's methenamine silver and Periodic acid–Schiff stains. Confirmation of the diagnosis could be done by culture. The genus and species of the fungus also could be identified in fresh tissues, or in paraffin embedded sections by panfungal PCR.[149,150]

Bluetongue virus

Bluetongue is an arthropod-borne, non-contagious viral infection of domestic and wild ruminants, and less often South American camelids caused by bluetongue virus (BTV). BTV is the type-species of the genus *orbivirus* in the family *reoviridae.* Currently, 28 serotypes of BTV are recognized worldwide. In the US, BTV 2, 10, 11, 13, and 17 are endemic, but infections with other serotypes occur sporadically.[151]

Transmission of BTV among susceptible hosts occurs through the bite of certain species of infected culicoides or biting midges. The main vector of BTV endemic serotypes in US is *Culicoides sonorensis* (*C sonorensis*; previously known as *C varipennis*). *C. insignis* is also identified in the southeastern US. More recently, new BTV serotypes (BTV-25, BTV-26, and BTV-27) were horizontally transmitted without vector involvement.[152]

Bluetongue virus abortion occurs most commonly in sheep and deer and sporadically in cattle and goats. Before the recent BTV-8 outbreak in Europe, the ability of BTV to cross the placenta and cause congenital infection in cattle had been largely limited to cell-adapted BTV strains (i.e. live attenuated vaccine strains).[153,154] In endemic areas, the epidemiological relevance of naturally and congenitally infected calves is believed to be negligible. BTV-induced brain malformations still occur infrequently among aborted bovine fetuses in California, but it is assumed that those bovine BTV-induced abortions are the result of infection with live-attenuated BTV strains present in vaccines licensed only for sheep.[153]

One of the characteristics of wild-type BTV-8 that circulated in northern Europe is its ability to cross the placenta. Transplacental transmission of wild-type BTV-8 is ~ 10 - 41.7% in cows and up to 69% in sheep.[155] Infection of pregnant cows with wild-type BTV-8 caused abortion, stillbirth, and fetal malformations (hydranencephaly).[156]

Serological assays available for demonstration of BTV antibodies include complement fixation, virus neutralization, the agar gel immunodiffusion test, and several ELISA formats. Presence of BTV antibodies in maternal serum indicates exposure at any given time and does not indicate that the abortion was caused by BTV.[151] Assays based on RT-PCR are used to detect BTV RNA in clinical samples (e.g. blood or spleen).[157]

Infectious bovine rhinotracheitis

Infectious bovine rhinotracheitis (IBR) is a major cause of viral abortion in cattle with abortion rates of 5 - 60% in naïve unvaccinated herds; it is caused by bovine herpesvirus-1 (BHV-1), a member of herpesviridae family in the alphaherpesvirinae subfamily.[158] BHV-1 is ubiquitous in cattle populations and is the cause of several clinical syndromes including abortion, vulvovaginitis, balanoposthitis, respiratory disease, conjunctivitis, encephalomyelitis, and fatal systemic infections in neonates.[159] All BHV-1 strains are capable of becoming latent infections. Stressful situations including transportation, calving, treatment with corticosteroids and other stressful situations could induce recrudescence of the infection and shedding of the virus in respiratory and reproductive secretions, or semen of latently infected animals. After infection in pregnant cows, BHV-1 may remain latent in the placenta and only invade the fetus after several weeks. Once the fetus is infected, it dies quickly and remains in utero for several days resulting in autolysis before expulsion. The subcutis is edematous and red-tinged. Large amounts of red-tinged fluid are present in the thoracic and abdominal cavities and in the pericardium.[130] In some cases, small, discrete white nodules are observed in the liver. Histologically, there are discrete areas of necrosis in the liver, kidneys, spleen, lungs and adrenal glands. Intranuclear inclusions characteristic of herpesvirus infections are difficult to find in hematoxylin and eosin-stained tissue sections but are most likely to be found in the adrenal glands. Lesions in the placenta consist of necrosis and vasculitis. Abortion generally occurs between 5 - 8 months of pregnancy. Bovine herpesvirus-4 has been detected in tissues of aborted fetuses.[160]

In general, the use of inactive vaccines is safer for pregnant females as well as in females of unknown pregnancy status or during early stages of pregnancy. In an experiment in which an inactivated BHV-1 vaccine was used to immunize females prior to breeding protection against pregnancy loss was similar to that of modified-live BHV-1 vaccines following substantial challenge infection performed around [180] days of pregnancy.[161]Use of modified live vaccines in naïve pregnant females can increase the risk of pregnancy loss. Therefore, the importance of a reliable clinical history is of paramount importance. A number of bovine abortions have occurred following administration of BHV-1 vaccines in the US, which was in part due to confusion about the appropriate use of modified-live virus products. Although most postvaccination abortions appear to reflect inadvertent extra label use of BHV-1 vaccines by owners and veterinarians (i.e. vaccinating pregnant cattle during pregnancy that were not vaccinated in the previous 12 months with an appropriate modified-live BHV-1 vaccine), some involve appropriately vaccinated heifers. Until there is a method to distinguish vaccine strains from field strains of BHV-1, diagnosticians will be unable to confirm whether the virus is from vaccine or wild type origin.[162-163] A retrospective study examined data on bovine abortion submissions from 5 veterinary diagnostic laboratories from 2000 to 2011 (IA, CA, WA, MN, and SD) and history of vaccination against BHV-1 in the herd was associated with reduced detection of BHV-1 positive abortion submissions.[164] In one study, several BHV-1 strains were sequenced using whole-genome sequencing technologies and the data analyzed to identify single nucleotide polymorphisms (SNPs). The outcome of this investigation showed promise for the differentiation of viral vaccine virus from field strains; however, more research is required.[165] A recent study involving BHV-1 field strains from Pennsylvania and Minnesota reported a novel SNP-based PCR assay that could allow differentiation of vaccine and clinical strains and accurately determine the incidence of BHV-1 and the association of MLVs with clinical disease in cattle.[166]

The prevalence of abortion declines in regions with a decline in BHV-1 naïve populations. Detection of BHV-1 in semen and elimination of contaminated samples is the most important procedure for controlling transmission. Detection of BHV-1 could be by real-time PCR or virus isolation (VI) from fetal lung, liver or other tissues, in whole-blood samples with EDTA, or semen of adult animals. Diagnostic tests revealed a moderate degree of agreement The prevalence of abortion declines in regions with a decline in BHV-1 naïve populations. Detection of BHV-1 in semen and elimination of contaminated samples is the most important procedure for controlling transmission. Detection of BHV-1 could be by real-time PCR or virus isolation (VI) from fetal lung, liver or other tissues, in whole-blood samples with EDTA, or semen of adult animals. Diagnostic tests revealed a moderate degree of agreement (kappa value = 0.498) between PCR and VI, with PCR being a more sensitive and specific technique for the diagnosis of IBR.[167]

Bovine viral diarrhea virus

Bovine viral diarrhea virus (BVDV) is an economically important pathogen of cattle worldwide. It is estimated that the cost of infection on productivity in cattle ranges from 0.50 to US$ 687.80 per animal.[168] Bovine viral diarrhea is caused by several different strains of bovine viral diarrhea virus, single-stranded RNA viruses belonging to the Pestivirus genus in the family Flaviviridae. Based on the genotype, BVDV is grouped

into type 1 and type 2 with multiple subtypes. Bovine viral diarrhea viruses also are classified into cytopathic (cp) and noncytopathic (ncp) biotypes.[169,170] Interspecies transmission between sheep and cattle with border disease virus (BDV), the small ruminant pestivirus is common and might represent a challenge in herds with a BVDV eradication programs because sheep are not included in eradication schemes.[171]

Infection with BVDV in cattle could result in various clinical manifestations. Acute disease in adult immunocompetent cattle could result in subclinical infection causing mild transient infection (TI), or in respiratory signs that might last 2 - 3 weeks and include fever, nasal discharge, pneumonia and death. Animals that recover of this form of BVD develop lifelong immunity. The infection also has been associated with diarrhea and a hemorrhagic syndrome.[172] The outcome of BVDV fetal infections in susceptible heifers and cows is dependent on the age of the fetus when exposed.[173] Fetal infection up to 45 days of pregnancy may result in embryonic death. Abortion may occur following cpBVDV infection between 45 and 175 days of pregnancy. When fetal infection with ncpBVDV occurs prior to fetal development of immunocompetence (usually between day 45 and 145 of pregnancy), the fetus may survive and become persistently infected (PI). These PI animals generally do not develop BVDV antibodies and shed the virus through a variety of body fluids including semen, and are the source of the majority of new acute and fetal infections. The majority of PI animals die before two years of age, often of mucosal disease that occurs when ncpBVDV mutates into cpBVDV causing super infection. BVDV superinfection also can result when PI animals are infected with cpBVDV or vaccinated with modified live virus vaccine containing a cytopathic strain. Fetal infection between 100 and 150 days of pregnancy may also result in the birth of a live calf expressing any number of fetal abnormalities including cerebellar hypoplasia, microencephalopathy, cataracts, microophtalmia, and thymic aplasia. When fetal infection occurs after 150 days of pregnancy, the fetus is generally capable of developing antibodies and clearing the virus. These fetuses are born clinically normal and have BVDV precolostral serum antibodies.[174]

The following diagnostic tests identify BVDV-infected cattle.[175-176]

1. BVDV pooled ear notch RT-PCR - this test is done using ear skin biopsies samples > 3 mm. Samples should be collected and labeled with the individual animal identification. If pooling is requested, the diagnostic laboratory will pool the samples after submission

2. RT-PCR assay is used to detect BVDV nucleic acid in fetal tissues, including spleen, lung, liver, and lymph node. This test is also used in semen and unclotted blood (with EDTA) from adult cattle, mostly for export purposes.

3. BVDV comprehensive serology. Includes BVD 1a (Virus Neutralization – VN), BVD1b (VN), and BVD 2 (VN).

4. BVD PI immunohistochemistry (IHC) utilizes ear skin biopsies fixed in 10% buffered formalin to detect BVDV PI cattle.

5. BVDV antigen capture ELISA. This test is used for detection of BVDV antigen in serum or ear skin biopsies to identify PI animals.

6. BVDV Type 1 (Singerstrain). Detects serum antibodies to BVDV Type 1 (Singer strain) by virus neutralization.

7. Bovine abortion panel. Includes bacterial abortion culture, histopathology, bovine herpesvirus 1 RT-PCR, BVDV RT-PCR, Leptospira spp. RT-PCR, and Neospora caninum RT-PCR.

Control of BVD should include detection of PIs, implementation of biosecurity measures and vaccination. BVDV vaccines available in the US include killed virus and modified live virus vaccines.[177]

Cache Valley virus

Cache Valley is an arthropod-borne viral infection, afflicting a variety of domestic and wild ruminants and humans. The majority of infections are subclinical, but embryonic mortality, fetal teratogenesis, abortion, and stillbirth might be common in sheep, goats and less common in other ruminants. Many other Bunyaviruses prevalent in North America including Main Drain virus, San Angelo virus and LaCrosse virus can cross the placenta and result in similar fetal lesions as Cache Valley virus.[178,179] Other viruses in the family Bunyaviridae, including Schmallenberg virus, Akabane virus, Rift Valley fever virus, and Aino virus that are exotic to North America also could cause fetal teratogenesis, abortion, and stillbirth in cattle and other ruminants.[178,180]

Neospora

Neosporosis is caused by the protozoan parasite, *Neospora caninum*, an obligate intracellular coccidian parasite. Until 1988, *N caninum* was confused with a closely related parasite, *Toxoplasma gondii*. *N. caninum* is regarded as an important infectious cause of pregnancy loss in cattle.[181] Approximately 10 to 20% of all cattle throughout the world are infected with *N. caninum* and it is recognized as the cause of ~ 20% of bovine abortions. Both endemic and epidemic patterns of abortion can occur in herds. Abortion rate in the endemic form is usually > 5% per year and persists year after year. In the epidemic form, > 30% of pregnant heifers and cows may abort over several months. Dogs and coyotes are the definitive host for *N. caninum*, whereas cattle and other ruminants are intermediate hosts.[181]

In cattle, *N. caninum* transmission might occur by 1 of 2 routes: horizontally by ingestion of feed or water contaminated with sporulated coccidial oocysts shed by the definitive host; or by vertical transmission through the placenta to the fetus from acutely or persistently infected dams. Fetal infection could

result in abortion (usually between 5 - 7 months of pregnancy), mummification, birth of weak compromised calves, or the birth of clinically normal infected neonates that preserve the infection in the herd. Vertical transmission occurs because fetal infection does not always result in abortion, but rather the fetus survives and becomes a persistently infected animal. Congenitally infected heifer calves remain persistently infected and are capable of passing the infection on to their offspring, thereby maintaining the infection in the herd. The clinical outcome of transplacental fetal infection with *N. caninum* is likely determined by the maternal and fetal humoral and cellular immune status. Cows that abort have no other clinical signs. Apparently, risk of abortion in subsequent pregnancies is lower.[181] Aborted fetuses are generally autolyzed. Pale areas are observed in the myocardium and skeletal muscle of some affected fetuses. There are no macroscopic lesions in fetal membranes. Microscopic lesions are more frequently observed in the brain and consist of areas of necrosis in the neuropile often surrounded by a rim of mononuclear leukocytes and gliosis. Occasionally, parasite cysts not associated with inflammation are observed in the brain of affected fetuses. Other fetal lesions consist of necrotizing myositis, multifocal epicarditis, nonsuppurative myocarditis, lymphocytic portal hepatitis, and necrotizing placentitis.[159]

Numerous tests should be used concurrently for the accurate diagnosis of neosporosis in aborted fetuses including RT-PCR and histopathology of fetal membranes, brain, liver, lung or heart, and fetal serology from blood clots in the heart or fetal fluid in cavities. ELISA testing of maternal serum is used to determine the infectious status of individual animals; however, on their own, the presence of Neospora maternal antibodies does not prove neosporosis as the cause of the abortion.[181]

Control of neosporosis in cattle herds should focus on reducing the number of congenitally infected heifers retained in the herd and by minimizing the likelihood of postnatal transmission from definitive hosts.[183]

Sarcocystosis

Infection with *Sarcocystis* spp is very common in cattle but abortion is rare. Cattle acquire infection through ingestion of feed or water contaminated with feces of canids containing infective parasites. Lesions in aborted fetuses consist of granulomas and gliosis in the brain and infiltration of mononuclear leukocytes in kidneys, liver, and heart. The organism can be identified by immunofluorescence in frozen sections of tissues.[184]

Trichomoniasis

Bovine trichomoniasis is a venereal disease caused by *Tritrichomonas foetus*, a flagellate protozoan. The parasite is more efficiently transmitted from an infected bull to susceptible cows than vice versa. In that regard, 95% of susceptible nulliparous cows became infected after a single mating with a *T. foetus*-positive bull.[185]

Infection might be asymptomatic or involve a transient balanoposthitis in bulls and vaginitis, cervicitis, and endometritis or pyometra in cows. In pregnant cows, infection is more often characterized by early embryonic death and less often by abortion. Most abortions occur during the first half of pregnancy, with a few as late as the 7th month. Large numbers of organisms might be observed microscopically in H&E-stained sections of fetal membranes. There is edema of the placental stroma , necrosis of the chorionic epithelium and infiltration of mononuclear leukocytes.186 Some aborted fetuses had bronchopneumonia with neutrophilic and macrophage exudation.[187] Bulls generally become persistently infected, whereas cows often clear the infection, usually a few months post-infection.

Control of trichomoniasis in cattle herds requires culling of infected carrier bulls. The required sample for detection of trichomoniasis in bulls is a preputial scraping. In aborting heifers and cows, the diagnosis is by detection of *T. foetus* DNA in placental fluids, fetal membranes, stomach contents of aborted fetuses, uterine washings, and pyometra discharges or vaginal mucus.

Conflict of interest

Authors have no affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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