REVIEW ARTICLE

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Current state of knowledge regarding bacterially-induced abortion in sheep

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Abstract

Introduction and Objective. Abortion can occur in sheep, among others, in response to bacterial infection. The present article reviews the latest reports on the various economic and health consequences for the herd, other animals and humans.
Review methods. Two independent reviewers searched in PubMed and Google scholar (any date to September 2021) for studies concerning bacterial abortion in sheep. Keywords for the search strategy were: bacteria, sheep, and abortion. Papers were reviewed for scientific merit and relevance as well as for current information.
Brief description of the state of knowledge. In the reviewed literature, much attention was paid to infections by Brucella spp., Campylobacter spp., Coxiella burnetti, Listeria spp., and Salmonella spp. As the presence of these bacteria varies according to region, any differential diagnosis should consider the most common pathogens in a given area. It also should be noted that most of the described pathogens have zoonotic potential and, as such, it is extremely important to observe safety rules when assisting in delivering births and when dealing with stillbirths.
Conclusions. Identification of the etiological agent seems to be a key factor in the management of abortions, especially in flocks where their numbers appear to be increasing; this is needed to manage and control disease in the flock, and to protect humans and other animal species on the farm. Most studies use molecular methods as diagnostic tools, mainly PCR, and use both foetuses and placenta as research material.

Key words

abortion, bacteria, Brucella spp, Campylobacter spp, Coxiella burnetti, ewes, Listeria spp, Salmonella spp, sheep

INTRODUCTION

In sheep, abortions can be caused by viral [1, 2] bacterial [3, 4] or parasitic [5, 6, 7] factors, as well as diet deficiencies [8], poisoning [9] and extreme weather conditions [10]. Furthermore, in addition to the significant economic losses [11], any deaths caused by zoonotic pathogens can also pose a risk to breeders, animal keepers or veterinarians [12].

OBJECTIVE

This paper aims to review the recent literature on abortions in sheep caused by bacterial agents such as *Brucella* spp. [13], *Coxiella burnetti* [14], *Campylobacter* spp. [15], *Helicobacter* spp. [16], *Mycoplasma* sp. [17], *Listeria* spp. [18] and *Salmonella* spp. [19], as well as other less common etiological agents [20, 21].

REVIEW METHODS

The PubMed and Google scholar (any date to September 2021) sites were searched for studies on bacterial abortion in sheep. The following keywords were used for the search strategy: bacteria, sheep, and abortion. In addition, the references in the articles were also reviewed to find potential additional articles. No formal meta-analysis or statistical analysis was conducted. Two reviewers independently extracted data. Papers were reviewed for scientific merit and relevance as well as for current information.

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BRIEF DESCRIPTION OF THE STATE OF KNOWLEDGE

***Brucella* spp.** Brucellosis is found worldwide and affects many species of animals as well as humans. *Brucella* spp. causes abortion and infertility in both livestock and wildlife [13]. In sheep, the most common etiological agent is *Brucella ovis,* known to be responsible for abortion in ewes, neonatal mortality in lambs and epididymitis in rams [22, 13]; in addition, the bacterium is transmitted sexually and can induce both subclinical and clinical infection [23, 24]. Another species known to cause abortion in sheep is *Brucella melitensis* [25, 26].

Recent data confirms that brucellosis remains an ongoing problem in sheep flocks. Endemic regions and flock size have been associated with a higher prevalence of *B. ovis* antibodies in flocks, while increased age, and certain types of breed, have been associated with seropositivity [27]. In addition, *B. melitensis* infection was more common in male than female foetuses [28]. Surprisingly, however, research conducted in Algeria found only an insignificant association between brucellosis seropositivity and abortion in sheep [29].

Recent data from sheep in Wyoming, USA, indicate 0.53% seropositivity in flocks and 22.5% among individual sheep [27]. Elsewhere, 0.71% seropositivity was noted in sheep in the Arabian Gulf [30] and 0% among 213 sheep tested in the Borana pastoral area in Ethiopia [31]. However, no new data has been obtained from other regions of the world, including Europe.

In addition to serological testing in live sheep, RT-PCR testing has been carried out on aborted foetuses. Although the latter has yielded positive results on occasion [32], RT-PCR demonstrated slightly lower sensitivity and specificity for diagnosing *Brucella* spp. in aborted foetuses compared to bacterial culture [33].

Recent studies have been performed with the aim of developing vaccines against *B. meltinesis* [34] and detecting virulence genes [35]. The findings may contribute to easier disease management in flocks.

Coxiella burnetti. *Coxiella burnetti* is a Gram-negative obligate intracellular bacterium which causes infections in a wide range of hosts, including sheep, and has zoonotic potential. Although domesticated ruminants are considered to be the primary reservoirs, ticks also play a role in transmission [36]. Infection is usually manifested as infertility, abortions and metritis [37]. *C. burnetii* are typically shed with secretions during parturition [38], and humans can become infected by inhaling contaminated aerosols and consuming unpasteurized dairy products [39]. It should be noted that during the initial phase of infection, the only available diagnostic tool may be serological investigation: recent studies suggest that *C. burnetii* shedding can remain undetectable after an outbreak, even in the absence of vaccination [40].

Interesting results have recently been obtained in a study of Q fever in sheep in a region of India. In this case, 38% of tested sheep were found to have a positive ELISA result, while 7% were found to be positive based on nested PCR testing of vaginal swabs. These findings suggest that Q fever may be still be real problem in sheep in this region of the world [41]. Studies have also revealed *C. burnetii* to be an important agent causing abortion in sheep and goats in Ethiopia [31, 10].

Following a recent outbreak of Q fever in The Netherlands [42], studies have been performed on small ruminants in some European countries. However, none of the studied groups demonstrated high seroprevalence, e.g. 11.4% in Portugal [43] and 5% in Switzerland [44]. Interestingly, real-time PCR quantification of *C. burnetti* indicated shedding rates higher than 104 bacteria/ g in 13.4% of 97 samples of aborted material from sheep and goats [44].

Higher prevalence scores have been noted in Asian countries. For example, IS1111 transposase gene amplification indicated a high percentage of positive sheep in Pakistan (46.9%) [45]. The seroprevalence of *C. burnetii* was found to be 19.5% in Iran in 2011–2012 [46], and 13.64% in the Lorestan province in the west of the country [47]. In Bangladesh, the seroprevalence in sheep was found to be 9.52%, which was higher than in cows and goats [48]. In contrast, in Saudi Arabia, the seroprevalence in sheep was the lowest of the three species, amounting to 5.8% [49].

Higher *C. burnetti* seroprevalence has been noted in sheep in parts of Africa. For example, seropositivity values of 28.4% have been recorded in Ghana [50] and 22.7% in Egypt [51]. By comparison, concurrent RT-PCR testing found 33.6% of the tested sheep to be positive [51].

***Campylobacter* spp.** In sheep, abortion can also be caused by *Campylobacter* spp.. The most common etiological agents are believed to be *Campylobacter fetus* subsp. *fetus, Campylobacter fetus* subsp. *veneralis* and *Campylobacter jejuni* [52, 53]. Lately, *C. jejuni* has replaced *C. fetus* as the predominant species in the US [54] this has been attributed to the expansion of a tetracycline-resistant *C. jejuni* sheep abortion (SA) clone [55] associated with antibiotic use. This clone is much rarer in the United Kingdom [53]. The SA clone has also been found to cause abortion in experimentally-infected sheep [56].

Campylobacter species have recently been labelled the most common abortigenic pathogen in Australia [18]. As these commonly cause abortion in sheep [57], there is a need to identify new treatment and prevention approaches [58]. For example, the administration of tulathromycin to pregnant *C. jejuni*-exposed ewes resulted in a reduction of abortions caused by *C. jejuni* [59]. New diagnostic techniques are being developed, such as those based on the use of fluorescence *in situ* hybridization (FISH) [60], and the course of pathogenesis is becoming better understood [52, 54].

***Mycoplasma* spp.** Mycoplasmas are the smallest bacteria discovered to-date. They lack a cell membrane and hence are resistant to antibiotics which target cell walls. A number of pathogenic species have been identified, including many which affect humans.

In sheep, *Mycoplasma*-induced abortion is most commonly associated with *Mycoplasma ovis* and *Mycoplasma agalactiae*, both of which only affect animals: neither are zoonotic. *M. agalactiae* is also considered to be the one of the main mycoplasmas affecting small ruminants, causing such ailments as mastitis or arthritis [61]. However, while it is not considered an abortifacient agent in itself, it has been found to cause abortion in chronically-infected animals [61]. *M. agalactiae* is also suspected of being the sole cause of Contagious Agalactia (CA). CA mainly causes chronic interstitial mastitis but has been found to be responsible for abortion in <15% of cases [62]. The condition has been reported in several countries, including India, Egypt and Iran, as well as in a number of European countries. The disease is also suspected to be present in the USA and Canada.

M. agalictiae was also found to be present in seven of 183 aborted sheep foetuses in Iran, with one being simultaneously infected with *Chlamydophila abortus*. The most important risk factors associated with infection and abortion were flock size (P=0.174) and vaccinations against *M. agalactiae* (P=0.029) [61]. While it might seem to be counter-intuitive for there to be more abortions in vaccinated flocks, it is possible that only the flocks at risk of contagious *M. agalactiae* infections were vaccinated. Unfortunately, no other studies on abortions caused by *M. agalactiae* could be identified.

A few studies have examined the influence on *M. ovis* on abortion, and most have only focused on infection rates in specific flocks. Nevertheless, a 2019 study in the United States identified *M. ovis* in three-quarters of tested flocks throughout the country, suggesting a possible association between *mycoplasma* infection and abortion rates [17].

Finally, a study in China suggests that *Mycoplasma* infections may also be influenced by breed: Deng et al. [63] identified 22.2% seropositivity in Hazake sheep and 8.3% in Suffolk sheep, with the overall abortion rate being 17.6%.

***Listeria* spp.** *Listeria* is a Gram-positive intercellular bacterium most commonly found in soil, water and food.

One species, *Listeria monocytogenes*, is responsible for listeriosis in humans and many animal species. The most common symptoms include headaches, fatigue and other flu-like symptoms, which in time can develop into sepsis, meningitis and encephalitis, and even result in death [64].

Another highly-pathogenic species is *Listeria ivanovii* which most commonly infects sheep, and occasionally other ruminants; infections in humans and other species are rare [65]. The species demonstrates a similar pathology to *L. monocytogenes*, associated with sepsis, enteritis and abortion; however, infection is often asymptomatic, with the only indicator being abortion.

Listeria infection can also occur though silage, particularly silage that has spoiled or is of poor quality [66]; indeed, sheep are commonly infected during cold and wet weather when silage is most susceptible to spoilage. *Listeria* is known to replicate well in poorly-fermented silage, i.e. with a pH above 5.5, and can reach extremely high CFU levels [67] In addition, *Listeria* can also breed in good-quality silage, being present in bedding and water [67].

Silage with a pH >5 was found to be the most common source of *Listeri*a infection in the United Kingdom, despite being responsible for fewer than 5% of total ovine abortions in the 2018 lambing season [68]. This rate has remained constant over time, with only 596 cases of ovine abortion diagnoses being attributed to *Listeria spp.* in the United Kingdom between 2002 – 2019 [69].

Abortions can result from *Listeria* haematogenously crossing the placental barrier, although vaginal transmission is also possible [67]. During late pregnancy, the risk of infection is thought to be increased by lower cell-mediated immunity. Such ovine abortions typically occur after week 20 of gestation [64].

Few studies have investigated *Listeria spp.* infections in ovine abortions in Europe; nevertheless, while this can still be a problem on individual farms, widespread infections are rare and seem to be generally under control.

In Australia, a study found 25% of ovine abortions investigated between 2000 – 2018 to be caused by *Listeria spp.* This was found to be the second highest cause of infectious abortion after *Campylobacter spp.* which was responsible for 32% of abortions [18]. In the State of Victoria, Australia, infections by *L. ivanovii* were found to account for at least 25 of 54 *Listeria spp.* cases, while *L. ivanovii* seems to be the most common species in alS states. It is not clear why *Listeria* infections are so common in Australia, nor why the prevalence is so high in Victoria State; however, many studies are based on small sample sizes and more research is needed in this area [18].

A study of 100 aborted ewes between April – October 2020 in Egypt [70] found 11 to be positive for *Listeria spp.* Of these, the highest frequency was observed for *L. ivanovii* (36.8%), followed by *L. monocytogenes* (31.6%), *L. innocua* (21.1%) and *L. grayi* (10.5%).

Similarly, a 2019 study found older ewes seemed to be more susceptible to abortions caused by *Listeria spp.* Of the total number of ewes which aborted due to listerosis, 8.3% were under the age of two years, 15.1% were aged two to three years, and 23.3% were older than three years [71]; the authors also note that some breeds appeared to be more susceptible to infections than others. However, contradictory results have been obtained in other studies [70] and more research is also needed in this area. Despite this, Shehab & El-Ash, also note a correlation between *Listeria spp.* infection and type of housing: 23.1% of the affected ewes were kept in closed sheep houses and only 6.8% in open sheep houses. This is in line with current knowledge about *Listeria spp.* and its behaviour.

***Salmonella* spp.** Several strains of *Salmonella* can also cause abortions in sheep, including *S. abortusovis, S. Arizona, S. Dublin* and *S. Typhimurium*. Such cases have been recorded worldwide. One study based on aborted placental tissue from a flock in Connecticut, United States, obtained whole-genome sequences, genotypic virulence and phenotypic and genotypic antibiotic sensitivity data for *S. enterica* subspecies *diarizonae* serovar 61:(k):1,5, and completed a comparative sequence analysis to examine its zoonotic potential. This subspecies is believed to be the most common serotype identified in sheep [72]. Although none of the tested isolates were resistant to any of the tested antibiotics, they contained genes associated with antibiotic resistance. Similar results have also been obtained in other flocks in other countries [72, 73, 74]. Two more studies, one in China [66] and another in Iran [28] reported a low prevalence (~1%) of *Salmonella spp.* infections in regions where abortions were occurring.

Vaccines against *Salmonella spp.* are under development, with some already available [75, 76]. García-Seco et al. [76] found a new inactivated vaccine against *S. abortusovis* to significantly reduce the risk of abortion associated with infection, as well as bacterial shedding by infected ewes.

Some less common bacteria can also cause abortion in sheep, one of which is *Helicobacter*: a genus known to infect sheep and to demonstrate zoonotic potential [77]. Some limited studies suggest that the predominant species in sheep is *Helicobacter canis* [77], while others indicate that sheep might be natural hosts of *Helicobacter pylori* [78]. Although little is currently known about the impact of *Helicobacter* infection on abortion in sheep, *Helicobacter bilis* and *Helicobacter trogontum* have been found to be potential agents in New Zealand [16].

Some cases of *yersinia* have been identified in aborted ovine foetuses in the United Kingdom, Australia, Sweden, Italy and The Netherlands, among others [79, 80, 18]. Clune et al. [18] reported eight *Yersinia* spp. ovine abortions between 2000 – 2018 in Australia; in these cases, *Y. enterocolitica* and *Y. pseudotuberculosis* were identified in the tested samples, either separately or together.

Some cases of abortion have also been associated with *Francisella tularensis* infection. These cases were associated with an increased number of ticks on sheep in season, and the main consequence of tularemia was late miscarriage or lethargy and death in lambs [21]. In endemic areas, tularemia should be considered in the differential diagnosis when examining late abortions or outbreaks of fatal disease in young lambs, especially in years of high tick activity and occurrence of characteristic necrotic lesions in the spleen, liver and lungs.

CONCLUSIONS

This brief review indicates that in addition to *T. gondii*, bacterial agents play a significant role as abortion-causing agents in sheep. It should be noted that most of the described pathogens also have zoonotic potential and,as such, it is extremely important to observe safety rules when assisting in delivering births and dealing with stillbirths. Identification of the etiological agent plays a key role in the management of abortions, especially in cases where their number is increasing in the herd. This is also important for the management and control of disease in the sheep herd and for taking appropriate steps to protect humans and other animal species in farm. The main diagnostic tools are molecular methods, particularly PCR, and both the foetus and placenta should be collected for analysis.

Housing type and diet also seem to play an important part in the spread of pathogens, especially *Listeria spp.* Countries with a high standard of animal welfare, where animals are housed and allowed to graze outside, demonstrate significantly lower infection rates and abortions; in addition, access to correctly-prepared and stored silage is also important. Aside from the welfare aspects, a potential correlation appears to exist between climate and infection rates; this could be a possible explanation for the high rates of *Listeria spp.* infections in Australia and Asia compared to Europe.

Many vaccinations are already in use or are currently being developed which are welcome tools for preventing abortions. However, other precautions should be taken, especially if not all animals are vaccinated or if animals are moved between flocks. Eliminating any potential sources of infection is essential, even in vaccinated flocks. Some studies suggest that abortion and infection rates could be breed-dependent, with some breeds showing higher infection rates than others; however, while there is some evidence to support this, the tendency could vary according to the tested pathogen and testing conditions, and more research is needed in this area.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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