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Interactions between parasitic infections and reproductive efficiency in sheep

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ABSTRACT

This review article summarises the many reports in the literature, confirming that, in sheep, parasitic infections can adversely affect reproductive efficiency; examples, which refer to all parts of the reproductive cycle of sheep, are as follows: trichostrongylosis in ewe-lambs (which can lead to delayed attainment of puberty), myiosis of the prepuce (which can cause impediment of mating), chorioptic mange or trypanosomosis in rams (which can lead to testicular degeneration or azoospermia, respectively), trypanosomosis or sarcoptic mange in pre-conceptual ewes (which can lead to poor conception rates or reduced number of ovulations, respectively), toxoplasmosis or neosporosis in pregnant ewes (which are causes of abortion), trichostrongylosis or trematode infections in lactating ewes (which can cause reduction of milk yield and can be a risk factor for mastitis, respectively), cryptosporidiosis in newborn lambs (which can be a cause of deaths), coccidiosis in growing pre-weaned lambs (which can cause suboptimal growth rate). In other cases, the reproductive status of the animal can influence the parasitic infection; examples are as follows: the increase in faecal parasitic output during the peri-parturient period (as a consequence of the peri-parturient relaxation of immunity), the heavier trichostrongylid infections of twin lambs compared to lambs from single parities (as a consequence of developmental origin issues in twin lambs). All the above examples support the idea of presence of interactions between parasitic infections and reproductive efficiency in sheep.

1. Introduction

In sheep, 'reproductive efficiency' includes the ability of ewes to ovulate, be mated, conceive with semen from fertile rams, carry foetuses to term and, finally, lamb live-born lambs, which will be weaned in the appropriate time at an optimal bodyweight. The term implies efficient conception through active gametes, uninterrupted pregnancy, normal delivery of the newborn(s) ('eutocia'), unimpaired lactation of the ewes and survival and optimal growth of the lamb(s). In sheep flocks, increased reproductive efficiency is the cornerstone for profitability; the naturally occurring anoestrus period (the duration of which differs according to the location of flocks) can impede the reproductive efficiency. Hence, maintenance of high reproductive performance of sheep should be a priority for everybody involved (Amiridis and Fthenakis, 2012).

Parasitic infections are widespread in sheep (Papadopoulos and Fthenakis, 2012). A variety of endo- or ecto-parasites can affect these animals and their adverse effects on health, production and welfare have been repeatedly documented (Taylor et al., 2007; Sargison, 2009).

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Within this frame, trichostrongylid gastrointestinal infections currently are among the major challenges in sheep health management, due to the widespread anthelmintic resistance in many parts of the world (Papadopoulos et al., 2012; Torres-Acosta et al., 2012), which increases potential adverse effects in health and welfare of animals.

The present paper reviews and discusses interactions between parasitic infections and reproductive efficiency in sheep. The article focuses only on direct effects of parasites on the reproductive efficiency of sheep. Nevertheless, it is noteworthy that many arthropods (flies, midges, ticks, etc.) can transmit various infective agents, which may adversely affect the reproductive efficiency of sheep. Examples of such agents include *Anaplasma phagocytophilum* (Stuen and Longbottom, 2011), as well as various viruses, e.g., the Bluetongue virus (Osburn, 2007), the Rift Valley Fever virus (Bath, 2007) and the Schmallenberg virus (Lievaart-Peterson et al., 2012), which have a foetopathic and/or abortifacient effect. In this article, the topics are organised in a pattern according to the reproductive cycle of small ruminants.

2. Attainment of puberty by ewe-lambs

Puberty is the end point of a series of events affecting the development of the 'hypothalamo–pituitary–gonadal' axis leading to reproductive competence. From a practical point of view, puberty for females is the age at which the animal can support pregnancy to term. Puberty is a complex mechanism involving primarily the reactivation of the gonadotropin-releasing hormone (GnRH) secretory system, affected by various factors (Senger, 2003; Ebling, 2005). Among those, energy-deprived animals have been found to have a delayed puberty that has been attributed to a lesser frequency of GnRH pulses and accordingly of luteinizing hormone (LH) pulses (Foster and Olster, 1985; Foster et al., 1985; I'anson et al., 1997; Polkowska et al., 2003). The age at which ewe-lambs are mated, is crucial for productivity of a flock, since cost is high for maintaining unbred animals in a flock. Management of ewe-lambs for enhanced reproductive performance requires increased energy availability. This can be achieved by either increasing energy intake by the animal (i.e., availability of high-energy ration or increased quantity of feed) or by reducing its energy drains (e.g., anthelmintic treatment) (Valasi et al., 2012). Possibly therefore, parasitic infections can have an effect in attainment of puberty through interaction with energy intake as discussed herebelow.

There is evidence that parasitic infections, specifically gastrointestinal trichostrongylid (Mavrogianni et al., 2011) or *Trypanosoma congolense* (Osaer et al., 1999) infections, can adversely affect onset of puberty and age at first lambing by depressing weight gain of affected animals. Administration of a long-acting nematocide anthelmintic, which effectively protected treated ewe-lambs for up to 85 days post-ram introduction, allowed treated animals to exhibit their full reproductive potential during that time (Mavrogianni et al., 2011). Treated ewe-lambs showed earlier reproductive activity, as expressed by short 'interval to first mating after ram introduction' and increased 'cycling rate'; this resulted in significantly younger 'age at first mating' (Mavrogianni et al., 2011). Anthelmintic-treated ewe-lambs reached heavier bodyweight, which is a determinant for puberty in sheep (Valasi et al., 2012); thus, they were mated and conceived earlier than untreated controls. There are also similar findings in cattle, showing that nematode-infected heifers reach puberty with a delay compared to uninfected animals (Díaz-Torga et al., 2001).

3. Mating

Genital myiosis caused by various dipteran insects, can lead to vulvar oedema and subcutaneous fistulae around the vulva in ewes and to difficult/partial exteriorising of penis and markedly thickened prepuce with subcutaneous fistulae along the tissue in rams (Fragkou et al., 2013). These lesions can impede mating. Development of myiosis lesions takes place during the summer months (Wall, 2012). At para-Mediterranean areas and other locations of similar (north hemisphere) or of respective (south hemisphere) geographical latitude, summer months coincide with the sheep reproductive season; at more northern (north hemisphere) or more southern (south hemisphere) latitudes, they precede that period (Abecia et al., 2011, 2012).

Tick predilection for the genital organs (vulvar mucosa, scrotum) of sheep has been reported (Fourie and Kok, 1995; Mbuh et al., 2008) and may be responsible for local nuisance and/or inflammatory reaction, which may also adversely affect mating. One may also suggest that ectoparasitic infections with intense pruritus (e.g., heavy lice infestation, mange) could lead to reduced mating activity of rams, as these animals would be busy scratching rather than being sexually active.

4. Testicular function

Ridler et al. (2012) have proposed that parasitic diseases can affect the scrotal circumference of rams and that parasite control is important for keeping rams sound for breeding. Scrotal circumference in rams has been associated with their reproductive performance (Kafi et al., 2004; Gouletsou and Fthenakis, 2010). However, Gaglio et al. (2010) have not identified a significant effect of gastrointestinal trichostrongylid infection to semen parametres in rams.

(Rhodes, 1975, 1976) has presented evidence that extensive chorioptic mange in the scrotum of rams led to reduced quality of their semen, due to seminal degeneration, as a consequence of long-standing increased intra-scrotal temperature due to the inflammation; semen quality was restored after cure of the skin lesions. Lopes et al. (2009) have identified that *Toxoplasma gondii*-infected rams have produced smaller volumes of ejaculate than healthy animals, whilst Sangare et al. (2010) have reported azoospermia in *Tr. congolense*-infected rams. Finally, Sarasa et al. (2011) have reported that sarcoptic mange can cause reduction of the testicular mass in *Capra pyrenaica* (a wild small ruminant); these findings may have implications for sheep, in which species sarcoptic mange is a significant health problem (Doukas et al., 2007).

Moreover, parasitic agents may be transmitted through the semen of rams. *T. gondii* shedding has been identified in the semen of rams (De Moraes et al., 2010a,b) and the possibility for transmission of the parasite to ewes during mating has been described (De Moraes et al., 2010a,b) depending on the tachyzoite content of semen. In a recent study, DNA of *Neospora caninum* was detected in the semen of experimentally infected rams (Syed-Hussain et al., 2013), although none of the ewes mated with those rams developed the disease.

No relevant studies are available regarding *Besnoitia* infection of rams. Nevertheless, experimental work performed in bucks has indicated that *Besnoitia caprae* can affect their genital system, with cysts of the protozoon identified in the testicular parenchyma and the scrotum (Oryan et al., 2011). Other clinical studies have indicated that *Besnoitia besnoiti* can affect the testicular parenchyma and scrotum of bulls (Sekoni et al., 1992; Dubey et al., 2013), leading to reduced libido and suboptimal semen quality, although in subsequent studies the protozoon could not be detected in the semen of affected bulls (Esteban-Gil et al., 2014).

In general, there is still little published evidence to corroborate an adverse association between parasitism and testicular function (which is reflected in semen quality), although available results point out to that direction. Possibly, parasitic infections can directly affect semen quality of rams and, hence, influence conception rates in a flock. Alternatively, changes in testicular function can lead to reduced production of testosterone, which is a determinant of a ram's sexual behaviour and social ranking within a flock (Parkinson, 1996); this may lead to changes in social interactions and behaviours during mating period. All the above can affect conception rates in a flock, especially if the ram:ewe ratio is at the lower acceptable level or if reproductive management techniques are applied in the flock. This is an area where further work will elucidate mechanisms and potential interactions between parasitism and reproduction.

5. Number of ovulations and conception

The period immediately before and around conception is a potentially vulnerable period. During that period, adverse developmental origin of the foetus might initiate, as the result of reduced availability of nutrients to the female animal (Fleming et al., 2012). The significance of increased energy available to ewes in the pre-conception period has been recognised for a long time (Clark, 1934; Walkden-Brown et al., 1999; Dobson et al., 2012). Increased energy is provided to ewes by means of modifying the nutritional regime in the period before ewes would be put with rams for mating. At the start of the mating season, ewes should have a body-condition score of '3' to '3.5' on the five-point scale (Lovatt, 2010). 'Flushing' consists of administration of an additional quantity of concentrate feed mixture, on top of the ration administered to cover maintenance requirements of the animals and should commence at least 35 days before start of the mating period; that interval is equivalent to the length of two full oestrous cycles of sheep. In animals with appropriate body-condition score, this increased energy feeding aims to producing higher ovulation numbers, leading to greater number of lambs born per ewe. In animals at lower body condition score, there is a benefit to other reproductive parametres (e.g., earlier start of the annual reproductive activity, improved cycling and lambing rate), but no significant improvement in their fecundity (Heasman et al., 1998; Fthenakis et al., 2012).

The converse is also true. Poor body condition of ewes is associated with reduced fertility, characterised by delayed oestrus development and reduced 'cycling rate' in a flock. Ovulation rates decrease as body condition score of the animals deteriorates (Dobson et al., 2012), whilst embryo mortality at the early stages of pregnancy is higher in undernourished animals (Gunn and Doney, 1975). In general, decreased energy availability around the peri-conceptional period, depresses reproductive performance of extensively (Hill Farming Research Organisation, 1979) or intensively (Orskov, 1982) managed sheep and leads to reduced cyclic activity, reduced ovulation rates and suboptimal ova survival, as well as increased risk of early embryonic deaths (Gunn, 1967). Decreased energy availability at the post-conception period leads to compensatory changes in the gravid uterus later in pregnancy, e.g., increased vascular density of the placentomes (Zhu et al., 2007), which in turn can lead to higher risk of foetal infection with parasitic abortifacient agents (Section 6.1), especially in multiple pregnancies; health of the lamb(s) after birth is also adversely affected (Fleming et al., 2012).

Lambs from multiple parities were found to be more heavily infected with trichostrongylids than lambs from single parities (Hayward et al., 2010). Twin foetuses develop a between-them competition for nutrients, are enveloped by a smaller placenta than single foetuses and live in a restricted physical space (Fthenakis et al., 2012). The findings of Hayward et al. (2010) are in line with the 'Developmental Origins of Health and Disease' concept (formerly known as foetal programming or the Barker hypothesis), which implicates early *in utero* development and the maternal environment experienced during that period as being of significance to development of disease in adulthood (Fleming et al., 2012).

The most significant energy-drain of clinically healthy sheep is parasitism by gastrointestinal helminths. The effects of these parasites in reducing energy availability for their hosts have been well documented (Coop and Kyriazakis, 1999). These authors have proposed that gastrointestinal nematodes can reduce nutrient availability to the host, through a reduction in voluntary feed intake and/or a reduction in the efficiency of absorbed nutrients; the relative contribution of each of these two mechanisms depend on the species of parasite and its location in the gastrointestinal tract (Coop and Kyriazakis, 1999). With regard to trematode infections, reduced feed conversion efficiency, present even in low burden infections (Hawkins and Morris, 1978), as well as depressed appetite and feed intake, also occurring in these helminthoses (Taylor et al., 2007; Rojo-Vázquez et al., 2012), contribute to decreased energy availability for affected sheep.

It thus becomes evident that parasitism by the above helminths may affect reproductive efficiency in ewes during the peri-conception period, mostly through the decreased energy availability for the animals. The precise adverse effects can vary depending on the level of parasitism and the general condition of the animal. It is also noteworthy that reduced feed intake occurring in such cases, would reduce the benefits of supplementation with high-energy feed before mating ('flushing'), as animals would not benefit from all energy provided.

Similar results have been published in cases of *T. congolense* infection (Osaer et al., 1998). Affected animals showed lower rates of conception and pregnancy and had lower concentrations of progesterone, which is a major factor in establishment of pregnancy, with a function to synchronise development of the maternal endometrium with intrauterine arrival of the embryo (Wilmut and Sales, 1981; Lawson and Cahill, 1983). As an association between luteal phase progesterone blood concentrations and embryo survival has been suggested (Noakes, 1996), perhaps the reduced progesterone levels may be responsible for the conception problems in affected ewes.

Fthenakis et al. (2001) reported that *Sarcoptes scabiei*-infested ewes had fewer ovulations than uninfested animals and attributed that to nutrient availability at the pre-conception period. Nevertheless, when progesterone and equine chorionic gonadotrophin were administered exogenously, no differences were evident between infested and healthy animals. This indirectly suggests reduced hormone concentrations in the parasitised animals during the peri-conceptional period, which lends further support to the idea of sarcoptic mange influencing embryo implantation and survival.

In sheep, there are no reports directly associating quality of female gametes (ova) with parasitism. Nevertheless, some relevant results have been published in cattle. *Tritrichomonas foetus* has been reported to damage oocytes (Benchimol et al., 2007). Also, *N. caninum* has been detected in bovine follicles during assisted reproduction manipulations (Silva et al., 2012), as well as in bovine foetuses (Marques et al., 2011), although there are reports suggesting that embryo transfer is a safe method to avoid vertical transmission of these protozoon (Landmann et al., 2002; Moskwa et al., 2008). These implications should be borne in mind, as assisted reproductive technologies for sheep are developing and being applied in larger numbers of animals (Amiridis and Cseh, 2012).

In view of the above, one should consider the strategic administration of anthelmintic drugs before the start of the mating period, with a view to improve reproductive efficiency. In fact, Mavrogianni et al. (2011) have reported that ewes given a broad-spectrum long-acting anthelmintic before the start of the mating period had a higher 'cycling rate' reflecting better functionality of the genital system of the treated animals and higher 'total lambs born per ewe' and 'liveborn lambs per ewe' indicating increased number of ovulations during the peri-conceptional period. In dairy-type production systems, anthelmintic administration at the pre-conception period (which coincides with the end of a lactation period) would also contribute to maintaining a longer persistency of lactation (another energy-dependent function), although drug withdrawal periods (Athanasiou et al., 2009) should be taken into account when designing strategic treatments. Finally, anthelmintic administration before the mating season has the added advantage of avoiding the inadverted administration of albendazole or netobimin, broad-spectrum anthelmintics with confirmed embryotoxic properties (Delatour et al., 1981; Navarro et al., 1998), to ewes at the first stage of pregnancy.

As sheep have a seasonal pattern of reproductive activity, depending on the geographical latitude, the pre-mating period would also differ according to location. Hence, administration of anthelmintics at that period would have differing effects from a parasitological viewpoint, resulting from the difference in season. This should be taken into account when strategic treatments are carried out at the pre-mating period. Furthermore, one should have in mind the possibility of promoting anthelmintic resistance that way and should consider an appropriate cost-benefit analysis.

One should always take into account that in para-Mediterranean areas and locations of similar latitude (in the north hemisphere), as well as in locations of respective latitude in the south hemisphere, reproductive activity of sheep would start at the beginning of the summer (hence, anthelmintic administration should be planned for late spring). Moreover, in more northern (north hemisphere) or more southern (south hemisphere) areas, reproductive activity of sheep would start in the autumn (hence, anthelmintic administration should be planned for late summer).

6. Pregnancy

6.1. Foetopathic effects of protozoa

Foetopathies and abortions are significant problems in pregnant ewes and major sources of financial losses in sheep flocks (Menzies, 2012). Various protozoa can cause abortion in ewes.

The principal problem by parasites in pregnant ewes is toxoplasmosis, caused by the intracellular protozoon *T. gondii*, which is a confirmed abortifacient agent (Buxton and Rodger, 2007). Ewes often become infected through consumption of oocyst-contaminated concentrate feed, given to the animals as an energy-supplement (Buxton and Rodger, 2007). If infection takes place before the 61st–80th day of gestation, embryonic death occurs, followed by absorption or expulsion of small embryos, rarely being noticed. If infection takes place later, up to the 110th–115th day of gestation, then abortion takes place. Finally, if infection takes place after that, congenitally infected lambs are born. In embryos, the organism causes coagulative necrosis in the placental cotyledons, as well as microglial foci, representing an immune response (Buxton and Rodger, 2007). Toxoplasmosis has been well-studied around the world, with many scientific references describing all aspects of the disease (Buxton and Rodger, 2007; Dubey, 2009).

Neosporosis, caused by the protozoon *N. caninum*, is an emerging reproductive problem in ewes; many facets of the disease still remain unclear (Dubey and Schares, 2011). In the initial literature, the infection had not been always associated with abortion (Otter et al., 1997; Chanton-Greutmann et al., 2002), despite evidence showing the abortifacient role of the organism in experimental infections (Buxton et al., 1998, 2001). Progressively, however, reports from various parts of the world have associated the parasite with abortion in ewes (Masala et al., 2007; Spilovská et al., 2009; Howe et al., 2012; Moreno et al., 2012), although frequency and clinical significance of the problem require further elucidation (Dubey and Schares, 2011). The organism establishes itself in the maternal caruncular septum, before crossing to the foetal placental villi. A direct foetopathic effect of the organism has been described to be the cause of abortion (Innes, 2007; Gibney et al., 2008), although further studies are necessary to fully clarify the pathogenesis of the infection.

Other protozoa that have been reported with an abortifacient role, include *Sarcocystis ovicanis* (*S. tenella*), *S. arieticanis*, *Trypanosoma brucei* subsp. *brucei*, *T. congolense*, *T. vivax* and *Theileria* spp. (Buxton, 1998; Heckeroth and Tenter, 1998; Bawa et al., 2000; Nagore et al., 2004; Batista et al., 2009).

6.2. Peri-parturient rise in faecal parasitic output: Pre-partum period

The relaxation of acquired immunity to parasites around lambing and its consequences have been well documented (Armour, 1980; Gibbs, 1986; Barger, 1993). This is manifested with a rise in faecal parasitic output and had initially, for nematode infections, been associated with increased prolactin concentrations. Fleming, 1993, 1996) investigated the potential role of prolactin and prostaglandin $F_{2\alpha}$ (two hormones, the concentrations of which increase at the end of pregnancy); they found that total egg production by *Haemonchus contortus* in infected sheep increased after administration of prolactin, but not after 'administration of prostaglandin $F_{2\alpha}$, to those animals.

Prolactin is a peptide hormone, responsible for initiating and sustaining lactation in ewes (Castro et al., 2011). It acts in a cytokine-like manner and as an important regulator of the immune system (Rovensky et al., 1991). Blood concentrations of prolactin in pregnant ewes start to increase from the 115th–135th day of gestation (Banchero et al., 2006). Beasley et al. (2010a,b) reported that, in ewes experimentally infected with *Trichostrongylus colubriformis*, the rise in faecal egg counts at the end of pregnancy had been preceded by a decrease in the immunological competence of the ewes; this was shown by reduced numbers of circulating eosinophils and by decreased total antibody and IgG_1 titres. The changes coincided with increased prolactin concentrations at the end of pregnancy, but, nevertheless, the authors considered that they were unrelated to hormonal effects; this confirmed a similar earlier hypothesis by Coop et al. (1990). As significant differences have been reported in blood concentrations of prolactin according to season (Gomez Brunet and Lopez Sebastian, 1991), the peri-parturient rise in faecal parasitic output should have differed in accord with time of the year. According to Coop and Kyriazakis (1999), this relaxation of immunity and the ensuing increase in faecal egg counts appear to have a nutrition-based background. Under the conditions of high metabolic demand, which occur at the end of pregnancy, susceptibility of ewes to gastrointestinal parasites is increased (Kahn et al., 2003). Finally, Coop and Kyriazakis (1999) proposed a nutritional, rather than an endocrinological, involvement in the relaxation of immunity during that period and presented the following arguments: (a) grade of immunity expression in pregnant ewes is consistent with the reproductive effort, i.e., the number of foetuses borne, (b) termination of pregnancy leads to abrupt restoration of immunity and (c) nutritional management of pregnant ewes can alter the time of first observation of the relaxation. Beasley et al. (2012) reported that feeding ewes a low quality diet resulted in a peri-parturient rise in faecal parasitic output starting 24 days before lambing and increasing substantially thereafter, whilst in ewes fed a high quality diet there was only a short rise of small magnitude; these findings lend further support to the above theory.

A peri-parturient increase of oocyst/cyst output has also been recorded in *Cryptosporidium* (Xiao et al., 1994; Ortega-Mora et al., 1999) and *Giardia* (Xiao et al., 1994) infections of pregnant ewes. In both cases, the authors recorded an increase of oocyst/cyst numbers in faeces of pregnant ewes, as well as an increase in the number of ewes, which excreted oocysts/cysts in their faeces.

Perhaps, a combination of all above factors may determine the whole process. The parasites can also play a role in increasing the metabolic pressure in pregnant ewes. The increased parasitic output during the pre-partum period has significant consequences for the epidemiology of the respective diseases. Lambs are born in a contaminated environment and, thus, are exposed to the infective forms of the various parasites at a very young age.

6.3. Metabolic problems caused by parasitic infections

In sheep, pregnancy is a metabolically demanding period. During the first 100 days of pregnancy, there is a slow foetal growth (Blanchart and Sauvant, 1974; Economides and Louca, 1981); during the second month of pregnancy, when foetal attachment has been established and placental growth has been completed, foetus(es) can acquire up to 15–25% of their future birth bodyweight; finally, at the last stage of pregnancy, the ovine foetus(es) can develop rapidly, to acquire up to 75–80% of their future birth bodyweight (Fthenakis et al., 2012). Hence, energy requirements of pregnant ewes increase, as the end of pregnancy is approaching. In the final month of gestation, protein requirements of pregnant ewes also increase, due to foetal requirements and the need to prepare colostrum in the mammary glands (Fthenakis et al., 2012). The situation may be aggravated in cases of heavy parasitic infections, as parasites increase the energy requirements of their hosts (Coop et al., 1977; Dakkak, 1990), as well as protein synthesis by the host, and consequently protein requirements, due to tissue invasion and damage (Solomons, 1993).

Recently, Papadopoulos et al. (2013) have shown that trematode infections (*Fasciola hepatica* and *Dicrocoelium dendriticum*) in pregnant adult ewes led to increased β-hydroxybutyrate concentrations in blood, thus indicating a potential association between trematode infections and pregnancy toxaemia. The authors attributed that on the direct effects that trematodes exert on the liver of affected sheep, as well as on the general energy drain effects of parasitism on the pregnant animals; they suggested that in flocks where many risk factors for pregnancy toxaemia would accumulate (e.g., suboptimal feeding), synergistic effect of those, coupled with trematode infection, could lead to clinical cases of pregnancy toxaemia.

Valderrábano et al. (2006) took the opposite approach and reported that increased feeding allowance during pregnancy resulted in improved response of pregnant sheep against *H. contortus* infection. The findings support the idea that response of pregnant ewes to parasitic infections during pregnancy may be enhanced by increased nutrition planes in the earlier stages (Valderrabano and Uriarte, 2003).

Potential metabolic problems caused by parasitic infections are expressed, ultimately, in the birth bodyweight of lambs born. Osaer et al. (1999) have reported that lambs born from *T. congolense*-infected ewes were of smaller bodyweight than those born from healthy animals. Moreover, Gatongi et al. (1997) and Fthenakis et al. (2005) have administered a nematocidal treatment to ewes at the end of pregnancy and found that birthweight of lambs from treated ewes was higher than that of lambs from untreated animals.

6.4. Foetopathic effects of antiparasitic drugs

Albendazole and the respective pro-benzimidazole, netobimin, have a confirmed teratogenic effect to sheep embryos, causing skeletal, renal and/or vascular malformations (Navarro et al., 1998), when administered to ewes during the first stage of gestation. Active metabolites of these drugs can cross the placenta and reach the foetal blood circulation (Capece et al., 2002). Often, the affected foetuses are absorbed or expelled, so ewes will be seen as barren animals at the end of the lambing season. Consequently, if there is a need for administration of these drugs, they should be given before start of the mating period, as pre-conception administration of the drug does not appear to cause a foetopathic effect during the subsequent pregnancy (Teruel et al., 2011). Otherwise, anthelmintic drugs with no foetopathic effects must be used. The precaution should extend to later stages of the breeding season, if rams remain with ewes for a long period of time, as there is always the possibility for some ewes to have been mated later in the season (Fthenakis et al., 2012).

Levamisole has also been reported to potentially cause abortion if administered in late pregnancy (Braun, 1997), hence, it should better be avoided at that period.

7. Lambing

Tissue lesions caused by genital myiosis may result to development of connective tissue in the vaginal and vulvar regions; these lesions can cause dystocia at lambing, due to possible foetomaternal disproportion, as a result of the lesions narrowing the birth canal (Arthur and Bee, 1996). Also, presence of connective tissue can lead to difficulties in dilatation of the birth canal, which may also lead to dystocia. Dystocia may also occur in cases of births of malformed embryos, formed consequently to albendazole/netobimin administration at the first stage of pregnancy (Section 6.4). Finally, Leontides et al. (2000) have postulated that *D. dendriticum*-infection may act as a risk factor for retention of foetal membranes in ewes during the subsequent lambing; they attributed the effect to the reduced energy availability of parasitised ewes, which may affect leucocyte function of ewes, a determinant of placental retention (Azawi, 2008), that way potentially associating the parasitic infection with the increased incidence of the reproductive disorder in ewes.

8. Lactation

8.1. Peri-parturient rise in faecal parasitic output: Post-partum period

The increase in faecal parasitic output ('peri-parturient egg rise') continues after lambing and contributes to lambs for acquiring the infective forms of the various parasites at a young age. Beasley et al. (2012) found that increased parasitic output from infected ewes was evident for up to 1.5 months after lambing, but, again, suggested that an association with endocrinological factors was unlikely (bar, possibly, a potential role for cortisol), concluding that some other factor(s) would be contributing to the relaxation of immunity to nematodes and the consequent increase in faecal parasitic output during the post-partum period (Beasley et al., 2012).

8.2. Milk yield and milk composition

Suarez et al. (2009) and Cruz-Rojo et al. (2012) have documented that gastrointestinal nematode parasitism can cause 10–15% reduction in milk yield of affected ewes, as well as shorter persistency of lactation. Anthelmintic treatment has also been found to increase milk production (Rinaldi et al., 2007). More specifically, Fthenakis et al. (2005) and Cringoli et al. (2009) have reported that administration of an anthelmintic with a long persistent activity at the final stage of pregnancy, resulted in a significant (up to 40%) increase in total milk production throughout the subsequent lactation period. Finally, Fthenakis et al. (2000) have identified a lower milk production in ewes with sarcoptic mange: up to 18% compared to healthy animals.

The situation regarding potential effects on milk composition is not clear. Cruz-Rojo et al. (2012) have described that milk from ewes with gastrointestinal nematode parasitism had lower fat and total protein content during the last stage of lactation, but Sechi et al. (2010) have not found a significant effect of parasitism on milk composition.

It is clear that parasitism leads to reduction in milk production of affected animals. The above studies have been carried out in dairy breeds, with a view to estimate milk production and financial effects of parasitism for dairy farmers. Results of direct studies of potential milk yield reduction due to parasitism, in the growth of lambs of the affected ewes are not available and can only inferred from the above reports. Reduced milk yield of ewes leads to suboptimal growth rate of lambs (Fthenakis and Jones, 1990) and, during the neonatal period, even to increased death rate of lambs (Dwyer, 2008; Brozos et al., 2011). In this context, it is noteworthy the report by Juste Jordán and García

Pérez (1991), who found that adverse effects of parasitism in milk yield were more pronounced at the final stage of lactation, when, however, there is little dependence of lambs on maternal milk, as they consume solid feed. The nutritive value of milk is also dependent upon its composition. Nevertheless, a variety of factors can influence milk composition (e.g., nutrition, genetics, stage of lactation, mammary health), which may be difficult to control in order to test potential adverse effects of parasitism; that may explain the unclear results among the respective studies.

8.3. Mastitis

The major defence mechanism against bacteria invading into the mammary gland is phagocytosis (Craven and Williams, 1985). The process is regulated through a variety of factors, among them energy resources of the host (Greenberg and Grinstein, 2002; Stuart and Ezekowitz, 2005), which may indicate a potential adverse role for parasites.

In two recent publications, Mavrogianni et al. (2012, 2014) have shown the effects of gastrointestinal parasitic infections to development of mastitis in ewes. In a field study, trematode infections (*F. hepatica* and *D. dendriticum*) in lactating multiparous ewes have led to increased incidence of clinical or subclinical mastitis during the first two weeks post-partum (Mavrogianni et al., 2014). In an experimental study, deposition of *Mannheimia haemolytica* into the teat duct of trichostrongylid-infected ewes resulted to development of clinical mastitis, whilst healthy controls developed only subclinical disease after challenge (Mavrogianni et al., 2012).

The above studies were the first to confirm that parasitic infections predispose ewes to mastitis, both diseases being significant health and welfare problems in sheep flocks. It is interesting to note that in one of these studies (Mavrogianni et al., 2014), the association between trematode infection and mastitis was shown in the immediately post-partum period, when relaxation of immunity (Sections 6.2 and 8.1) would be present. In the other one of the above papers (Mavrogianni et al., 2012), the authors have presented evidence of impaired local defence mechanisms in the mammary glands of parasitised ewes, which might explain pathways for the association observed.

9. Sucking lambs

9.1. Newborn lambs

During infections with the various abortifacient parasitic agents, foetuses may survive depending upon their age at infection (Section 6.1). In such cases, weak lambs, usually congenitally infected with the respective agent, may be born. Such lambs may die soon after birth, from attacks of predators or from hypothermia, as often they are unable to stand up on time, suck and respond to external stimuli (Wilsmore, 1984).

A significant and well documented (De Graaf et al., 1999; Fayer, 2004; Taylor et al., 2007; Shahiduzzaman and Daugschies, 2013) health problem in newborn and young lambs is cryptosporidiosis. The disease is an infectious enteritis that causes high morbidity and mortality of affected animals. It is caused by the enteric protozoa *Cryptosporidium* spp., which can affect newborns alone or in mixed infection with *Escherichia coli* or viruses affecting the intestinal tract (e.g., *Rotavirus*, *Coronavirus*) (Chatzopoulos et al., 2013). *Cryptosporidium* spp. are located at the microvilli in the intestine of affected lambs and impair intestinal function. The disease causes suboptimal growth rate and often death of affected animals, leading to heavy economic losses in the sheep industry. Lambs which survive infection at a young age, remain asymptomatic carriers and shed oocysts, contributing to increased environmental contamination and infection of newborn lambs.

9.2. Growing pre-weaned lambs

Giardia spp. is an intestinal protozoon affecting lambs at the end of the neonatal period (O'Handley and Olson, 2006). Infection is often asymptomatic, although it can cause diarrhoea, which becomes severe and life-threatening in cases of co-infection with other enteric pathogens (Andrew Thompson et al., 2008). Specific works in lambs have not been reported. In calves, infection with *Giardia duodenalis* can lead to loss of the epithelial barrier function, villus atrophy and crypt hyperplasia in the small intestine, changes which may result in clinical disease usually characterised by intermittent diarrhoea (Ruest et al., 1997). In any case, the lesions would cause malabsorption, leading to suboptimal weight gain, reduced feed-efficiency and ill-thriftiness of the affected animals (Olson et al., 1995; Buret, 2007; Sweeny et al., 2012). In general, the significance of this infection has not yet been fully elucidated and further studies are needed.

Eimeria spp. are well-described enteric protozoa (Taylor et al., 2007; Andrews, 2011; Taylor, 2012), which can affect growing lambs from the age of 20 days onwards, causing coccidiosis. Up to 11 different species have been reported to affect lambs; *E. crandallis* and *E. ovinoidalis* are considered to be the most pathogenic, perhaps because they cause extensive damage in both the small and the large intestine. Infections usually remain inapparent, although affected lambs may not be thriving as expected. Watery, haemorrhagic diarrhoea can occur and may result to death, if the infection is not properly managed.

The onset of intense infection of lambs with gastrointestinal helminths (tapeworms and nematodes) coincides with the start of consumption of solid feed by these animals, specifically grazing. Tapeworms (*Moniezia* spp., *Avitellina* spp., *Stilesia* spp., *Thysaniezia* spp.) are regarded of little pathogenic significance, only in heavy infections causing suboptimal growth rate and possibly clinical signs (Taylor et al., 2007).

The effects of gastrointestinal nematode parasitism on the growth of unweaned lambs have been well documented. These parasites are of importance in mutton-type production systems, where lambs remain with their dams for over 100 days of age (Sargison, 2009). In contrast to that, in dairy-type production systems, lambs are weaned at a younger age (Gelasakis et al., 2010) and, usually, are taken for slaughter; hence, chances for building up a significant production-limiting parasitic burden are minimal. Gastrointestinal nematode infections cause significant growth retardation or delay in age of slaughter, which have been documented repeatedly in the older to the more recent scientific literature (Coop et al., 1984; Sweeny et al., 2012). The significant financial losses associated with the growth retardation of unweaned lambs have led to the need for frequent anthelmintic treatments in these animals, which, in turn, have led to development of widespread anthelmintic resistance in sheep flocks around the world (Papadopoulos et al., 2012; Torres-Acosta et al., 2012). Currently, many strategies for anthelmintic treatment of lambs in mutton-type production systems have been advocated, with emphasis given to strategic administration of the drugs (Sargison, 2011, 2012).

10. Concluding remarks

The review has covered many aspects of interaction between parasitic infections and reproduction in sheep. In the majority of cases, parasitic infections lead to reduced reproductive efficiency, although there are a few cases where the reproductive stage of the animal influences the parasitic infection. Further collaboration of parasitologists with obstetricians, endocrinologists and immunologists will contribute to deeper investigations into these topics and the elucidation of potential relationships, in order to improve health, welfare and production of sheep.

Conflict of interest statement

The authors have nothing to disclose.

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