
Archives of Razi Institute Journal

Volume 80, NO. 3, 2025

Journal homepage: www.archrazi.areeo.ac.ir

Review Article

Prevalent Infectious Causes of Abortion in the Ruminant Population in Iran- A Literature Review

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Article Info:
Received: 21 January 2024
Accepted: 2 March 2024
Published: 30 June 2025

Keywords:

Abortion, Infectious Agents, Ruminants, Iran.

ABSTRACT

Abortion is one of the most crucial problems for ranchers in Iran, in terms of economics, animal healthcare, and zoonotic diseases. The farm animal industry in Iran suffers major economic losses due to abortion each year. Until now, some epizootological studies have been conducted on infectious agents of ruminant abortion in Iran. However, there is no comprehensive information on the ruminant abortion status in Iran. Our goal was to collect all the available information on common infectious causes of abortion in ruminants in Iran to better understand the situation in the country. This review covers all published documents in the main English and Persian-language databases on infectious agents causing abortion inruminants (cattle, sheep, goats, camels and buffalo) in Iran from 1980 to May, 2024.Although ruminant abortion in Iran has multifactorial etiologies, the present study identified infectious diseases as a significant risk factor for abortion in ruminants . Important putative infectious agents that cause abortion in sheep and goats include toxoplasmosis, chlamydiosis, brucellosis and coxiellosis, while in cattle, the important infectious agents include neosporosis, BVDV and BoHV-1. According to our results, a well-defined control strategy for preventing and controlling infectious abortion in Iran should be based on further epidemiological studies on the cause of abortion, accurate recordkeeping, laboratory analysis, control of animal trafficking from neighboring countries and from one region to another within the country, the employment of good biosecurity practices that inhibit the introduction and spread of infectious causes of abortion, and the use of vaccination programs.

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How to cite this article: **Hassani M, Menzies P, Alamian S, Esmaeili H. Prevalent Infectious Causes of Abortion in the Ruminant Population in Iran- A Literature Review. *Archives of Razi Institute*. 2025;80(3):663-678.** DOI: 10.32592/ARI.2025.80.3.663

1. Introduction

Abortion is one of the most important problems of livestock production worldwide, causing severe economic losses including loss of fetuses, uterine infections, increased calving/lambing/kidding interval and infertility, costs for additional inseminations to impregnate cows or heifers, veterinary cost, reduced milk production, dietary costs for extra days open, culling or death of animals, loss of potential to produce calf/lam/kid replacements, increased time and labor costs for managing an abortion outbreak ,and human disease costs, given that many abortion agents are zoonotic (1–3). The abortive agents in farm animals vary greatly and their epidemiological patterns differ greatly between geographical areas ,depending on climate, population density, housing and breeding systems, the introduction of new infectious agents, and control measures such as vaccination and processing technologies. Agents responsible for livestock abortion can be classified as infectious and non-infectious. Infectious agents are the leading causes of abortion in ruminant compared to non-infectious agents and are often infectious to humans (3–5). The main zoonotic etiological agents are *Brucella*, *Salmonella*, *Campylobacter*, *Leptospira* and *Listeria* species, *Chlamydia abortus*, *Coxiella burnetii* and *Toxoplasma gondii*. These agents can be transmitted from animals to humans through contact with infected animals, during obstetrical procedures or after birth. Transmission can also occur through milking abortive females or drinking infected or contaminated milk (6).With approximately 70 million head of cattle, sheep, goats, camels and buffalo; Iran's ruminant industry accounts for approximately 11% of the Gross Domestic Product. Infectious abortion is one of the most economically significant diseases in ruminant production in Iran,causing losses in both production and veterinary services and posing zoonotic risk, particularly to ranchers and veterinarians. Since the 1940s, various epizootological studies have examined infectious agents of ruminant abortion across different states and time periods in Iran, However, there is no comprehensive information on ruminant abortion situation in Iran. Our aim is to provide a clearer understanding of the situation in Iran. Specifically, we aim to identify the key pathogens involved, their incidence and/or prevalence, their impact on ruminant production, the practices used to prevent and control them, and their impact on the health of humans who rely on ruminants and their products in Iran.

2. Data Acquisition

2.1. The study Area: Iran

The literature reviewed was limited to studies conducted in Iran. Iran is located in the Middle East, western Asia, between latitudes 24°–40°N, and longitudes 44° and 64° E. Iran shares borders with Armenia, the Azeri exclave of Nakhichevan, and the Republic of Azerbaijan, Turkmenistan, Afghanistan, Pakistan, Iraq and Turkey. It covers 1,648,195 km^2 and with a population of over seventy million people. Iran's climate ranges from arid and semi-aridto subtropical along the Caspian coast and in the northern forests.Temperatures range from over +50°C in summer to -40°C in winter in some areas. There are two large deserts in the central region that receive nearly no rainfall, whereas the northern regions receive more than 2,000 mm of rainfall per year (Figure 1).

2.2. Search Criteria

To gather information on infectious causing abortion in ruminant (cattle, sheep, goats, camels and buffalo) in Iran, we searched eight databases for articles published in English or Farsi from 1980 until May 2024. The five English databases werePubMed, Google Scholar, Science Direct, Web of Science and Scopus, and three Persian databases were Magiran, Irandoc and the Scientific Information Database (SID). Additionally, we searched dissertations and all abstract books from scientific congresses in Iran from 2000 to May 2024. To avoid missing any articles, we reviewed the citations of the included articles to identify other relevant studies. The search terms used alone and/or combined included ‘‘Brucellosis,’’ ‘‘*Brucella abortus*,’’ ‘‘*Brucella melitensis*,’’ ‘‘*Brucella ovis*,’’ ‘‘Listeriosis,’’ ‘‘*Listeria monocytogenes*,’’ ‘‘*Listeriosis ivanovii*,’’ ‘‘Salmonellosis,’’ ‘‘*Salmonella Abortus-ovis*,’’ ‘‘Vibriosis/Campylobacteriosis,’’ ‘‘*Campylobacter jejuni* subsp. *jejuni*,’’ ‘‘*Campylobacter fetus* subsp. *fetus*,’’ ‘‘*Campylobacter fetus* subsp. *venerealis*,’’ ‘‘Leptospirosis,’’ ‘‘*Leptospira interrogans*,’’ ‘‘Chlamydiosis,’’ ‘‘*Chlamydia abortus*,’’ ‘‘Coxiellosis,’’ ‘‘*Coxiella burnetii*,’’ ‘‘*Escherichia coli*,’’ ‘‘*Streptococcus* spp.,’’ ‘‘*Staphylococcus* spp.,’’ ‘‘*Bacillus* spp.,’’ ‘‘*Pasteurella multocida*,’’ ‘‘*Mannheimia hemolytica*,’’ ‘‘*Haemophilus somnus*,’’ ‘‘*Arcanobacterium pyogenes*,’’ ‘‘*Yersinia pseudotuberculosis*,’’ ‘‘*Pseudomonas* spp.,’’ ‘‘*Mycoplasma mycoides*,’’ ‘‘*Mycoplasma agalactiae*,’’ ‘‘*Ureaplasma diversum*,’’ ‘‘Neosporosis,’’ ‘‘*Neospora caninum*,’’ ‘‘Toxoplasmosis,’’ ‘‘*Toxoplasma gondii*,’’ ‘‘Trypanosomosis,’’ ‘‘*Trypanosoma evansi*,’’ ‘‘Tritrichomonasis,’’ ‘‘*Tritrichomonas foetus*,’’ ‘‘Sarcocystis,’’ ‘‘Bovine viral diarrhea virus,’’ ‘‘Bovine herpesvirus-1,’’ ‘‘Bluetongue virus,’’ ‘‘Border Disease virus,’’ ‘‘Caprine herpesvirus type 1,’’ ‘‘Bunya virus,’’ ‘‘Rift Valley fever,’’ ‘‘Akabane virus,’’ ‘‘Cache Valley virus,’’ ‘‘Nairobi Sheep Disease Virus,’’ ‘‘Schmallenberg,’’ ‘‘Aspergillusis,’’ ‘‘*Aspergillus fumigatus*,’’ ‘‘*Absidia* spp.,’’ ‘‘*Mucor* spp.’’ ‘‘*Rhizopus* spp.’’ ‘‘*Candida* spp.,’’ ‘‘abortion,’’ ‘‘epidemiology,’’ ‘‘animals,’’ ‘‘ruminant,’’ ‘‘cattle,’’ ‘‘bovine,’’ ‘‘sheep,’’ ‘‘ovine,’’ ‘‘goat,’’ ‘‘caprine,’’ ‘‘camel,’’ ‘‘buffalo’’ and ‘‘Iran.’’ All of the listed terms were searched in Persian as well. Articles that did not contain complete information about the infectious agents of abortion were excluded.

Figure 1. The map of Iran with different climate regions (Iran-climate.png.). This figure is shared under a CCBY 3.0 Share-Alike 3.0 Unported license.

3. Results

3.1. Literature Reviewed

After eliminating duplicates based on title and abstract, articles describing the infectious causes of abortion in aborted fetuses of ruminants (cattle, sheep, goats, camels and buffalo) in Iran were selected. Based on the sampling strategy, studies with non-random samples from one herd were excluded from this research because of creating bias. Furthermore, the studies with small sample size (<10) were excluded from the review. Most of the reports were PCR-based studies focusing on aborted sheep fetuses in Iran no studies concerning buffalo were found. As shown in Table 1, we classified the infectious causes of abortion in Iran into bacteria, viruses, protozoa and fungi. Based on our literature review, side effect estimated the incidence of abortion caused by these agents as low, medium or high. Further details on PCR-based studies are summarized in Tables 2 through 8 and are categorized by animal group, study area, and the number and type of samples.

3.2. Status of Abortion in Livestock in Iran

Numerous factors and a wide range of infectious or noninfectious agents may induce abortions in livestock, which can occur sporadically or as enzootic outbreaks (7). Infectious agents are more commonly associated with abortion in domestic animals than noninfectious causes., Some infectious agents are zoonotic and can be transmitted from animals to humans , significantly effecting human health (6). The prevalence of abortion varies according to production systems and locations. In healthy flocks and herds of ewes and does, the visibly aborting rate is usually less than 2% (4). Noninfectious abortions related to traumatism, pregnancy toxaemia, vitamin E/Se deficiency, stressful handling, overcrowding, or even consuming toxic plants rarely result in more than 2% of the flock aborting.When the percentage is higher an infectious cause of abortion is highly likely (4,8). An abortion rate of more than 2%, a clustering of abortions within a short time (e.g., 2 weeks),or a clustering of abortions a given location (e.g., pen or farm) should be taken seriously.Efforts should be made to determine the cause, and measures should be taken to control the abortion (4). Unfortunately, there's no official data on the incidence of abortion in the country. However, the incidence of abortion could vary greatly in different areas due to the wide spectrum of climate conditions, husbandry systems, species and breed variation in Iran.Outbreaks of abortion are reported annually in sheep and goat herds in various regions of Iran. However, the lack of reliable statistics on the incidence of abortion and the proportion of stillborn lambs and kids has contributed to the neglect of controlling this disease in these species (9). (9). A cross-sectional survey on 757 sheep flocks in Iran revealed that 213 (28.1%) had an abortion rate below 2%.The remaining 544 flocks(71.8%) had pathological abortion rates (> 2%), and infectious agents were diagnosed as a cause of abortion in 287 flocks (37.9%) (10). According to the abortion definition of fetal loss between 60 and 260 days of pregnancy, the overall cattle abortion rate from years 2004 to 2014, as determined by calving records gathered from herds in different regions of Iran, was 15.5% (11.2-18.7%). The highest incidence abortion was found in second parity cows. The highest and lowest abortion rates took place in mild and cold climate, respectively. Furthermore, the incidence rate of abortions was highest in the spring and lowest in the autumn (11). There are insufficient studies on the abortion rate in other ruminants in Iran (12). In 2014, an outbreak of abortion storm in camel herds was documented in Qom province, affecting 58.4% of pregnant camels and 77.8% of herds . The abortion rate in herds ranged from 14% to 100%.

3.3. Economic Impact of Abortion on Production in Iran

According to the Ministry of Agriculture of Iran's latest report (2019), there are approximately 44 million sheep, 17 million goats, and 8 million cattle in various regions of the country. Iran is also home to more than 220,000 Azeri

Table 1. Infectious causes of abortion and its potential zoonosis and incidence in ruminant population in Iran.

Pathogen agent	Potential zoonosis	Cattle	Sheep and goat
***Brucella* spp.**	Yes	Low	High
Listeria monocytogenes	Yes	Low	Low
***Salmonella* spp.**	Yes	Low	Low
***Campylobacter* spp.**	Yes	Low	Low
***Leptospira* spp.**	Yes	Moderate	Low
Chlamydia abortus	Yes	Low	High
Coxiella burnetii	Yes	Low	Moderate
Other bacteria	Yes	Low	Low
Toxopllasma gondii	Yes	Low	High
Neospora caninum	Yes	High	Low
Bovine viral diarrhea virus	No	High	-
Bovine herpesvirus1	No	Moderate	-
Bluetongue virus	No	-	Low
Border disease virus	No	-	Low
Fungal	Yes	Low	Low

Table 2. Infection rate of brucellosis in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetus sample type	No. of samples	Species: No. of positive (%)
Mohammadi, 2016	Sheep	Golestan	Abomasal contents	57	*B. melitensis*: 10 (17.5)
Mahdavi Roshan et al., 2018	Sheep	Sistan va Baluchistan	Abomasal contents & spleen	78	*B. melitensis*: 15 (19.2)
Mahzounieh et al., 2019	Sheep	Different regions	Abomasal contents	98	*B. melitensis*: 15 (15.3)
Amouei et al., 2019	Sheep	Mazandaran	Abomasal contents	57	*B. melitensis*: 2 (3.5)
Hamali et al., 2013	Cattle	East Azerbaijan	Different tissues	76	*B. abortus.*: 6 (7.8)
Nemati et al., 2019	Cattle	Golestan & Razavi Khorasan	Different tissues	22	*B. abortus.*: 1 (4.5)

breed buffalo and two camel species: *C. dromedarius* and *C. bactrianus* with the populations of approximately 190,000 and around 100-300, respectively. The annual milk and meat production of cows and small ruminants is estimated to be around 10,000 and 500 and 460 and 360 (× 1000 tons) , respectively (14). Information on the annual cost of abortion to the Iranian sheep and goat industry isn't available but huge financial losses associated with direct and indirect costs. Some of these indirect costs are associated with increased lambing/kidding intervals, fewer replacement lambs available, increased time to reach marketable weight , increased costs of production resulting from birth of small, weak lambs/kids , decreased growth rates ,and increased veterinary treatment costs. Abortion and reproductive failure are the most prevalent reason of culling cows in Iran (15). Depending on factors such as pregnancy rate, feed and milk prices, milk production, days in milk, the time of insemination after parturition, semen costs, insemination time, and labor costs, each abortion in cattle costs an Iranian producer about 810,000 to 12,760,000 Rials (approximately 82–1302 US$).

3.4. Health Management Procedures For Controlling Infectious Abortion in Iran

In Iran, most livestock are still raised by smallholders on traditional breeding farms. There are two systems: village and migratory (nomadic). Animals havw direct contact with shepherd and stray dogs. In a few cases especially regarding cattle breeding, intensive production systems are employed that have higher level of hygiene, nutrition ,and animal welfare (Kamalzadeh et al., 2008). A defined control program against brucellosis , a priority disease in the Middle East, has been setup since 1949. Howevet,there is no national program for abortion control of within the Iranian Veterinary Organization ,and measures are instituted at the herd level at the discretion of the individual producer. The following are some of the major problems with abortion control in Iran:

1- Traditional breeding system: In a traditional breeding system, health and reproductive complications are common due to geographical, economic, and cultural factors, as well as a lack of sufficient information on farm animal husbandry. Stress factors are also prevalent in these systems. Therefore, herds and flocks suffer from weaknesses in actions such as maintaining the general health and immune function of animals by providing balanced feed and clean water; improving hygiene by isolating purchased livestock before entering the herd; keeping aborted animals separate from other livestock; and completely disposing of aborted material, which is routinely fed to shepherd dogs and other stray animals in Iran. This allows the life cycles of Toxoplasma gondii and Neospora caninum, important protozoal abortion-causing agents, to survive. Using vaccination programs and good record keeping, including abortion events, vaccinations,

nutrition, possible exposure to toxic or teratogenic plants or drugs, and possible environmental factors, such as extreme heat or stress, can help focus diagnostic investigations.

2- Animal movement control: There are weaknesses in animal movement control within the country, especially because of nomadic and semi-nomadic conditions.

3- Geographic situation: Iran geographic location can be an important risk factor for the spread and persistence of contagious diseases from neighboring countries such as Iraq, Pakistan & Afghanistan. Most of these countries lack high- quality veterinary services to controlling animal diseases, and there are weaknesses in the border quarantine system and animal trafficking from these countries into Iran.

4- Diagnosis and Treatment Limitation: The high cost of laboratory work to aid in the diagnosing abortion and implementing control and treatment measurements also exacerbates the problem in Iran. On the other hand, laboratories only conduct routine aerobic cultures on blood agar and MacConkey agar.Thus , many factors remain hidden.

3.5. Infectious Causes of Livestock Abortion in Iran

3.5.1. Bacterial Infections

3.5.1.1. Brucellosis

Brucellosis is one of the most important zoonosis that cause stillbirth, abortion, infertility and reduction of the efficiency of milk and meat production in livestock. Brucellosis in cattle is most commonly caused by *B. abortus* although *B. melitensis* can occasionally be involved. *B. melitensis*, is the cause of brucellosis in sheep and goats but, *B. abortus* infection can also occur in these animals (17–19). Brucellosis in Iran's cattle population was first diagnosed in 1944 with *B. abortus* isolation from an aborted fetus (20). Since then, *B. abortus* biovars 1, 2, 3, 4, 5 and 9 as well as *B. melitensis* biovars 1, 2 and 3, have been identified in Iranian cattle.However, *B. abortus* biovar 3 is the most prevalent (21). Prevalence of brucellosis among industrial and semi-industrial dairy cattle is 0.3% (22). The national control plan for cattle brucellosis includes vaccination as well as test and slaughtering. Vaccination programs have been begun in 1949 using the Strain 19 vaccine, but since then, (year) vaccination of adult cows and 4 - 12-month-old female calves have been vaccinated with reduced and full doses of the RB51 vaccine, respectively. Testing and slaughtering are based on serological screening using RBPT and, followed by confirmation of positive results using STAT and 2ME tests on all industrial farms. In rural and nomadic areas, control measures are implemented following outbreaks of animal or human brucellosis, as well as villages that sell milk to milk processing plants (22,23). There are potential hazards related to the use of the Rev.1 vaccine in national control programs, because cattle and small ruminant are kept close together in traditional farms, and sheep and goats vaccination (Rev.1) can be a source of *Brucella* abortion in cattle (24). Furthermore, there are reports on abortion in cows with *B. abortus* vaccine strain RB51 in Iran (25,26). Since 1949, when Brucella melitensis was first isolated from the milk of an aborted goat, brucellosis in small ruminants has been studied (23). The prevalence of brucellosis among small ruminants in Iran was calculated to be 2.1% (27). According to the some reports; *B. melitensis* biovar 1 is endemic and widely spread in Iranian sheep and goats, but *B. melitensis* biovars 2 and 3,as well as *B. abortus* biovar 3, have also been found (21). Sheep and goats were first vaccinated in 1963 with the full-dose Rev. 1 vaccine produced at Razi Institute in Iran. In 2003, adult vaccination with a reduced dose of Rev-1 vaccine replaced the full dose, and testing and slaughter were eliminated except in breeding centers, industrial farms and areas with abortion outbreaks (23,27). Some reports revealed that reduced dose of Rev-1 vaccine was implicated as the cause of abortion in some regions of Iran and was isolated from the fetus of aborted small ruminants (28). According to the serological tests, brucellosis prevalence in Iranian buffalo and camels is between 1.5 to 20.5% and 1.3 to 9.3% ,respectively (21,29). Bacterial culture studies conducted in Iran in the 1980s revealed an infection rate of 25.3% (426/1,680) and 43.5% (875/2,009) in aborted fetuses of small ruminants and cattle, respectively (30). Table 2 shows that recent studies have revealed the abortion rate in sheep and cattle ranges from 3.5% to 19.2% and from 4.5% to 7.8%, respectively, in different provinces. These results indicate that animal vaccination has had a noticeable effect on controlling the infection in Iran.

3.5.1.2. Listeriosis

Listeria monocytogenes is an important zoonotic, foodborne pathogen that can cause various clinical forms in ruminants, ranging from mastitis, keratoconjunctivitis, uveitis, gastroenteritis, encephalitis, neonatal septicaemia, as well as premature birth or abortion (31,32). There are few reports of listeriosis- related abortion in ruminants in Iran. Two studies of aborted small ruminant fetuses submitted to Iranian veterinary diagnostic laboratories found *L. monocytogenes* in 0.0-2.8% of examined ovine and caprine aborted fetuses (33,34).

3.5.1.3. Salmonellosis

Salmonellosis is an infectious, zoonotic disease caused by *Salmonella* ssp. which can cause foodborne poisoning in human through animal products and cause abortion and mortality in the newborn ruminants (35,36). Outbreaks of salmonellosis in sheep herds, associated with mortalities and abortions, have been documented in Iran. Some surveys using bacterial culture and PCR, have revealed that the abortion rate in ewes due to *S. abortus ovis* ranges from 1.3% to 33% in different provinces (37–39). In the only report on *Salmonella* outbreak in Iranian camels, Muhammadi and Mosleh (2017) examined the gallbladder contents and amniotic fluids of 10 aborted dromedary fetuses in Khorasan Razavi Province , isolating the pathogen in 2 cases (40).

3.5.1.4. Campylobacteriosis

Campylobacter species are significant zoonotic causes of bacterial foodborne infection .In ruminants, *Campylobacter fetus* subsp. *fetus*, *venerealis*, and *jejuni* are the most important species associated with lowered fertility and abortion (41–43). Infection with *C. fetus* infection as an abortive agent was confirmed in numerous abortion outbreaks in sheep population in Iran (44,45). Based on PCR studies shown in table 3, the prevalence of campylobacteriosis infection in ovine aborted fetuses is between 3.5% to 10.6% (Table 3). Bacterial culture and PCR studies conducted on the cattle population in Iran revealed an infection rate of 4.2% (50/1186) and 3.9% (3/76), respectively (26,46).

3.5.1.5. Leptospirosis

Leptospirosis is an important zoonotic disease of mammals caused by pathogenic spirochaetes of the species *L. interrogans*. Cattle are relatively susceptible to clinical infection, resulting in production losses including reduced milk yield, reproductive failure, abortions, premature birth or stillbirth (47,48). In Iran, seroprevalence of leptospirosis in unvaccinated cattle, sheep and goatsis 25.6% (95% CI= 19.8-32.3%), 17.4% (95% CI= 12.4-23.8%) ,and 14% (95% CI= 11.9-17.5%), respectively, and the most prevalent serovars are *grippotyphosa*, *Pomona*,and *canicola* (49). PCR studies have detected *Leptospira* DNA in up to 21.0% and 8.6% of bovine and ovine aborted fetuses in Iran, respectively (Table 4).

3.5.1.6. Chlamydiosis

Chlamydia abortus ,a zoonotic pathogen, previously known as *Chlamydophila abortus* and *Chlamydia psittaci* biotype 1/serotype 1, is a common cause of abortion in ruminants, specially in sheep and goats (50–52). Few surveys have been carried out on the seroepidemiology of chlamydiosis among ruminants in Iran. In a2011 study investigating the presence of *C. abortus* in sheep and goats, Esmaeili *et al*. found 25.6% seropositivity in the individual level and 81.4% in unvaccinated flocks across seven provinces of Iran (53). Furthermore, a cross-sectional study was conducted on 834 vaginal and ocular swabs collected from 83 flocks in different regions of Iran,.DNA of *C. abortus* was detected in 117 samples from 504 sheep (23.2%) and 84 from 330 goats (25.5%) (54). Another studyreported 48.4% prevalence of *C. abortus* antibodies in aborted cattle on some farms around Tehran province (55). According to listed studies in table 5, *C. abortus* infection in farm animal aborted fetuses in Iran is considerable, up to 52% and 22.0% in sheep and goats ,respectively. Therefore, it can play a major role in abortions and economic losses in small ruminants breeding.

3.5.1.7. Coxiellosis (Q Fever)

Coxiellosis ,also known as Q fever, is a highly contagious zoonotic disease caused by *Coxiella burnetii*. This bacterium is a cause of sporadic abortions or abortion storms in sheep and goats, but is only occassionally associated with sporadic abortion in cattle (56,57). Q fever is an endemic disease in Iran, which is mostly reported in

Table 3. Infection rate of campylobacterosis in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetus sample type	No. of samples	Species: No. of positive (%)
Fallah et al., 2014	Sheep	East Azerbaijan	Different tissues & placenta	132	*C. jejuni*: 2 (1.5) *C. fetus fetus*: 12 (9.1)
Kabiri et al., 2016	Sheep	Different regions	Abomasal contents	98	*C. fetus*: 5 (5.1)
Mohammadi, 2016	Sheep	Golestan	Abomasal contents	57	*C. fetus*: 2 (3.5)
Hossein Abadi et al., 2018	Sheep	Sistan va Baluchistan	Abomasal contents & spleen	78	*C. fetus*: 6 (7.7)
Malekadeh Arasteh, 2021	Sheep	Khorasan Razavi	Liver	91	*C. fetus*: 6 (6.6)
Hamali et al., 2011	Cattle	East Azerbaijan	Different tissues & placenta	76	*C. fetus fetus*: 0 (0.0) *C. fetus venerealis*: 3 (3.9)

Table 4. Infection rate of leptospirosis in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetal sample type	No. of sample	No. of positive (%)
Badii et al., 2010	Cattle	Tehran	Different tissues	251	32 (12.8)
Hamali et al., 2013	Cattle	East Azerbaijan	Different tissues	76	16 (21.0)
Kaveh et al., 2017	Cattle	Qazvin	Different tissues	128	18 (14.1)
Froutani et al., 2014	Sheep	East Azerbaijan	Different tissues	70	6 (8.6)
Kabiri et al., 2016	Sheep	Different regions	Abomasal contents	98	0 (0.0)

Table 5. Infection rate of *Chlamydia abortus* in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetal sample type	No. of sample	No. of positive (%)
Mahzounieh & Pourahmad, 2014	Sheep	Charmahal va Bakhtiari	Abomasal contents	48	25 (52.1)
Ebadi et al., 2015	Sheep	Alborze	Abomasal contents	100	37 (37.0)
Mohammadi, 2016	Sheep	Golestan	Abomasal contents	57	0 (0.0)
Alem et al., 2017	Sheep	East Azerbaijan	Different tissues & placenta	50	13 (26.0)
Heidari et al., 2018	Sheep	Fars	Abomasal contents	183	15 (8.2)
Hosein Abadi et al., 2019	Sheep	Sistan va Bluchestan	Abomasal contents & spleen	78	0 (0.0)
(M Mahzounieh et al., 2019	Sheep	Different regions	Abomasal contents	98	7 (7.1)
Hamedi et al., 2020	Sheep	Different regions	Abomasal contents & Lung	150	36 (24.0)
Mosavi Yengejeh, 2021	Sheep	East Azerbaijan	Different tissues	48	4 (4.2)
Sharifi, 2021	Sheep	Khorasan Razavi	Liver	100	20 (20.0)
Heidari et al., 2018	Goat	Fars	Abomasal contents	117	18 (15.4)
Hamedi et al., 2020	Goat	Different regions	Abomasal contents & Lung	50	11 (22.0)

human and domestic animals in nearly all of the provinces of the country (58). The prevalence of *C. burnetii* antibodies in unvaccinated sheep, goat and cattle in Iran is 24.6% (95% CI= 19.8–29.5%), 31.9% (95% CI= 20.9–42.9%), 13.3% (95% CI= 2.9–23.6%), respectively (59). PCR-based studies have indicated that *C. burnetii* has a crucial role in abortions in small ruminants (0.0-21.8%) and cattle (21.7-25%) in Iran (Table 6).

3.5.1.8. Other, less common bacteria

Several other bacteria have been isolated from aborting sheep and goats. These bacteria cause sporadic problems in individual animals and do not represent a serious problem for flocks. Most infections are mechanistically associated with initial septicemia in the dam, followed by localization of the bacteria to the uterine caruncle and infection of the placental cotyledons (60). In Iran, bacteria including *Escherichia coli*, *Staphylococcus* spp., *Streptococcus* spp., *Bacillus* spp., *Mannheimia haemolytica*, *Mycoplasma agalactiae* and *Erysipelothrix rhusiopathiae* have been isolated from aborted fetuses of ruminants (33,34,61–67).

3.5.2. Protozoal Infections

3.5.2.1. Toxoplasmosis

Toxoplasma gondii, the protozoan that causes toxoplasmosis, is an important zoonotic pathogen that causes abortion, mummification, stillbirth, and the birth of weak newborns in sheep and goats (68,69). Cats and other members of Felidae family, as definitive hosts, play an important role in the epidemiology of toxoplasmosis. These hosts become infected by ingesting food contaminated by oocysts or containing tachyzoites ,or tissue cysts from infected mice. Cats excrete oocysts for up to 14 days after infection and sporadically thereafter. Sheep and goats become infected by ingesting contaminated food or pasture with environmentally resistant oocysts excreted in cats' feces (70–72). Stray cats are probably the main source of *T. gondii* infection in Iran. The seroprevalence rate of toxoplasmosis in cats in Iran is considerable (33.6% (95% CI= 22–46.4)), which can pose a potential threat to the health of humans and animals due to the high environmental contamination with oocysts (73). The overall prevalence rate of toxoplasmosis in Iran was estimated to be 31% (95% CI= 26.0 35.2%) in sheep, 27 % (95% CI= 14.0- 42.5%) in goats, and 18.1% (95% CI= 9.9-28.2%) in cattle (74,75). Based on PCR studies shown in table 7, toxoplasmosis has a major role in ovine abortion,wth up to 68.2% of ovine fetuses testing positive in Iran. An outbreak of ovine congenital toxoplasmosis was reported in 2010-11 in Khorasan Razavi province, Iran. The flock consisted of 240 ewes with no history of abortion. During one month, 65 lambs were aborted at late pregnancy period, 12 lambs were born weak and 4 of them died 4 to 5 days after birth, and eight lambs were too weak and with motion disabilities (76).

3.5.2.2. Neosporosis

Neospora caninum is considered as a significant cause of bovine abortion in most of the major cattle-producing areas of the world. Domestic dogs and other species of canines are definitive hosts for *N. caninum*. After ingesting *N. caninum*-infected body tissues from intermediate hosts, they can temporarily shed oocysts (70,77). Intermediate hosts become infected either via ingestion of contaminated food and water with oocysts (horizontal transmission), or via transplacental transmission from infected dams to their offspring (vertical transmission). Healthy calves which have been prenatally infected remain persistently infected and can pass the infection to their own calves (70,78). The overall seroprevalence of *N. caninum* in cattle population in Iran is estimated 23.6% (95% CI= 19.8-27.9%) based on a meta-analyses study (79). Also documented studies in Iran show that the presence of farm dogs can be a risk factor for *N. caninum* infection in dairy farms with the infection rate between 0 to 54.6 % (80). *N. caninum* infection in dairy cattle in Iran can be an important agent of abortion. Reports on the prevalence of *N. caninum* infection in cattle indicate

Table 6. Infection rate of *Coxiella burnetii* in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Abortion fetal sample type	No. of sample	No. of positive (%)
Asadi, 2013	Sheep	Shiraz & Isfahan	Different tissues	67	0 (0.0)
Khalili et al., 2015	Sheep	Hamedan	Different tissues	30	0 (0.0)
Abiri et al., 2016	Sheep	Khorasan Razavi	Different tissues	92	16 (17.3)
Heidari et al., 2018	Sheep	Fars	Abomasal contents	183	5 (2.7)
Mahdavi Roshan et al., 2018	Sheep	Sistan va Bluchestan	Abomasal contents & spleen	78	13 (16.6)
Mahzounieh et al., 2019	Sheep	Different regions	Abomasal contents	98	0 (0.0)
Mohabati Mobarez et al., 2021	Sheep	Different regions	Different tissues	94	20 (21.8)
Heidari et al., 2018	Goat	Fars	Abomasal contents	117	1 (0.8)
Abiri et al., 2016	Cattle	Khorasan Razavi	Different tissues	60	PCR: 15 (25.0)
Mohabati Mobarez et al., 2021	Cattle	Different regions	Different tissues	46	PCR: 10 (21.7)

Table 7. Infection rate of *Toxoplasma gondii* in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetal sample type	No. of sample	No. of positive (%)
Rassouli, 2011	Sheep	Khorasan Razavi	Brain	200	27 (13.5)
Habibi et al., 2012	Sheep	Qazvin	Brain	18	12 (66.6)
Danehchin, 2014	Sheep	Khorasan Razavi	Brain	37 112	20 (54.0) 18 (16.1)
Sanjarani, 2017	Sheep	Sistan va Baluchestan	Brain	79	13 (16.4)
Nourmohammadi, 2017	Sheep	Lorestan Khuzestan	Brain Brain	142 127	10 (7.0) 10 (7.8)
Amouei et al., 2019	Sheep	Mazandaran	Brain	57	11 (19.3)
Shahbazi et al., 2019	Sheep	Ardabil	Brain	75	48 (64.0)
Salehi & Nezami, 2019	Sheep	North Khorasan	Different tissues	133	14 (10.5)
Partoandazanpoor et al., 2020	Sheep	Kurdistan	Brain	111	9 (8.1)
Malekifard et al., 2020	Sheep	West Azerbaijan	Brain & Placenta	130	7 (5.3)
Arefkhah et al., 2020	Sheep	Kohgiluyeh va Boyer-Ahmad	Brain	100	2 (2.0)
Nosrati et al., 2020	Sheep	Gilan	Brain	44	30 (68.2)
Azimi et al., 2021	Sheep	Mazandaran	Brain	48	8 (16.6)
Moravvej Hariri, 2021	Sheep	East Azerbaijan	Different tissues	30	0 (0.0)
Azimi et al., 2021	Cattle	Mazandaran	Brain	52	7 (13.4)
Partoandazanpoor et al., 2020	Goat	Kurdistan	Brain	10	1 (10.0)

that 11.0–45.0% of the PCR-examined aborted fetuses tsted positive (Table 8). *N. caninum* infection have also reported in 1.1–6.8% of sheep, 6.2-10.8 % of goats, 19.2-55.9% of water buffalo and 3.2–27.0% of camels in Iran (80). However , *N. caninum* occasionally causes clinical infections in sheep and goats. Several research projects on neosporosis abortion in sheep have been carried out in Iran, indicating *N. caninum* may act as a causative agent of abortion in sheep.,DNA from *N. caninum* has been detected up to 15.6% of samples derived from aborted fetuses (Table 8).

3.5.2.3. Trypanosomosis

The most important protozoal disease affecting camels is trypanosomosis ,also known as surra,which is caused by *Trypanosoma evansi* and is currently considered as a zoonotic disease.In camels, the disease is characterized by recurrent fever, anemia, emaciation and diarrhea, atrophy of the thigh muscles, lacrimation, corneal opacity, edema, abortions, premature births and death (81). The disease was confirmed in Iranian camels in 1935, and since then, numerous studies have reported the prevalence of trypanosomosis in dromedary camels to range from 0 to 19.5% (20,82). Outbreaks of trypanosomosis associated with abortion have been documented in dromedary herds of Iran (83); however, only one study has examined the role of *T. evansi* infection in camel abortion (84). In this PCR study, 41 out of 244 (16.8%) abomasal contents of aborted fetuses were collected from eastern provinces were infected with *T. evansi*.

3.5.3. Viral Infections

3.5.3.1. Bovine Viral Diarrhea Virus

Bovine viral diarrhoea virus (BVDV) is a member of Pestivirus genus and Flaviviridae family. It is one of the most important viral pathogens of cattle and is responsible

Table 8. Infection rate of *Neospora caninumin* in aborted fetuses of ruminants from different regions of Iran based on polymerase chain reaction (PCR).

Reference	Group	Study area	Aborted fetal sample type	No. of sample	No. of positive (%)
Razmi et al., 2007	Cattle	Khorasan Razavi	Brain	100	13 (13.0)
Razmi et al., 2010	Cattle	Khorasan Razavi	Brain	151	18 (11.9)
Razmi et al., 2013	Cattle	Khorasan Razavi	Brain	200	23 (11.5)
Kamali et al., 2014	Cattle	Different regions	Brain	395	179 (45.0)
Rafati & Jaafarian, 2014	Cattle	Chahar Mahal va Bakhtiari	Brain	100	11 (11.0)
Kaveh et al., 2017	Cattle	Qazvin	Different tissues	128	39 (30.5)
Khani et al., 2018	Cattle	Markazi	Brain	38	10 (26.3)
Amouei et al., 2019)	Cattle	Mazandaran	Brain	9	2 (22.2)
Salehi et al., 2021	Cattle	Mazandaran	Brain	78	16 (20.5)
Asadpour et al., 2013	Sheep	Northwest regions	Different tissues	70	6 (8.5)
Sasani et al., 2013	Sheep	Different regions	Brain	109	1 (0.9)
Razmi & Naseri, 2017	Sheep	Khorasan Razavi	Brain	71	7 (9.8)
Amouei et al., 2019	Sheep	Mazandaran	Brain	57	2 (3.5)
Malekifard et al., 2020	Sheep	West Azerbaijan	Brain & Placenta	130	3 (2.3)
Salehi et al., 2021	Sheep	Mazandaran	Brain	51	8 (15.6)

for major economic losses in dairy industries worldwide (85). BVDV causes multiple clinical syndromes, including bovine viral diarrhea, mucosal disease, respiratory problems,and reproductive complications including embryonic resorption, abortion, stillbirth, infertility, congenital defects, or the birth of persistently infected (PI) calves, which are the principal reservoir of the virus in nature (86,87). The prevalence of BVDV in unvaccinated bovine in Iran has been reported to range from 20% to 90% based on the detection of antibody against BVDV (88). While the precise prevalence of BVDV-induced abortion in cattle is not well-documented in Iran, several PCR studies have revealed that the rate of BVD-infected aborted fetuses ranges from 20.3 to 25.2% in different provinces (89,90).

3.5.3.2. Bovine herpesvirus type 1 (BoHV-1)

Infection with Bovine herpesvirus type 1 (BoHV-1) can lead to several clinical syndromes ,including inflammatory reactions in both respiratory (Infectious Bovine Rhinotracheitis) and genital tracts (infectious pustular vulvovaginitis/balanopostitis), conjunctivitis, encephalitis, abortion, infertility, mastitis, enteritis, dermatitis. There is also a systemic form that affects visceral organs in newborn calves (91–93). The total seroprevalence of BoHV-1 in unvaccinated cattle in Iran is 402% (95% CI= 32.3–48.6) at the animal level and 75.5% (95% CI= 63.9–84.2), at the herd level. Some investigations using PCR reported the prevalence of abortion caused by BHV-1 in bovine is between 6.8 to 13.3%, indicating that BHV-1 could be a significant cause of abortion in the cattle population in Iran (90,94).

3.5.3.3. Bluetongue Virus

Bluetongue is an infectious but non-contagious disease caused by an Orbivirus of the family Reoviridae,which is mainly transmitted by insects. It can cause erosions in mouth, nasal mucosa, limbs, as well as abortion in affected animals. In the pregnant ewes,it may lead to abortion, fetal mummification, and the birth of weak lambs with potential congenital defects (95,96). The infection is widespread in Iran,with high seroprevalence among unvaccinated sheep (50.4% (95% CI= 43.5–57.2%)) and goat (79.9% (95% CI= 70.7–85.8%)) at animal level (97). The only study conducted on the occurrence of abortion owing to bluetongue in Iran was conducted by Mahzounieh *et al*., (2014),who detected no positive cases in 50 aborted lambs using RT-PCR in Chaharmahal and Bakhtiari and Isfahan provinces (98).

3.5.3.4. Border Disease Virus

Border disease is caused by Border Disease Virus (BDV), a pestivirus belonging to the Flaviviridae family, and is closely related to Bovine Virus Diarrhoea Virus (BVDV). The disease is characterized by abortions, congenital abnormalities, and stillbirths, the birth of small weak lambs and persistent infections of offspring in sheep and goats flocks (99,100). Some serological investigations have been conducted on the presence of BDV antibodies in different regions of Iran, showing individual prevalence of 3.2-79.5% in sheep and 64.0-70.9% in goats. However, there are only one RT-PCR studies on BDV as an aborted agent in sheep in Iran. Mokhtari and Manshoori (2017) investigated the role of this viral infection in sheep abortion in Chaharmahal va Bakhtiari province, determining that 9 (9.0%) out of 100 samples were BDV -positive (101).

3.5.3.5. Bunyavirus

Several Bunyavirus infections are potentially teratogenic and abortifacient in ruminants, including Akabane, Cache Valley, Rift Valley fever, Nairobi Sheep Disease and Schmallenberg viruses. In Iran, some surveys revealed the

presence of Akabane virus (102,103), Rift Valley fever virus (104) and Schmallenberg virus (105) in ruminants. However, none of these viruses were detected in aborted cases (106,107).

3.5.4. Fungal Infections

Mycotic abortions are normally sporadic, though they may occur at rates of 5–10% in some herds. The majority of mycotic abortions in cattle are caused by *Aspergillus fumigatus*. Infections by other *Aspergillus* spp., *Absidia* spp., *Mucor* spp., *Rhizopus* spp. and *Candida* spp. occur less frequently (60,108). There are not enough studies on mycotic abortion in Iran. Vandyousefi and Zoghi (1988) isolated mycotic agents from 50.5% (60/119) samples of bovine and ovine aborted fetuses. No other infection agents were found on microbiologic examination (109). Esmaeili *et al*. (2022) revealed the contamination rate of 1.5% at flock level by mycologic examination of abomasal contents of ovine aborted fetuses collected from various parts of Iran, (10).

4. Conclusion

This study reflects the current state of knowledge regarding infectious agents of ruminant abortion in Iran. However, this knowledge may not be exhaustive as it relies on available clinical and scientific reportssupplemented by the unpublished experiences of the authors in areas where data are scarce. Other infectious agents may be present in Iran because they have not yet been detected or included in published reportsfor various reasons. This information could open new opportunities for researching the eradication and control of agents that cause abortion in ruminants. Although occurrence of abortion in the ruminants in Iran has multifactorial etiologies, but the present study suggests that infectious diseases are a major risk factor in predisposing farm animals to abortion. Important putative infectious agents that cause abortion in sheep and goats include toxoplasmosis, chlamydiosis, brucellosis and coxiellosis in cattle include neosporosis, BVDV and BoHV-1. Several of theses pathogens are also zoonotic. Therefoe, regardless of whether there is a perceived incidence of abortion in the flock or herd, pregnant women should be advised to avoid contact with animals or dirty work wear from the ranching environment.
According to our findings, a well-defined control strategy for preventing and controlling infectious abortion in Iran should be based on further epidemiological studies of the causes of abortion, accurate recordkeeping, laboratory analysis, control of animal trafficking from neighboring countries and from one region to another within the country, the employment of good biosecurity practices that inhibit the introduction and spread of infectious causes of abortion, and the use of vaccination programs.

Acknowledgment

The authors would like to thank all the authors whose research papers are included in this literature review.

Authors' Contribution

Conception and research design: MH. Collection of data: MH and SA. Supervising and writing the draft of the manuscript: MH. All authors contributed to helpful discussions and approved the final manuscript.

Ethics

We hereby declare that all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

No grants were provided by funding agencies in the public, commercial, or not-for-profit sectors was provided for the present research.

Data Availability

The data that support the findings of this study are available from the corresponding author upon request.

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