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Infectious causes of embryonic and fetal mortality

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Abstract

The purpose of this review is to summarize bacterial, fungal, protozoan, and viral causes of reproductive dysgenesis in cattle, sheep, goats, pigs, horses, dogs, and cats. The clinical presentations of disease due to reproductive pathogens are emphasized, with a focus on assisting development of complete lists of causes that result in abortion and infertility in these species. Clinicians are encouraged to assess clinical presentation, create complete lists of differential diagnoses, obtain appropriate diagnostic samples, maximize diagnostic laboratory support, and avoid zoonotic infections resulting from reproductive pathogens of animals. The foundation of an accurate diagnosis of reproductive loss due to infectious pathogens facilitates the prudent use of immunization and biosecurity to minimize reproductive losses.

Keywords: Embryo; Fetus; Pathogen; Abortion; Infertility

1. Introduction

The purpose of this review is to summarize infectious causes of reproductive dysgenesis that compromise viability of domestic animals prior to parturition. For sake of clarity, the embryo is defined as the part of the conceptus that gives rise to the neonate, from fertilization to completion of organogenesis (Day 42 of pregnancy in cattle). Furthermore, the fetus is defined as that part of the conceptus that gives rise to the live neonate from completion of organogenesis to completion of the second stage of parturition. Although more deaths occur at and around birth than between 1 week of age and weaning, embryonic losses are usually higher than perinatal losses. Notably, maternal infections during pregnancy may or may not impact fetal development. The impact on fetal development may be caused directly by infectious agents or their toxins, or indirectly by placentitis. Furthermore, detection of a reproductive pathogen should not preclude further diagnostic testing, as dual infections are not uncommon.

Embryonic or fetal death may result in resorption, mummification, maceration, or abortion. Factors that impact the outcome of embryonic and fetal death include gestational age, cause of death, and source of progesterone for pregnancy maintenance (Table 1). Aborted fetuses may be autolytic due to death 24–48 h before abortion. Fetal mummification occurs most commonly in polytocous species (e.g. swine). Bacterial infections are usually not involved in mummification; however, viruses are a common cause of mummification in pigs, dogs, and cats. Fetal maceration results when abortion or parturition fails to occur following fetal death and CL regression (occasionally in bovine

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Table 1
Infectious causes of infertility and abortion in domestic animals

Bacterial	Fungal	Protozoan	Viral
Bovine (not luteal dependent during middle and late fetal development)			
Campylobacter fetus[a,b,c,d]	*Aspergillus fumigatus*[b,c,d]	*Neospora caninum*[b]	Bovine herpesvirus 1[a,b,c,e]
Histophilus somni[c,d]	*Mucor* spp.[b,c,d]	*Tritrichomonas fetus*[a,f,d]	Bovine viral diarrhea virus[a,f,b,e,g]
Ureaplasma spp.[c,d]	*Morteriella wolfii*[b,c,d]	*Toxoplasma gondii*[d]	Bluetongue virus[f,d]
Brucella abortus[c,h,i]		*Anaplasma marginale*[c,d]	Epizootic bovine abortion[c]
Leptospira spp.[c,e]			Akabane virus
Listeria monocytogenes[c,d]			
Arcanobacterium pyogenes[b,c,d]			
Chlamydophila spp.[c,d]			
Salmonella[d]			
Coxiella burnetti[c,i,h]			
Ovine (not luteal dependent during middle and late fetal development)			
Campylobacter spp.[c,i,g,e]		*Toxoplasma gondii*[a,f,c,j,k,g,e]	Border disease virus[f,b,c,j,k,g,e]
Listeria monocytogenes[c,e,i]			Bluetongue[e,b,k]
Brucella spp.[c,d]			Akabane virus
Salmonella spp.[i,e]			Cache valley virus[a,k]
Chlamydophila abortus[c,j,k,l,e]			
Coxiella burnetti[c,h]			
Anaplasma phagocytophilum			
Yersinia spp.			
Caprine (luteal dependent)			
Listeria monocytogenes[c,e,i]		*Toxoplasma gondii*[f,c,j,k]	Akbane virus[k]
Chlamydophila abortus[c,k,l]		Sarcocystis[b]	Caprine herpesvirus[c]
Brucella melitensis[c,h]			Border disease virus[a,e]
Coxiella burnetti[c,h]			
Mycoplasma spp.[c]			
Leptospira spp.[c]			
Salmonella abortus-ovis[c,i]			
Campylobacter spp.[c]			
Yersinia pseudotuberculosis			
Porcine (luteal dependent)			
Brucella suis[a,f,b,c]		*Toxoplasma gondii*[f]	Porcine parvovirus[a,f,b,j,k,g,e]
Erysipelothrix rhusiopathiae[k]			Porcine enterovirus and teschovirus[a,f,j,k,e]
Leptospira pomona[b,c,e]			Pseudorabies[a,f,b,c,j,k,l,g,e]
Streptococcus suis[b,e]			Classical swine fever[a,f,b,c,k,e]
Chlamydia spp.[c,k]			Porcine reproductive and respiratory syndrome[j]
Actinobacillus[i]			Encephalomyocarditis virus[k]
Mycoplasma suis[b]			Porcine cytomegalovirus[k]
			Rubulavirus[k]
			Menangle virus[k]
			Porcine circovirus type 2[c,k]
			Japanese encephalitis virus[f,b]
			African swine fever
Equine (not luteal dependent during middle and late fetal development)			
Streptococcus zooepidemicus[b,c,i]	Mycotic abortion[b,c]	*Trypanosoma equiperidum*	Equine herpesvirus 1[c]
Taylorella equigenitalis[i]			Equine viral arteritis[b,c]
Canine (luteal dependent)			
Brucella canis[a,c,j]		*Toxoplasma gondii*	Canine herpesvirus[c,j,k]
Streptococci		*Neospora caninum*[f,j,k]	Canine distemper
Campylobacter			Canine parvovirus type 1[j]
Salmonella			
Escherichia coli			
Mycoplasma and *Ureaplasma*[j]			

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Table 1 (*Continued*)

Bacterial	Fungal	Protozoan	Viral
Feline (not luteal dependent during late fetal development)			
Bacterial pathogens		*Toxoplasma gondii*	Feline herpesvirus Feline immunodeficiency virus Feline infectious peritonitis virus[c,j] Feline leukemia virus[j,k] Feline panleukopenia

[a] Embryonic death.
[b] Middle fetal death.
[c] Late fetal death.
[d] Low herd abortion rate.
[e] Variable herd abortion rate.
[f] Early fetal death.
[g] In utero infection might cause persistent or prolonged infection of epidemiologic significance.
[h] High herd abortion rate.
[i] Metritis.
[j] Resorbtion.
[k] Mummification.
[l] Maceration.

trichomoniasis and vibriosis). The majority of abortions are not epizootic but sporadic, with <5% of pregnant animals in a group aborting. Severe maternal illness resulting in high fever (e.g. mastitis, pneumonia), hypoxia (e.g. anaplasmosis, severe anemia), or endotoxemia may result in abortion. Although very few lesions are pathognomonic, gross fetal lesions may be characteristic for mycotic abortion (fresh dysmature fetus with dermatitis) and epizootic bovine abortion (fresh fetus with a nodular liver).

When multiple fetuses are present in utero, infectious pathogens may result in different outcomes in different fetuses. Sows physiologically terminate pregnancies comprised of less than four embryos and subsequently exhibit a regular interestrus interval. Thus, litters of four or less liveborn piglets suggest embryonic or fetal death, even if stillbirths or mummified fetuses are not clinically observed.

2. Bovine reproductive pathogens

Numerous bacterial, viral, protozoan and fungal pathogens have been associated with infertility and abortion in cattle. These pathogens can result in substantial economic losses, indicating the need for control measures to prevent infection or disease.

2.1. *Leptospira spp.*

Leptospira spp. are zoonotic spirochetes. Cattle are the maintenance hosts for *Leptospira interrogans* serovar hardjo (type hardjoprajitno) and *Leptospira borgpetersenii* serovar hardjo (type hardjo-bovis) and incidental hosts for serovar pomona which is maintained in swine [1]. Transmission among maintenance hosts is through contact with infected urine, milk, placental fluid, transplacentally, or venereally. Transmission to an incidental host occurs via contact with an environment contaminated with infected urine. The bacteria gain access through the mucous membranes of the eyes, nose, vagina, or abraded skin. Infection in pregnant animals can lead to abortion, stillbirth, or birth of weak calves. Abortion following infection with serovar pomona occurs in the last trimester, whereas abortion caused by serovar hardjo occurs from 4 months of gestation to term. Abortion rates within a temporal ''outbreak'' are generally higher following infection with serovar pomona compared with hardjo. Infertility is also considered to occur with serovar hardjo infections.

2.2. *Campylobacter fetus subsp. venerealis*

Campylobacter fetus subsp. *venerealis* is a gram-negative rod transmitted venereally among cattle [1]. It might also be transmitted through contact with contaminated bedding or instruments or other infected animals. Infection of the vagina, cervix, endometrium and placenta can occur. Infected animals can experience signs of infertility due to early embryonic death and abortion between 4 and 7 months of gestation. Infected cows usually clear the organism within 3–6 months.

2.3. *Histophilus somnus*

Histophilus somnus is part of the normal bacterial flora of the reproductive tract, but has rarely been

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associated with bovine abortion [1]. The organism might also lead to infertility by binding to the zona pellucida of embryos [2]. Transmission occurs via contact with materials contaminated by infected respiratory or vaginal discharges; the bacteria then spread hematogenously to the fetus.

2.4. *Brucella abortus*

Brucella abortus is a zoonotic, gram-negative coccobacillus, transmitted via ingestion of fetus, placenta, uterine discharge, or materials contaminated by these products [1]. Through hematogenous spread, the bacteria localize in the trophoblasts. Abortions generally occur after the fifth month of gestation. Retained fetal membranes and metritis often occur.

2.5. *Listeria monocytogens*

Listeria monocytogens is a zoonotic, gram-positive coccobacillus, transmitted through ingestion of spoiled feed or feed contaminated with infected fetus, placenta or uterine discharge [1]. The organism spreads hematogenously to the placenta and fetus. Abortion generally occurs in the last trimester. Infected cows can show clinical signs of fever, weight loss, endometritis, and retained fetal membranes.

2.6. *Ureaplasma diversum and Mycoplasma spp.*

Although *Ureaplasma diversum* and *Mycoplasma* spp. are part of the normal flora of the reproductive tract, they can also cause reproductive failure [1,3]. Transmission can occur through direct contact, environmental contamination with infected urine, and venereally. Infection with *U. diversum* can lead to granular vulvitis, infertility, abortion, and birth of weak calves. *Mycoplasma bovigenitalium* infection can cause granular vulvovaginitis, infertility, and endometritis. Experimentally, *Mycoplasma bovis* can cause endometritis, salpingitis, infertility and abortion.

2.7. *Chlamydophila spp.*

Chlamydophila abortus and chlamydia-like *Waddlia chondrophila* can infect cattle [1,4,5]. Infection with *C. abortus* can result in abortion (6–8 months of gestation) or birth of weak calves. *W. chondrophila* also causes abortion. Transmission occurs through ingestion or inhalation of feces, urine, or contaminated discharges (feces, nasal, ocular, vulvar, uterine, placenta). The organism causes endometritis and can multiply in cotyledons. These pathogens are zoonotic and may cause abortion in women.

2.8. *Other bacterial pathogens*

Abortions can also be caused by other bacterial pathogens that are part of the normal microflora or present in the environment [1,6]. These bacteria might include: *Arcanobacterium pyogenes*, *Bacillus* spp., *Escherichia coli*, *Pasteurella* spp., *Pseudomonas* spp., *Salmonella* spp., *Staphylococcus* spp., and *Streptococcus* spp. Bacteria are able to spread hematogenously to the fetoplacental unit and cause abortion, usually late in gestation.

2.9. *Infectious bovine rhinotracheitis (Bovine herpesvirus 1)*

Bovine herpesvirus 1 is an alpha herpesvirus that can lead to respiratory and genital infections, as well as abortion [7,8]. Transmission occurs through contact with upper respiratory, conjunctival or genital tract mucous membranes, aborted fetuses, or through venereal transmission. Abortions are most commonly associated with the respiratory form of the disease and not the genital form. Cows can have fever, anorexia, red nasal mucosa, coughing, and conjunctivitis, followed by abortion in 15–64 d. Abortion generally occurs between 4 and 8 months of gestation. Infection also can result in early embryonic death [9]. Bovine herpesvirus 1 establishes latent infections in the trigeminal and sacral ganglia; following immunosuppression, the virus can become reactivated. Therefore, these animals serve as a source of infection for unexposed cattle.

2.10. *Bovine viral diarrhea virus (BVDV)*

Bovine viral diarrhea virus is a *Pestivirus* that is transmitted transplacentally or through inhalation or ingestion of material contaminated with infected secretions [8,10]. Animals with acute infection present with fever, nasal discharge, enteritis, and leukopenia. Pregnant animals infected up to 45 d of gestation can have decreased fertilization rates and embryonic death. Infection between 45 and 175 d of gestation can result in abortion; however, fetuses that survive infection with a noncytopathic strain of BVDV between 70 and 150 d of gestation usually become persistently infected (PI). Animals that are PI shed large amounts of BVDV and generally do not produce antibodies to BVDV. These animals can be stunted in growth or appear normal.

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Fetal infection occurring at 100–150 d of gestation can result in congenital abnormalities, including cerebellar hypoplasia, microencephalopathy, cataracts, microopthalmia, and thymic aplasia. Fetuses infected between 150 and 285 d of gestation are usually able to clear the virus, develop normally, and exhibit precolostral neutralizing antibodies to BVDV.

2.11. Bluetongue virus

Bluetongue virus is an orbivirus that is transmitted by a midge (*Culicoides variipennis*) [8]. Fetuses infected during the first 100 d of gestation, resorb or abort. Infections between 75 and 100 d of gestation can result in stillbirths, birth of weak calves, or birth of calves with cerebral abnormalities. Infection after Day 150 of gestation does not generally have a negative effect on the fetus.

2.12. Epizootic bovine abortion

Epizootic bovine abortion is a disease that results in late-term abortion [11,12]. Abortion does not generally occur the next year. The disease is possibly caused by an unnamed bacteria in the delta subdivision of the class Proteobacteria and in the order Myxococcales. The organism is transmitted by the tick *Ornithodoros coriaceus*. The disease occurs in California, Nevada, Oregon, and southern Idaho.

2.13. Akabane virus disease

Akabane disease is caused by a *Bunyavirus* [13]. The disease occurs in Australia, Japan, the Middle East, South Africa, and Turkey, and affects cattle, sheep and goats. In Japan, the virus is transmitted by mosquitoes and in Australia transmission occurs via the midge (*Culicoides brevitarsis*). Fetuses infected in the first trimester usually die shortly after birth or have sensory, motor and optical nerve damage. Infection during the second trimester can result in arthrogryposis, neurogenic torticollis, kyphosis, and scoliosis.

2.14. Tritrichomonas foetus

Tritrichomonas foetus is a flagellated protozoa that causes venereal disease in cattle [14]. Infected cows can experience early embryonic death, infertility, and abortion in the first half of gestation. Some cows develop postcoital pyometra. Generally, the infection is cleared within 90 d.

2.15. Neospora caninum

Neospora caninum is a protozoa that can cause abortion early in the second trimester [15]. Infected cows can abort repeatedly. The definitive host for the organism is the dog that ingests tissue cysts. The cow then ingests sporulated oocysts in feed, water or soil contaminated with the dog feces. Tachyzoites can then be transmitted through the placenta to infect the fetus. Infected cows are asymptomatic.

2.16. Mycotic pathogens

Mycotic abortions can be caused by various molds and yeasts [6,16,17]. *Aspergillus fumigatus* is the most common pathogen, with *Morteriella wolfii* being common in the southern hemisphere. Other pathogens include other *Aspergillus* spp., *Absidia* spp., *Rhizomucor pusillus*, *Rhizopus arrhizus*, *Pseudallescheria boydii*, species of *Penicillium*, *Candida*, and *Torulopsis*. The disease occurs sporadically, usually occurring when animals are housed indoors or in small pens and fed hay. The fungal pathogens might enter the respiratory or gastrointestinal tract and then gain access to the systemic circulation and spread to the placentomes. Abortion generally occurs between 6 and 8 months of gestation. Placentitits and retained placenta are frequent occurrences. Other clinical signs are generally not seen. However, cows infected with *Morteriella wolfii* can have postabortion pneumonia and death within 72 h after abortion.

3. Ovine reproductive pathogens

Many of the bacterial, viral, and protozoan causes of ovine abortion are zoonotic. Thus, attendants should employ protective measures to prevent human infection.

3.1. Campylobacter spp.

Campylobacter is the most important cause of abortion in sheep in North America [18,19]. *Campylobacter jejuni* is responsible for sporadic abortions, whereas *Campylobacter fetus* subsp. *fetus* is associated with large outbreaks of recurring abortion. The zoonotic, gram-negative rods are transmitted by ingestion and shed in feces, aborted fetuses, placentae, and vaginal discharges of ewes that abort. Ewes are asymptomatic and abort in the third trimester, have stillbirths or give birth to weak lambs. Some ewes are

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persistently infected and continue to shed the organism in their feces.

3.2. Listeria monocytogenes

Infection with *Listeria monocytogenes* occurs through ingestion of the organism in poor-quality alkaline silage or pastures contaminated with feces containing the zoonotic organism [19]. Ewes can abort 7–30 d after infection. Prior to aborting, ewes might show signs of fever and decreased appetite. Following abortion, ewes often develop metritis. As well, *Listeria ivanovii* has also been shown to cause abortion in sheep.

3.3. Brucellosis

Abortion in sheep can be caused by *Brucella melitensis* or rarely *B. ovis* [18,19]. *Brucella* can be transmitted to the ewe through mucous membrane (vaginal, preputial, and conjunctival) contact with infected rams. Ewes are generally asymptomatic, but can abort in the third trimester, have stillbirth or give birth to a weak lamb. Ewes clear the bacteria within a few weeks following an abortion. *B. melitensis* has zoonotic potential, whereas *B. ovis* does not.

3.4. Salmonellosis

Abortion in ewes can follow infection with *Salmonella abortus-ovis*, *Salmonella montevideo*, or *Salmonella arizonae* [18,19]. Overcrowded conditions and shipping can predispose flocks to abortion storms. Affected ewes can be asymptomatic prior to aborting, or have clinical signs of fever, depression and diarrhea. Metritis and retained placenta can occur after aborting. These pathogens are zoonotic.

3.5. Chlamydophila abortus

C. abortus is responsible for causing ovine enzootic abortion [19]. The organism is transmitted through ingestion or exposure to aborted materials, vaginal discharge, or contaminated environment. When the infected ewe becomes pregnant, the organism is hematogenously spread to the trophoblast cells and by 95 d of gestation, has infected the cotyledons and intercotyledonary areas. Infection of the fetus and abortion may result. Prior to 95 d, stillbirth or resorption can occur. If the ewe is not pregnant at the time of infection, the organism can affect the subsequent pregnancy. Once abortion occurs, the immune system will prevent subsequent abortions, but the organism can continue to be shed in vaginal secretions. *C. abortus* can cause abortion in humans.

3.6. Coxiella burnetti

Coxiella burnetti is transmitted through inhalation, mucous membrane contact, ticks, and possibly semen [19]. Infected ewes might develop placentitis and abort late in gestation, although abortion is not as common as in does. Abortion is not likely to occur the next lambing season due to development of immunity within the flock. Humans can become infected when handling infected placentas or lambs, and from inhalation of contaminated dust. The clinical signs of infection in people may include prolonged illness, undulant fever, atypical pneumonia, hepatitis, myalgia, or endocarditis.

3.7. Tick-borne fever

Tick-borne fever occurs in Europe and is caused by *Anaplasma phagocytophilum* [20]. Clinically, the disease results in fever, inappetance and abortion of sheep, cattle and goats. The bacteria causes flu-like symptoms in humans.

3.8. Yersinia spp.

Yersinia pseudotuberculosis [21] and *Yersinia enterocolitica* (O serotype) [22] have been isolated from ovine abortion cases. Infection of ewes with *Y. pseudotuberculosis* can lead to abortion, stillbirth or birth of weak or healthy lambs. Infection with *Y. enterocolitica* resulted in placentitis and abortion, with subsequent normal pregnancies. Acute mesenteric lymphadenitis with fever, anorexia, vomiting, and diarrhea are common in people infected with these organisms.

3.9. Border disease virus

Border disease virus is a non-zoonotic pestivirus similar to bovine viral diarrhea virus and hog cholera virus [19]. Ewes infected before Days 60–85 of gestation have fetal resorption, abortion, maceration or mummification. If the fetus survives, it will be persistently infected with the virus, have potential cerebellar damage, shortened facial and long bones, and produce hair rather than wool. If infection occurs after Day 85 of gestation, abortion, birth of weak or normal lambs, or birth of antibody positive lambs can occur. No clinical signs are seen in the ewe.

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3.10. Bluetongue virus

Bluetongue virus, an orbivirus, is transmitted by a midge (*Culicoides variipennis*) [18,19]. Infected ewes can abort, have mummified fetuses or deliver lambs with congenital defects (hydranencephaly, porencephaly, cerebellar dysgenesis, skeletal deformities) [23]. The ewe can show clinical signs of fever, lameness, oral and nasal ulcers, and swollen tongue, ears or face [18,19].

3.11. Akabane virus disease

Akabane virus can cause abortion, stillbirth, mummified fetuses, and congenital deformities (arthrogryposis, hydranencephaly) in sheep [18].

3.12. Cache valley virus

Cache valley virus, a *Bunyavirus*, is transmitted by mosquitoes [19]. Infected ewes have fever, depression, and a reluctance to move. Infection at 28–32 d of gestation results in early embryonic death and mummification. Infection at 32–37 d of gestation causes CNS and musculoskeletal deformities (arthrogryposis, brachygnathia, hydranencephaly, agenesis of the spinal cord), whereas infection at 37–48 d leads to milder musculoskeletal deformities, with nonsuppurative encephalitis and encephalomyelitis. More than one clinical syndrome can be present in a litter.

3.13. Toxoplasma gondii

Ewes are infected by *Toxoplasma gondii* through ingestion of feed contaminated with sporulated oocysts [19]. The fetus can then be infected approximately 14 d after ingestion of the parasite. Whereas ewes are asymptomatic, infection occurring <40 d of gestation results in embryo resorption. Infection at 40–120 d of gestation leads to maceration, mummification or abortion, whereas infection after 120 d can result in stillbirth or birth of weak or healthy lambs. Different stages of fetal involvement can be seen within the flock and within the same litter. *T. gondii* is a zoonotic agent that can affect nonimmune individuals.

4. Caprine reproductive pathogens

Similar to ovine reproductive pathogens, caprine pathogens include many zoonotic organisms.

4.1. Listeria monocytogenes

Infection with *L. monocytogenes* early in gestation can result in abortion, whereas infection late in gestation results in stillbirth or birth of weak kids [18]. Prior to abortion, does may have fever, decreased appetite, and reduced milk production. The organism can be shed in the milk from the aborting doe. Generally, the encephalitic form of the disease does not occur simultaneously with abortions. *L. monocytogenes* can survive in soil and feces, and grows in poorly fermented silage. Abortions are reported after grazing on boggy, high-pH soils. *Listeria* is zoonotic and can cause neurologic disease in humans.

4.2. Chlamydophila abortus

C. abortus is the most common cause of infectious abortion in goats in the USA [18,24]. It is responsible for abortions, stillbirths, birth of weak kids, and neonatal pneumonia. The organism does not proliferate until 90 d of gestation, at which time fetal death and abortion can occur. Does can show anorexia, fever, and a bloody vaginal discharge 2–3 d before aborting. Following abortion, uterine clearance of *C. abortus* takes 3 months. The organism can reside in pigeons or sparrows and be transmitted via ticks or insects. The organism is shed in uterine discharge, fetus and placenta. *C. abortus* is zoonotic and can result in flu-like symptoms and abortion in pregnant women.

4.3. Brucella melitensis

Brucellosis is present in Africa, Mexico, the Middle East, India, Pakistan and parts of South America [18,24]. *B. melitensis* is transmitted to goats through ingestion of contaminated feed or water. In pregnant does, the bacteria can infect the placenta with resultant late-term abortion. Does might show clinical signs of fever, depression, weight loss, diarrhea, mastitis, lameness, and birth of weak kids. The bacteria is shed in milk, urine, feces, and for 2–3 months in vaginal discharge. The organism causes undulant fever (synonymous with Malta fever, Gibraltar fever, and Mediterranean fever) in humans that consume unpasteurized contaminated milk or cheese.

4.4. Coxiella burnetti

Coxiella burnetti is the causative agent of Q fever [25]. This gram-negative coccobacillus causes disease

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in sheep, cattle, goats, and other mammals. Affected animals might have no clinical signs of disease, but serve as a source of infection, or they can abort late in gestation and have stillbirths. The organism is transmitted in placenta, uterine fluids, milk, urine, feces, and aerosol droplets. Transmission occurs through contact, inhalation, or possibly ingestion. As well, the organism is zoonotic and can be transmitted to humans by dogs and cats. Affected individuals might have no clinical signs, or they might show fever, headaches, myalgia, coughing, fatigue, vomiting, respiratory disease, and rarely endocarditis.

4.5. *Mycoplasma spp.*

Mycoplasma can cause late-term abortion, mastitis, vulvovaginitis, arthritis and conjunctivitis [24,26,27]. Following abortion, does can shed the organism in milk, amniotic fluids, and the placenta [18].

4.6. *Leptospira spp.*

Leptospirosis can result in abortion in the last trimester, anorexia, fever, jaundice, anemia, and nervous signs in affected does [18,24]. Transmission occurs through exposure to environments contaminated with infected urine. Due to the zoonotic potential, humans should avoid contact with aborted tissues and infected urine.

4.7. *Salmonella abortus-ovis*

S. abortus-ovis infection of does can cause abortion, metritis, retained placenta, diarrhea, and systemic illness [18,24]. Although abortion can occur throughout gestation, it is more common at the end of gestation. The bacteria are transmitted through ingestion. *Salmonella* infections are zoonotic and can cause enteritis, abdominal pain and abortion in humans.

4.8. *Campylobacter spp.*

Although campylobacterosis is a common cause of abortion in sheep, it is less prominent in goats [18,24]. Does may exhibit late abortions, stillbirths, birth of weak kids, and a mucopurulent vaginal discharge. The placenta is edematous, with necrosis of the cotyledons. The does do not show evidence of systemic illness, but may have diarrhea. As well, *Campylobacter jejuni* causes mild gastroenteritis in humans.

4.9. *Yersinia pseudotuberculosis*

Y. pseudotuberculosis is transmitted by fecal–oral route [24]. Abortion and early neonatal death have been reported in goats [28]. The bacteria is zoonotic.

4.10. *Akbane virus disease*

Akabane virus is transmitted by mosquitoes and midges (*Culicoides brevitarsis*) [13,18,24]. It occurs in Australia, Japan, the Middle East, South Africa, and Argentina. Nonpregnant goats do not show clinical signs, whereas pregnant does can appear healthy but abort, have stillbirths or mummified fetuses. Kids have arthrogryposis and/or hydrencephaly that can result in dystocia.

4.11. *Caprine herpesvirus*

Caprine herpesvirus is an alpha herpesvirus that can cause late-term abortion without any prior clinical signs [29–32]. The virus can also cause vulvovaginitis and respiratory disease. Subsequent pregnancies are not affected by the virus [32]. Like other herpesviruses, caprine herpesvirus has a latent state that can be reactivated following stress, immunosuppression or possibly estrus in does. Following reactivation, the virus can be shed via the respiratory or genital route.

4.12. *Toxoplasma gondii*

Toxoplasmosis can cause abortion, stillbirth, fetal death, fetal resorptions, birth of a weak kid, or birth of a healthy kid [24,33]. Infection early in gestation (30–90 d) generally results in fetal resorptions or mummification, whereas infection in the last half of gestation results in asymptomatic does aborting 2–3 weeks prior to parturition. Abortion occurs due to necrosis of the cotyledons. The protozoa is transmitted to cats through ingestion of infected rodents or birds. Does ingest food or water that is contaminated with cat feces containing resistant oocytes; the organism then enters the bloodstream and spreads to the placenta and fetus. Toxoplasmosis has zoonotic potential.

4.13. *Sarcocystosis*

Sarcocystosis is caused by a cyst-forming protozoan [24]. Inoculation of pregnant does (75–105 d of gestation) with sporocysts of Sarcocystis resulted in abortion and neonatal death [34].

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5. Porcine reproductive pathogens

Unlike reproductive pathogens in other species, porcine reproductive pathogens are predominantly viruses. This is hypothesized to be due to the density of the swine population within many production units.

5.1. Brucella suis

Brucella suis is transmitted through direct contact with aborted fetuses and secretions, as well as venereally [35]. Infected gilts or sows might present with infertility. In addition, abortion can occur in the first trimester, if infection occurs at breeding, and during late gestation if infection occurs after Day 35 of gestation. The organism has zoonotic potential. Swine suspected of having brucellosis should be reported to state animal health authorities.

5.2. Leptospira spp.

Leptospirosis is caused by a gram-negative spirochete [35,36]. Transmission occurs through contact of oral, nasal or ocular mucosa with contaminated urine. Pigs are maintenance hosts for serogroups *Pomona*, Australis and *Tarassovi*, whereas incidental infections occur with strains of the *Canicola*, *Icterohaemorrhagiae*, and *Grippotyphosa* serogroups. Acute infection of leptospirosis is generally asymptomatic. However, chronic leptospirosis may manifest as abortions, stillbirths, infertility, and birth of weak piglets. Leptospirosis is an important occupational zoonosis for farmers and abbatoir staff in contact with pigs.

5.3. Erysipelothrix rhusiopathiae

Erysipelothrix rhusiopathiae is a gram-positive rod that causes erysipelas [35]. The bacteria is transmitted through oronasal exposure, followed by septicemia. The disease is characterized by abortion, fever, diamond-shaped skin lesions, arthritis, vegetative endocarditis, and sudden death. Abortion can occur at any stage of gestation, additionally, some piglets may become mummified. As well, embryo resorption can occur. The bacteria is zoonotic, causing erysipeloid in humans.

5.4. Streptococcus suis

Although streptococci are part of the normal flora of the vagina, they have also been associated with abortion, stillbirths, vaginitis, postparturient agalactia, and early neonatal death [35,37].

5.5. Chlamydia spp.

Chlamydiae are bacteria that can be transmitted by inhalation of aerosols, ingestion of contaminated feed, and venereally [38]. The species involved are *Chlamydophila psittaci*, *Chlamydophila pecorum*, and *Chlamydia trachomatis*. Chlamydial infections can be inapparent or have clinical signs of fever, dyspnea, pneumonia, conjunctivitis, pericarditis, and polyarthritis. In addition, gilts or sows may exhibit late-term abortions, birth of weak piglets, or mummified piglets.

5.6. Actinobacillus spp.

Actinobacillus suis, *Actinobacillus ross*, and *Actinobacillus equuli* have been suggested to cause abortion, metritis, and decreased litter sizes [35]. Mauch and Bilkei reported late-term abortions during the first and second parities due to *A. suis* [39]. *A. suis* and *A. ross* are normal flora of the vagina and upper respiratory tract of healthy sows, and the bacteria can be isolated from healthy herds [35,39]. Transmission of *A. suis* occurs via inhalation of aerosols or through abrasions in the skin and mucous membranes. Infected animals might demonstrate fever, erythematous skin lesions, and anorexia.

5.7. Mycoplasma suis

Mycoplasma suis is the causative organism of eperythrozoonosis [40]. *M. suis* attaches to and replicates on the red blood cell. It causes anemia, icterus, anorexia, immune suppression, and fever. Furthermore, infertility, abortion, stillbirth, and birth of weak piglets can also result from infection.

5.8. Porcine reproductive and respiratory syndrome virus

Porcine reproductive and respiratory syndrome virus (PRRSV) can be shed in nasal secretions, feces and urine; infected pigs can be long-term carriers [41–43]. The virus might be spread by contact, oral transmission and aerosol transmission. Experimentally, the virus is transmitted in semen [44]. Additionally, the virus can be transmitted transplacentally [41], most commonly in the last trimester. During the first phase of the disease, reproductive signs include abortions and irregular returns to estrus. Pulmonary edema or nephritis also can result in sows. During the second phase of the disease, pregnant animals can give birth to a

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combination of normal or weak piglets and stillborn, autolytic, or mummified fetuses.

5.9. Porcine parvovirus

Porcine parvovirus is endemic in most herds, with most gilts and sows exhibiting active immunity against the virus [45]. Gilts that do not have immunity to porcine parvovirus before conception are at a high risk of infection and reproductive disease. The virus is transmitted oronasally and transplacentally. Clinical signs manifest as reproductive failure. Infection of the embryo at Days 10–30 of gestation results in resorption and irregular return to estrus. Infection of the fetus at Days 30–70 of gestation results in mummification, whereas infection after Day 70 results in an immunocompetent healthy piglet. Other clinical signs may include infertility, stillbirth, neonatal death, and reduced neonatal vitality. During transplacental infection, part of a litter might become infected, with subsequent intrauterine spread of the virus to the other littermates. Thus, a combination of resorptions, mummification, and stillbirths can all occur in a single litter.

5.10. Pseudorabies

Pseudorabies is caused by an alpha herpesvirus [46,47]. The pig is the only natural host of pseudorabies, whereas infection in cattle, sheep, goats, dogs, and cats is fatal. Transmission is primarily through direct contact with nasal and oral secretions, but can occur by aerosols, venereally, or transplacentally. Like other herpesviruses, pseudorabies can establish latent infections. In naïve herds, the clinical signs might be severe. Infection during the first trimester results in resorption and a return to estrus, whereas infection during the second and third trimester results in abortion, stillbirth, or birth of weak piglets. Neonatal pigs may have 100% morbidity and mortality rates. The dam's immunity against pseudorabies determines the clinical signs seen in piglets. Piglets of dams lacking immunity have nervous signs (trembling, hypersalivation, ataxia, circling, paddling) and die within 1–2 d, whereas piglets of immune dams usually do not show clinical signs.

5.11. Classical swine fever

Classical swine fever, previously known as hog cholera, is caused by a *Pestivirus* [48]. Pigs are also susceptible to two other pestiviruses, bovine viral diarrhea virus and border disease virus. Pigs are the only natural host of classical swine fever virus. Transmission occurs through oronasal contact with infected pigs, ingestion of contaminated feed, airborne spread over short distances, indirectly by fomites, and potentially through semen [48,49]. Clinical signs include fever, anorexia, conjunctivitis, diarrhea, and respiratory signs. Transplacental infection can occur at any stage of gestation resulting in abortions, mummies and stillbirths. Infection at 50–70 d of gestation can result in the birth of persistently viremic piglets. These piglets appear normal initially, but subsequently develop congenital tremors and lose weight. They serve as a continual reservoir of classical swine fever virus.

5.12. Porcine enterovirus and teschovirus

Porcine enterovirus and teschovirus are Picornaviruses [50]. Transmission is through fecal–oral route, but transmission by fomites might also occur. Sows and gilts may experience infertility, embryonic death, stillbirths, and mummies, without any other clinical signs.

5.13. Encephalomyocarditis virus

Encephalomyocarditis virus is a Picornavirus that is isolated from several species [51]. In swine, the disease is primarily transmitted through feed or water contaminated by infected rodent feces, urine, or carcasses. Pregnant females might not show clinical signs, or they might experience abortion, mummies, or stillbirths [52].

5.14. Porcine cytomegalovirus

Porcine cytomegalovirus is a beta herpesvirus that is transmitted oronasally and congenitally [53]. Pigs >3 weeks of age are asymptomatic, whereas younger pigs might show coughing, nasal discharge, rhinitis, neurological signs, or death. Pregnant animals can have mummies and stillbirths without showing any other clinical signs. As well, preweaning mortality can be $\leq 25\%$.

5.15. Rubulavirus

Rubulavirus is a paramyxovirus that causes blue eye disease in swine in Mexico [54]. Transmission of the virus occurs through nose-to-nose contact or contact with fomites. Infected pigs of all ages develop corneal opacity. Pregnant animals show reproductive signs for approximately 4 months. These signs consist of stillbirths, mummies, decreased number of live births,

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increased number of animals returning to estrus, and an increase in weaning-to-service interval. In closed herds, the disease is self-limiting.

5.16. Menangle virus

Menangle virus is a paramyxovirus that has caused disease in New South Wales, Australia [54]. The virus causes disease in pigs, humans and fruit bats, which are the reservoir host. Transmission is suspected to be through fecal–oral or urinary–oral routes. The disease caused reproductive failure in sows [55]. Stillbirths and mummified fetuses were present, as well as stillborn piglets with congenital deformities such as arthrogryposis, brachygnathia, kyphosis, and degeneration of the brain and spinal cord. Many sows had a delay in return to estrus. Additionally, two farm workers were affected. They experienced fever and headaches, but fully recovered.

5.17. Porcine circovirus type 2

Porcine circovirus type 2 has been associated with reproductive disease, respiratory disease, postweaning multisystemic wasting syndrome, and porcine dermatitis and nephropathy syndrome [56]. The virus is thought to be transmitted by oronasal exposure. Reproductive disease is manifest as late-term abortion, stillbirths, and mummified fetuses [57].

5.18. Japanese encephalitis virus

Japanese encephalitis virus is a mosquito-borne virus that causes disease in humans and animals [58]. Swine are reservoir hosts that allow mosquitoes to transmit the virus to humans (dead-end hosts). The disease is manifest in pregnant sows and gilts as abortions, stillbirths, mummified fetuses, and birth of weak piglets that can have hydrocephalus and subcutaneous edema. Infection after 60–70 d of gestation does not appear to affect piglets.

5.19. African swine fever

Soft ticks (*Ornithodorus moubata* and *Ornithodorus erraticus*) are the reservoir and vector for African swine fever virus [42,59]. As well, the virus can be spread among pigs via oronasal secretions. The clinical signs of disease can vary from sudden death (with no previous clinical signs) to inapparent infection. Acute infections may consist of fever, anorexia, cyanosis, hemorrhages in internal organs and skin, and abortion.

5.20. Toxoplasma gondii

Toxoplasmosis occurs through ingestion of food, water or soil contaminated with sporulated oocysts or through ingestion of meat containing tissue cysts [60]. Whereas most infections are asymptomatic, abortion may occur [60,61]. Additionally, piglets may be born premature, dead, weak, or die soon after birth [60]. Prevention of toxoplasmosis in pigs is important to prevent infection of humans through ingestion of undercooked pork.

6. Equine reproductive pathogens

Pathogens that cause sporadic reproductive loss in mares may be due primarily to host factors, e.g. impaired reproductive defense mechanisms. Notably, other pathogens may cause disease, depending on variables of the environment (e.g. movement of horses that predisposes naïve mares to novel infections).

6.1. Streptococcus zooepidemicus

Streptococcus zooepidemicus is one of the most common bacteria isolated from mares with uterine disease [62]. Whereas the uterus of a healthy mare is more likely to clear the infection, the uterus of a mare with impaired defense mechanisms or poor genital conformation might become inflamed or develop an infection leading to infertility. As well, *Streptococcus zooepidemicus* can cause abortion via ascension through the cervix and infection of the fetus and placenta, or possibly through a maternal systemic infection [62,63]. Bacterial abortions usually occur at 5–10 months of gestation [62]. In addition to bacterial culture, diagnosis of infection is coupled with evidence of autolysis and inflammation of the fetus and placenta. Other bacteria implicated in infertility or abortion are *E. coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* var *genitalium*, *Staphylococcus aureus*, *Streptococcus equisimilis*, *Leptospira* spp., *S. abortus equi*, and nocardioform actinomycetes. Although no longer very common, *S. abortus equi* has caused abortion outbreaks [64]; in one of these, 21 of 26 mares aborted between 5 and 10 months of gestation [64].

6.2. Taylorella equigenitalis

Taylorella equigenitalis is a gram-negative coccobacillus that causes contagious equine metritis (CEM)

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[62]. *Taylorella equigenitalis* is transmitted venereally, highly contagious, and can cause a copious vulvar discharge [65]. Diagnosis is by bacteriologic culture of the organism from the clitoral fossa, clitoral sinuses, and endometrium or cervix. As well, polymerase chain reaction can be used to identify the organism. Serologic tests are also available to detect antibodies against *Taylorella equigenitalis* in the serum. Most mares recover spontaneously from CEM over a period of several months. Imported horses used for breeding should be quarantined and extensively tested. Any animals suspected of having CEM should be reported to state or federal animal health authorities.

6.3. Equine herpesvirus 1

Equine herpesvirus 1 can cause abortion, neonatal death, respiratory disease, and neurologic disease [66]. The virus is transmitted through inhalation of infectious aerosol droplets, or by direct contact with infectious secretions. Like other herspesviruses, equine herpesvirus 1 persists in a latent state that can be reactivated. Most abortions are sporadic and occur between 7 months of gestation and term. The abortions can occur up to 4 months after respiratory disease, which may have been clinical or subclinical.

6.4. Equine viral arteritis

Equine viral arteritis can cause sporadic abortions between 5 and 10 months of gestation [67]. The virus is transmitted by inhalation of infectious aerosol droplets or venereally. If clinical signs of disease are apparent, they can consist of fever, hind limb edema, nasal and ocular discharge, urticarial rash, anorexia, coughing, and dyspnea [68]. The virus can also cause uterine disease, with subsequent abortion in pregnant mares [69].

6.5. Trypanosoma equiperidum

Trypanosoma equiperidum is a venereally transmitted protozoa that causes dourine [65]. Although it has been eradicated from North America and most of Europe, the disease is still found in Africa, South and Central America, and the Middle East [70]. Clinical signs include a mucopurulent vulvar discharge, fever, and cutaneous raised plaques followed by ataxia, depression, severe anemia, and death [65,70]. Mortality can reach 50–70%. Strict quarantine, testing, and eradication of positive animals are recommended for control of the disease.

6.6. Fungal pathogens

Fungal pathogens account for up to 10% of reported sporadic abortions [71]. *Aspergillus fumigatus* is the most common fungal pathogen, but *Mucor* spp. and *Allescheria boydii* have also been reported. Infection of the uterus may occur via ascension through the cervix or hematogenously. Abortions usually occur at 8–11 months of gestation, and may be associated with a purulent vulvar discharge. The affected chorioallantois is thickened, yellowish, and covered with a mucoid exudate.

7. Canine reproductive pathogens

Infectious causes of canine reproductive losses include some pathogens with a zoonotic potential, as well as viruses that can quickly spread throughout a kennel if bitches are not adequately vaccinated.

7.1. Brucella canis

Brucella canis is a small, gram-negative intracellular coccobacilli. Infection can cause infertility, early embryonic death, fetal resorptions, and late-term abortion [72,73]. The bitch might not show any clinical signs prior to aborting. Following abortion, a serosanguinous vaginal discharge may be present for 1–6 weeks. Large numbers of bacteria can be present in the aborted material and postabortion vulvar discharge; therefore, caution should be exercised to prevent other dogs from contacting the fluid or aborted tissue. Whereas the zoonotic potential of *B. canis* is less than most *Brucella* sp., immunosuppressed or pregnant individuals should avoid contact with aborted fluid or tissue.

7.2. Streptococci

Streptococci are gram-positive cocci that are commensal microflora of the genital tract [74]. Although the bacteria have been associated with abortion, infertility and neonatal septicemia, its isolation does not confirm the cause of the reproductive problem.

7.3. Campylobacter

Campylobacter is a gram-negative curved rod. Although *Campylobacter jejuni* has been isolated from the feces of normal dogs [75], it has also been associated with abortions [76]. If *Campylobacter* is suspected, the

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diagnostic laboratory should be contacted to obtain instructions for sample submission and to be informed of the suspected pathogen [74]. Also, owners should be informed that the bacteria can cause enteric disease in humans.

7.4. Salmonella

Salmonella is a gram-negative bacilli that is transmitted through the gastrointestinal tract via contaminated water, food, or fomites [77]. Infection with *Salmonella* can cause abortion, stillbirth and birth of weak puppies. It is important that owners by notified of the zoonotic potential of *Salmonella*.

7.5. Escherichia coli

E. coli is commonly isolated in cases of metritis and pyometra [74]. It has also been isolated in the case of a partial abortion [78].

7.6. Mycoplasma and Ureaplasma

Mycoplasma and *Ureaplasma* can be isolated from the genital tract of both healthy and infertile bitches [79]. Although these organisms have been associated with infertility, fetal resorption, abortion, stillbirth and birth of weak puppies [74], it is recommended that culture results be interpreted in the context of other diagnostic findings to determine if antibiotic treatment should be instituted [80]. When submitting specimens to the diagnostic laboratory, samples should be placed in Amies medium (without charcoal) or modified Stuart bacterial transport medium and the laboratory informed of the suspected pathogen [80].

7.7. Canine herpesvirus

Canine herpesvirus can lead to abortion, stillbirth and embryonic resorptions [81]. A pregnant bitch can become infected through direct contact with mucosal secretions (respiratory or genital) [82,83]. As well, a latent infection might be reactivated during pregnancy with resultant virus shedding. Neonatal infection usually occurs at birth; however, transplacental infection can occur and lead to mummified or dead fetuses, stillbirth, or birth of weak puppies.

7.8. Canine distemper

Canine distemper is caused by a morbillivirus [84]. The virus has been shown to cause abortion, stillbirth and congenital infections in puppies [84,85]. Abortion can follow systemic infection of the bitch or transplacental infection [74]. Puppies infected transplacentally can develop neurologic signs within 6 weeks of birth [84].

7.9. Canine parvovirus type 1

Canine parvovirus type 1, the causative agent of minute virus of canines, can cause embryo resorptions, stillbirth, or birth of weak puppies [86].

7.10. Toxoplasma gondii

Toxoplasmosis can cause placentitis with spread of tachyzoites to the fetus [87]. Experimental infection of bitches caused congenital infection and abortion.

7.11. Neospora caninum

N. caninum has been shown experimentally to be transmitted transplacentally [88]. Neosporosis can result in early fetal death, mummification, resorption and birth of weak puppies [87]. However, it has not been shown to cause abortion.

8. Feline reproductive pathogens

Feline reproductive loss is more commonly attributed to a viral etiology than to bacterial or protozoan pathogens.

8.1. Bacterial pathogens

Although uncommon, abortions can occur when normal vaginal flora (*E. coli*, *Staphylococcus* sp., *Streptococcus* sp.) ascend into the uterus and cause fetal infection [89]. The queen might show clinical signs of infection, such as anorexia, pyrexia, abdominal discomfort, and vaginal discharge [90].

8.2. Feline herpesvirus

Feline herpesvirus 1 is an alpha herpesvirus that causes rhinotracheitis [91,92]. Experimental infection caused abortion and intrauterine fetal death [89]; however, the virus has not been isolated from the aborted fetal tissue [92]. Hickman reported that in a herpesvirus outbreak in a specific pathogen-free colony, only 1 of 51 queens pregnant at the initial time of the outbreak aborted part of her litter [91]. However, there was a 62% mortality rate within 1 week of birth among

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the kittens born to queens acutely infected during the perinatal period.

8.3. Feline immunodeficiency virus

Feline immunodeficiency virus (FIV) is a lentivirus, similar to human immunodeficiency virus [93]. The virus can be transmitted in utero resulting in abortion, stillbirth, arrested fetal development, and birth of viable, virus-infected kittens [94]. Weaver et al. reported that experimental inoculation of specific pathogen-free queens with FIV resulted in 60% of kittens being resorbed or having arrested fetal development [93].

8.4. Feline infectious peritonitis virus

Feline infectious peritonitis is caused by a coronavirus [90]. The virus is associated with late-term abortion, stillbirths, fetal resorptions, endometritis, and high mortality in kittens the first week of life. Some purebred cats have a genetic predisposition for FIP (heritability of 50%), and thus should not be used as breeding animals [95].

8.5. Feline leukemia virus

Feline leukemia is a retrovirus that can lead to abortion, infertility and fetal resorptions [90]. Generally, queens are asymptomatic prior to aborting.

8.6. Feline panleukopenia virus

Feline panleukopenia virus is a parvovirus that can cause abortion, stillbirth, and cerebellar hypoplasia in kittens [90]. These signs are not always associated with the classical gastrointestinal disease in the queen.

8.7. Toxoplasma gondii

Although not common, *T. gondii* is reported to cause abortion and congenital infections [89,90]. Infection can occur transplacentally or postnatally via milk [87].

9. Summary

Preparation is essential to maximize the potential for accurate diagnosis of reproductive pathogens. Whenever possible, entire fetuses, placental tissues, and serum and urine from the dam should be sent promptly, along with a complete case history, to the diagnostic laboratory. In many cases, listing the pathogens of concern on submission forms can improve diagnostic test selection. Effective communication with your diagnostic laboratory to ensure appropriate sample handling and prudent test selection can maximize your diagnostic support. It is noteworthy that appropriate precautions should be taken to avoid zoonotic infection of personnel (in clinical or diagnostic settings) with reproductive pathogens. Finally, appropriate immunization or biosecurity to prevent infection often can reduce reproductive losses in domestic animals.

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