

Review

Physiological, immunological and genetic factors in the resistance and susceptibility to gastrointestinal nematodes of sheep in the peripartum period: A review

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Summary

Parasitic diseases of sheep involving gastrointestinal nematodes (GIN) are one of the main problems that affect flock productivity, especially during the peripartum period. Around lambing, the ewes are immunosuppressed and the nematode faecal egg count (FEC) increases at four weeks before lambing, reaching a peak between the fourth and sixth week postpartum and subsequently decreasing towards weaning. Prolactin has been credited with a suppressive effect on immune system, along with other hormones that intervene in metabolism, such as leptin, which has an important role in the activation of other hormones. Cortisol has also been included; this is stimulated by any stressful event and inhibits the proliferation of T-cells and alters the function of immunoglobulins. Another related hormone is pepsinogen, which is considered a marker of the integrity of the abomasum mucosa, as well as the albumin concentration that increases in the presence of a GIN infection. The humoral and cellular immune response, as well as inflammatory reactions, are the main mechanisms of action against GIN. Lymphocytes direct the effector mechanisms in a Th2 cell response, including interleukins (IL-4, IL-5, IL-9, IL-10) and transforming growth factor beta (TGF- β) together with immunoglobulins (IgA, IgG, IgM and IgE), which prevent the invasion of pathogens. Eosinophils with a cytotoxic effect are indicators of a parasitic infection, with importance in the immune protection of infected individuals. The genetic selection of resistant individuals measured by FEC is dependent on the heritability (h^2), which is moderately inheritable and highly repeatable. Effects that influence the resistance or susceptibility of sheep to GIN infections in the peripartum period are determined by the interaction of various factors, such as genotype or breed, nutrition, age, type of birth, season and production system, etc., which are studied in this review.

Keywords: cellular immunity; humoral immunity; infection; nematode parasites; peripartum rise

Introduction

Gastrointestinal nematode (GIN) infections are one of the main parasitic diseases that affect small ruminants around the world (Torres-Acosta & Hoste, 2008), causing physiological and productive alterations. Much work has been done in the search for control

alternatives that minimise the consequences of parasitism that have an impact on the productive efficiency of flocks, particularly under grazing conditions (Mugambi *et al.*, 2005; Vázquez-Hernández *et al.*, 2006; Karrow *et al.*, 2014) with emphasis on young lambs and ewes during the peripartum period (Kahn *et al.*, 1999), when the problems of parasitism are accentuated by the increased fae-

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cal egg count (FEC) of ewes that are responsible for contributing to the contamination of the grazing area with GIN eggs (Beasley *et al.*, 2010), in turn constituting a source of infection for suckling lambs (Ng'ang'a *et al.*, 2004). In this period, immunosuppression occurs in sheep and goats, with interaction between physiological, immunological, nutritional and genetic factors, among others, which makes them susceptible to other infections.

From the immunological point of view, sheep with resistance to GIN are those that have the capacity to produce a greater number of cytokines derived from the Th2 response, related mainly to the reduced expulsion of eggs and the elimination of worms (Hayward, 2013). This being associated with high levels of IgE and eosinophils (Muñoz-Guzmán *et al.*, 2006; Sayers *et al.*, 2007; Lalramhluna *et al.*, 2020), and high concentrations of IgA, IgG and IgM, with strong local immunity, effective in limiting the establishment and/or eliminating the worm population (Beasley *et al.*, 2010; Albuquerque *et al.*, 2019). This answer is very important and there are reviews of immunoglobulins associated with resistance in sheep to GIN (Aboshady *et al.*, 2020). However, in goats appear to lack a functional IgA and eosinophil response against natural nematode infection (Basripuzi *et al.*, 2018). Susceptible animals present a reduction in the counts of lymphocytes, leukocytes, mast cells and eosinophils in the abomasum mucosa, as well as a reduction in the concentration of IgG, IgE, IgM and IgA, facilitating the invasion of pathogens (O'Sullivan & Donald, 1973; Beasley *et al.*, 2010; Albuquerque *et al.*, 2019). On the other hand, the identification of genes for resistance to infectious diseases is based mainly on the search in DNA or in chromosomal regions for related loci; when these are identified, it would be possible to select resistant sheep within a population (Stear & Murray, 1994; Houdijk, 2008; Zvinorova *et al.*, 2016). By developing resistant genotypes, associated with adequate feed consumption and balanced feeding, particularly in the peripartum period, an improvement in the immune response capacity of sheep will occur (Valderrábano *et al.*, 2006; Kidane *et al.*, 2010; Jones *et al.*, 2012; Beasley *et al.*, 2012; Werne *et al.*, 2013), coupled with better development of the mammary gland and milk production during lactation. The purpose of this document is to review some physiological, immunological and genetic foundations, as well as certain factors that intervene in the expression and variability of resistance of sheep to GIN in the peripartum period.

Material and Methods

This review was carried out with the aid of the Elsevier platform (Scopus and ScienceDirect) and the Google Scholar, Redalyc, and Scielo Services. A total of 161 documents, like papers, theses, books, and meta-analyses, were consulted. The manuscripts were related to topics that revealed evidence about physiological, immunological and genetic factors related with the resistance and susceptibility to gastrointestinal nematodes of sheep in the peripartum period.

Ethical Approval and/or Informed Consent

This article does not contain any studies with human participants or animals by any of the authors.

Results and Discussion

Periparturient relaxation of immunity (PPRI)

The peripartum relaxation of immunity happens when the circulating eosinophils and plasma antibodies decrease and remain low at end of pregnancy and during lactation in ewes. At local level, lower titers of antibodies (IgG1, IgM, IgA and IgE) as well as few cell counts (globule leucocytes, mast and goblet cells) in intestinal tissue (Beasley *et al.*, 2010).

There is a transitory increase in the excretion of eggs in the faeces, especially during the last third of pregnancy and the first weeks of lactation (Hamer *et al.*, 2019). This phenomenon has been widely studied in small ruminants, particularly in sheep, and is known as postpartum rise, lactation rise or peripartum rise (PPR) (Houdijk, 2008; Torres-Acosta & Hoste, 2008; Kidane *et al.*, 2010; Goldberg *et al.*, 2012a; Fthenakis *et al.*, 2015). In ewes, the number of eggs per gram (EPG) excreted in faeces increases from four weeks before lambing, reaching a peak between the fourth and sixth week postpartum (Courtney *et al.*, 1985; Goldberg *et al.*, 2012a), subsequently decreasing towards the time of weaning (Vázquez-Hernández *et al.*, 2006). The rise in the egg excretion rate in faeces is associated with the increase in the fertility of the parasitic females as a result of a group of immunological factors being depressed in the peripartum period. This event may be accompanied by clinical signs due to the effect of gastrointestinal parasitism (Ng'ang'a *et al.*, 2004; Werne *et al.*, 2013). Increased susceptibility to other infections may also occur during this period (Ng'ang'a *et al.*, 2004; Karrow *et al.*, 2014), especially in ewes with high susceptibility to GIN due to high variability within breed (Gonçalves *et al.*, 2018).

Physiological foundation of resistance in peripartum

In PPR, temporary alterations are characterised by physiological and metabolic changes associated to pregnancy and lactation (Ahmed *et al.*, 2020). These changes also occur in cells and proteins of the immune system, that result in a low response of sheep against any infection, particularly those caused by GIN (Gibbs & Barger, 1986; Barger, 1993; Kahn *et al.*, 1999; Goldberg *et al.*, 2012b; Jonsson *et al.*, 2013; Pereira *et al.*, 2020). The modulation of immune system is associated with disturbances in the endocrine system (Tembely *et al.*, 1998; Beasley *et al.*, 2010; Jonsson *et al.*, 2013). Physiologically, it has been indicated that oestrogens stimulate the cellular and humoral immune responses by inducing direct effects on multiple cell types including immune and vascular cells (Trenti *et al.*, 2018). In addition, in the peripartum period lactogenic hormones abound in the circulation and are antagonistic to oestrogens (Barger, 1993). Nutritional aspects (Jones *et al.*,

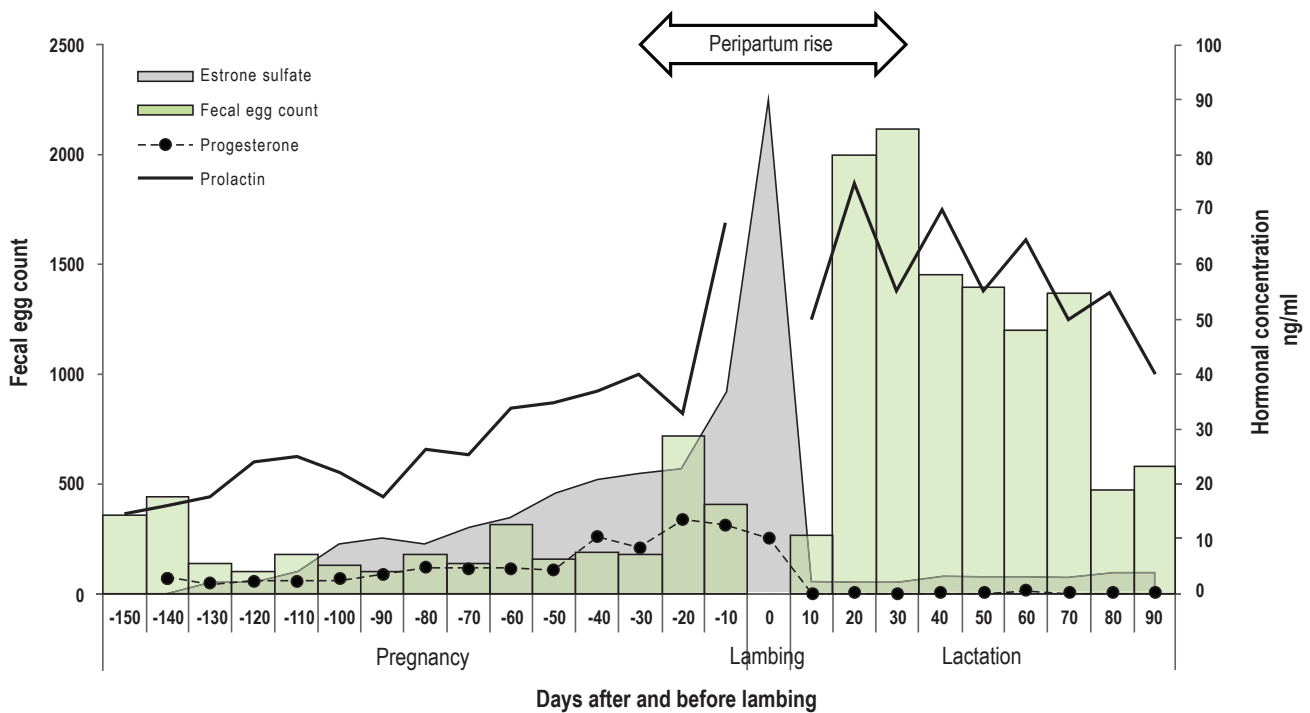


Fig. 1. Interaction of estrogenic and lactogenic hormones and nematode faecal egg count in the pregnancy and lactation of hair ewes. Elaborated with the information of several authors (Kann and Denamur, 1973; Convey, 1974; Ranilla *et al.*, 1994; González-Garduño *et al.*, 2014; Miura *et al.*, 2019).

2012), genetic influences (Kidane *et al.*, 2010) and stress triggers also play important roles (Tembely *et al.*, 1998). During the immediate prepartum period serum estrogens and estrone increase markedly. At partum withdrawal of progesterone the estrogens removes the block to lactation, and milk secretion results. Estrogen steroid decreased rapidly to low levels immediately postpartum and the release of growth hormone at parturition is required for normal lactation in ruminants (Convey, 1974) together with high levels of prolactin (Phillipps *et al.*, 2020), as observed in Figure 1.

Prolactin

Prolactin is responsible for initiating and maintaining lactation, with a stimulating effect by the suckling lambs (Fthenakis *et al.*, 2015). It has a suppressive effect on the host's immune system, by reducing the IgA levels necessary to prevent parasitic establishment at the intestinal level (Torres-Acosta & Rodríguez-Vivas, 1995; Kahn *et al.*, 1999; Houdijk, 2008), favouring growth of the nematodes and the fertility of the female worms. The increased levels of prolactin at lambing coincides with low number of circulating eosinophils and by decreased total antibody and IgG1 titers (Fthenakis *et al.*, 2015). Progesterone, the principal steroidal regulator of pregnancy, also has several immunosuppressive activities. However, in ovariectomized sheep, prolactin alone had a greater effect on the reduction of FEC (Fleming & Conrad, 1989). Although prolactin together with progesterone reduces the num-

ber of cells such as eosinophils, but in pregnancy the FEC are not high, suggesting that other mechanism and hormones are involved (Torres-Acosta & Rodríguez-Vivas, 1995; Kahn *et al.*, 1999; Houdijk, 2008; Beasley *et al.*, 2010; Fthenakis *et al.*, 2015). The results show that *Haemonchus contortus* larvae have possible receptors to progesterone and respond to progesterone by inhibiting their moulting and, in consequence, their development. These results suggest that progesterone participates in larval arrest (Gutiérrez-Amézquita *et al.*, 2017). In pregnant Angora goats, a high EPG value is associated with a high concentration of prolactin, compared to non-pregnant goats, which maintain low levels of prolactin and EPG, with a correlation of 0.83 between these characteristics (Rahman & Collins, 1992). In dairy goats, the level of resistance/resilience is negatively correlated with the amount of milk produced (Hoste & Chartier, 1993; Chartier *et al.*, 1998).

Leptin

During pregnancy, the placenta is the main provider of leptin. The levels increase at this stage and decrease gradually as the lambing date and lactation approaches (Ingvarsen & Boisclair, 2001; Mcfadin *et al.*, 2002; Beasley *et al.*, 2010). Ewes with high milk production and properly supplemented have a large amount of peri-renal fat, which in turn is related to a higher concentration of leptin in the blood and allows them to ensure fat tissue reserves and maintain good body condition (Rocha *et al.*, 2011). On the

other hand, leptin is an important regulator of the metabolic mechanisms of animals, and it has an important function in the immune system and in the activation of other hormones (Valderrábano *et al.*, 2006). The function of leptin is linked to haematopoiesis and the induction of inflammation with activation of T lymphocytes, the production of Th1 cytokines and suppressing the production of Th2 cytokines (Ingvarsen & Boisclair, 2001). Beasley *et al.* (2010) found in infected Merino sheep approaching lambing that their leptin levels decreased and EPG increased. Ewes not supplemented or with reduced intake during pregnancy tend to lose body condition and energy reserves and presenting reduced leptin levels, which are related to loss of immune capacity against infections (Rocha *et al.*, 2011).

Cortisol

Cortisol is a glucocorticoid that is released with any stressful event (Caroprese *et al.*, 2010), as occurs just before lambing. Circulating cortisol stimulates the production of anti-inflammatory cytokines and inhibits the production of pro-inflammatory cytokines such as interferon gamma (IFN- γ), tumour necrosis factor (TNF- α) and interleukin-12 (IL-12); in addition, it inhibits the proliferation of T cells, modifies the action of Complement cells and alters the function of immunoglobulins (Aleri *et al.*, 2016). All this leads to immunosuppression, increasing susceptibility to disease. At parturition in ewes, the neutrophilia is commonly due to high cortisol levels at this time, which contributes to downregulation of surface adhesion molecules expression, in addition to an enhanced release of cells from the bone marrow (Ahmed *et al.*, 2020). High cortisol levels in dairy cattle have been correlated with calcium and phosphorus deficiencies, causing hypocalcaemia problems in cows during the peripartum and provoking sensitivity to other infections (Kim *et al.*, 2012).

Pepsinogen

Pepsinogen is a precursor to pepsin secreted by epithelial cells in the abomasum, the concentration of which generally increases at the time of expression of the immune response (Kidane *et al.*, 2010), which coincides with the PPR from 4 weeks before lambing (Houdijk *et al.*, 2000). An increase in pepsinogen concentrations is related to parasitism by *Ostertagia* spp. in abomasum (Simpson, 2000). As the parasite burden increases in the peripartum, the concentrations of pepsinogen and gastrin increase, the abomasum pH is altered, the abomasum permeability is increased and acid secretion is reduced (Houdijk *et al.*, 2000; Davies *et al.*, 2005; Angulo-Cubillán *et al.*, 2007; Kidane *et al.*, 2009), this being able to present diarrhoea (Miller & Horohov, 2006). In this sense, pepsinogen is considered as a marker of the integrity of the abomasum mucosa and a pathological indicator (Dominik, 2005; Kidane *et al.*, 2009; Cei *et al.*, 2016).

Albumin

Protein levels in the diet are responsible for the concentrations of

blood components during an infectious process (Louvandini *et al.*, 2006). From two weeks before lambing and during lactation, ewes supplemented with high-protein diets maintain high concentrations of albumin and urea (Houdijk *et al.*, 2000; Kidane *et al.*, 2010), which coincides with a reduced excretion of eggs in the faeces; conversely, decreases in the level of albumin and urea favour an increase in EPG (Zárate Frutos *et al.*, 2014). A low albumin concentration is also considered a pathological indicator of the presence of an infection (Dominik, 2005).

Globulins

Globulins are altered during de PPR in sheep infected with GIN. Regardless of the protein content in the diet, globulin levels increase from four weeks before lambing (Houdijk *et al.*, 2000; Zárate Frutos *et al.*, 2014). The increase at final pregnancy stage is related to the presence of infectious or parasitic diseases (Zárate Frutos *et al.*, 2014). Immunoglobulins constitute a natural defence mechanism in sheep, associated with inflammatory processes and the formation of antibodies. At the same time, increases in serum globulin levels are related to the quality of colostrum (Obidike *et al.*, 2009).

Immunological mechanisms against parasitic infections

Once the host is infected by the nematode larvae, the epithelial cells are stimulated to generate an immune response, together with complement fixation and mucus secretions constitute the innate response to resist the primary infection (Hendawy, 2018), characterised by the action of some cytokines (Klion & Nutman, 2004). In addition, the small proteins and various cell types are stationary, such as interferons (IFNs) and virus-infected cells, or mobile, such as circulating leukocytes, monocytes, dendritic cells and lymphocytes. Leukocyte-derived cytokines are known as interleukins (ILs), and those originating from monocyte-macrophages are called monokines, both of which are produced as a protection mechanism for the host animal (Finkelman *et al.*, 1997; Lippi *et al.*, 2013; Karrow *et al.*, 2014). Despite the fact that the immunological mechanisms are not very clear, the innate and acquired response capacity are those that have the greatest influence in the grade of infection (Muñoz-Guzmán *et al.*, 2006). The acquired response dependent on previous exposure of the host to a foreign agent (González-Garduño *et al.*, 2019) and characterised by specificity and antigen memory is the more important (Karrow *et al.*, 2014). The immune response focuses on humoral and cellular responses (Gauly *et al.*, 2002; Sayers & Sweeney, 2005), as well as in inflammatory reactions (Angulo-Cubillán *et al.*, 2007). These immunological bases are considered important because parasites, mainly those hosted in the intestinal lumen, are capable of producing immuno-modulatory substances that escape the host's immune response (Moreau & Chauvin, 2010).

Complement system recognition

The innate response is the first line of defence, capable of rec-

ognising molecular patterns associated with the pathogen in a shorter time, and occurs mainly through the Complement system (Fujita *et al.*, 2004). A group of plasma proteins interact with bound antibodies and surface receptors that promote the elimination of pathogens (Castellano *et al.*, 2004). By activating the classical and alternate pathways, high amounts of the enzyme C3 convertase are generated, depositing a large number of C3b molecules in the pathogen, attaching some molecules (opsonins) to its surface (Castellano *et al.*, 2004; Fujita *et al.*, 2004; Muñoz-Guzmán *et al.*, 2006); through this opsonisation processes the elimination of pathogens occurs. In addition to this, the generated C3a and C5a peptides facilitate the mobilisation of eosinophils and neutrophils, favouring the inflammatory reaction; Complement activation regulates the cytotoxicity of eosinophils against larvae in the early stages of infection (Muñoz-Guzmán *et al.*, 2006).

Cellular response

In the peripartum period, the immunological differences between lactating and dry ewes are notable, so that the immunological relaxation in the peripartum include the low cellular and humoral response affected by hormonal and nutritional aspects modified by season changes (Beasley *et al.*, 2012). The elements involved in the immune resistance or susceptibility of sheep consider the following concepts. T lymphocytes are responsible for directing the effector mechanisms once they are stimulated by antigens. When activated, CD4+ T cells differentiate into two groups: helper T cells or lymphocytes, Th1 and Th2 (Muñoz-Guzmán *et al.*, 2006; Sykes, 2010). Th1 cells are responsible for increasing the expression of interleukins IL-2, IL-3, IL-13, IL-25, IFN- γ and TNF- α (Finkelman *et al.*, 1997; Miller & Horohov, 2006; Hayward, 2013), as well as an increase in mRNA expression for IL-6 as an indicator of gene expression, while Th2 cells include IL-4, IL-5, IL-9, IL-10 and TGF- β , with effector mechanisms in the cellular immune response (Finkelman *et al.*, 1997; Maza-Lopez *et al.*, 2020). The expression of these components induces a local inflammatory reaction in which different types of cells, such as basophils, eosinophils, neutrophils and lymphocytes are involved, together with specific antibodies, the gastrointestinal mucosa and inflammatory mediators (Meeusen *et al.*, 2005; Ingham *et al.*, 2008; Karrow *et al.*, 2014); in addition, dendritic cells (DCs) and natural killer cells (NK) appear (Angulo-Cubillán *et al.*, 2007). These immunological mechanisms facilitate a reduction in the number, size and fertility of worms (Rowe *et al.*, 2008). Intracellular parasites generally involve the Th1-type response, whereas GIN such as *H. contortus* involve the Th2-type response (Miller & Horohov, 2006; Muñoz-Guzmán *et al.*, 2006; Moreau & Chauvin, 2010), although there are situations in which Th1 and Th2 responses are involved for certain parasites (Murphy *et al.*, 2013). Results found by Bricarello *et al.* (2008) in Nelore cattle indicated that the immune response to *Cooperia punctata* was probably mediated by Th2 cytokines (IL-4 and IL-13) in resistant animals, and by Th1 cytokines (IL-2, IL-12p35, IFN- γ and MCP-1) in the susceptible group.

Eosinophilia

As cellular components of immunity, eosinophils with a cytotoxic effect are one indicator of a parasitic infection. These cells have importance in the immune protection of infected animals (Hohenhaus *et al.*, 1998; Davies *et al.*, 2005). In the presence of GIN infections, effector immune responses characterised by the production of IgE and peripheral and tissue eosinophils associated with the production and activation of interleukins IL-4 and IL-5 are induced (Finkelman *et al.*, 1997; Klion & Nutman, 2004). Once in circulation, eosinophils release the content of their toxic granules or metabolites onto the nematode cuticle, increasing cellular cytotoxicity, with release of proteins and mediators of inflammation (Klion & Nutman, 2004), favouring a lesion of the cuticle and the adherence of more eosinophils. In this way, regulation of the growth of GIN occurs together with the expulsion of eggs in the faeces of the host. Ewes in peripartum show a reduction in eosinophil count (Beasley *et al.*, 2010; Pereira *et al.*, 2020).

Humoral immune response

With GIN infection, the pro-inflammatory cytokines IL-4, IL-5, IL-9, IL-10 and IL-13 are involved in different mechanisms of the humoral response. One of these is through the IgA, IgG, IgM and IgE antibodies, which, being antigen receptors, prevent the invasion of pathogens through endocytosis of the antigen (O'Sullivan & Donald, 1973; Beasley *et al.*, 2010); another is due to delayed maturation, reduced fertility and induction of parasite death. They are also involved in intestinal contractility, allowing the expulsion of worms (Miller & Horohov, 2006; Sayers *et al.*, 2007; Houdijk, 2008; Hayward, 2013; Murphy *et al.*, 2013; Wilkie *et al.*, 2015). The surrounding IgA levels in the mucosa have been associated with reductions in the fertility and length of *H. contortus*, as well as a reduction in the parasite burden at the intestinal level (Amarante *et al.*, 2005; Davies *et al.*, 2005; Karrow *et al.*, 2014; Hernández *et al.*, 2016). Some studies have associated plasma IgA with FEC as an important immune response (Bowdridge *et al.*, 2015; González-Garduño *et al.*, 2018). High IgE levels are also involved in the expulsion of worms and in the regulation and activation of mast cells, eosinophils and basophils (Alba-Hurtado & Muñoz-Guzmán, 2013; Murphy *et al.*, 2013; Karrow *et al.*, 2014). The expulsion of worms due to the effect of IgE occurs through the release of vasomotor amines: compounds that stimulate the contraction of smooth muscle and increase vascular permeability, allowing fluid to escape into the intestinal lumen, resulting in displacement and expulsion of most of the nematodes implanted in the intestinal mucosa of the animal. IgG concentrations are associated with a reduction in excreted eggs in faeces (Murphy *et al.*, 2013).

Genetic foundations of resistance

Resistance against GIN is polygenic in nature (Sayers & Sweeney, 2005; Zvinorova *et al.*, 2016) and is quantitative; that is, it is influenced by a large set of genes or loci with small effects (Hayward,

2013; Karrow *et al.*, 2014). The identification of genes related to resistance to GIN involves procedures based on molecular genetics, through the use of molecular markers, and the application of different strategies such as mapping of quantitative traits locus (QTL) regions by linkage disequilibrium, identification of candidate genes, the use of maps of high-density single nucleotide polymorphism (SNP) and complete genome (genome-wide) association studies (Keane *et al.*, 2006; Bishop & Morris, 2007; Wilkie *et al.*, 2015; Zvinorova *et al.*, 2016), as well as microarray analysis, are very useful in determining post-infection gene expression. All these procedures offer advantages and opportunities to investigate resistance genetics and parasite–host interactions (Hayward, 2013).

Genetic selection criteria

The ability to express resistance between and within breeds is genetically regulated (Stear & Murray, 1994), which is why selection can be made either directly through identifying the genes or alleles involved by means of molecular genetic techniques or indirectly through phenotypic indicators such as worm counts, FEC (Beh & Maddox, 1996; Davies *et al.*, 2005; Good *et al.*, 2006), packed cell volume (PCV), antibody levels, specifically IgA and IgE (Karrow *et al.*, 2014), eosinophil count, pepsinogen concentration (Beh & Maddox, 1996) or other variables related to the immune response. One of the main variables by which the parasite burden is determined has been the EPG count, and this is one of the main phenotypic selection criteria. It must be evaluated by measurements over time, establishing the dynamics of the curve in the peripartum period and the correlation with other productive characteristics (Goldberg *et al.*, 2012b).

Genetic selection is dependent on the heritability (h^2), which in the case of FEC is considered moderately inheritable and highly repeatable (Bishop & Morris, 2007; Saddiqi *et al.*, 2010), similar to other productive characteristics. Values from 0.15 have been observed (Vanimisetti *et al.*, 2004), but other authors indicate values of 0.25 to 0.30 (Sréter *et al.*, 1994; Kahn *et al.*, 1999) and even up to 0.63 (Miller & Horohov, 2006; Alba-Hurtado & Muñoz-Guzmán, 2013). Selective breeding of the maternal line for nematode resistance has potential epidemiological benefits by reducing pasture infectivity (Vineer *et al.*, 2019).

Identification of genes related to resistance

The genetic basis of resistance is closely related to the immunological component, most of the loci involved with immunological processes are located in the Main Histocompatibility Complex (MHC), a highly polymorphic region that consists of a group of closely linked genes involved in the presentation of antigens in the host's immune system. Association of the FEC with the MHC I and MHC II regions adjacent to chromosome 20 of sheep has been found (Stear & Murray, 1994; Karrow *et al.*, 2014) with the amount of FEC (Keane *et al.*, 2006; Karrow *et al.*, 2014; Zvinorova *et al.*, 2016). The DRB1 locus of MHC II has been associated

with resistance to GIN, particularly with increases in IgA and IgE levels (Dominik, 2005; Hassan *et al.*, 2011; Hayward, 2013; Karrow *et al.*, 2014). Also, with IFN- γ gene located on chromosome 3, a strong association between one allele of this gene has been detected with the reduction in FEC and an increase in the levels of specific antibodies (IgA) against *Ostertagia circumcincta* in lambs (Karrow *et al.*, 2014). However, some authors have cited that expression of the IFN- γ gene does not directly influence resistance to GIN (Dervishi *et al.*, 2011; Alba-Hurtado & Muñoz-Guzmán, 2013; Karrow *et al.*, 2014). Likewise, with the IgE gene (Díaz *et al.*, 2005; Pettit *et al.*, 2005; Keane *et al.*, 2006; Sayers *et al.*, 2007; Karrow *et al.*, 2014) a strong Th2 cell response has been detected during infections, with overexpression of IL-13, IL-5 and TNF- α (Alba-Hurtado & Muñoz-Guzmán, 2013). The OMHC1-188 and OLADRB2-282 alleles of the MHC influence the differentiation between genotypes in the antigen-presenting mechanisms (Alba-Hurtado & Muñoz-Guzmán, 2013). Of the TLR variants, the TLR4 gene is reported to be involved with the immune response to parasitic infections, as are other nearby genes, TNFSF8 and TNFSF15, which encode cytokines belonging to TNF- α (Lin *et al.*, 2016).

After evaluating the ALOX15, CD109, CD163, CPA3, EMR3, IL-13, KIT and MAP3K5 genes, it was found that ALOX15 and IL-13 play important roles in resistance to GIN (Wilkie *et al.*, 2015) and were significantly increased in resistant animals and expression was negatively correlated with FEC. The expression of different genes at the intestinal level has been evaluated in two divergent lines by means of microarray analysis, with the highest expression in susceptible animals of HLA-A, MSH6, GPX2, IF135, UBD, SERPING1 and TFF3, the expression being generally associated with the stress caused by parasitic infection, such as in the case of GPX25; in contrast, resistant animals showed higher expression of the RAC2, ITGB2, DAP3 and TRADD genes associated with neutrophilia and post-infection cellular processes and of importance in innate immunity (Keane *et al.*, 2006). As indicators of the genetic influence on resistance, the presence of QTL regions for EPG on chromosomes 1, 2, 3, 6, 14, 19 and 20 has been revealed for different nematodes, including *H. contortus*, and on chromosome 1 for haematocrit (Bishop & Morris, 2007). Other authors have reported different QTL regions in sheep for *H. contortus*, such is the case of chromosomes 1, 3, 6, 8, 14, 20 and 22 (Miller & Horohov, 2006; Zvinorova *et al.*, 2016).

Factors influencing resistance and susceptibility

The physiological, immunological and genetic effects that influence the resistance or susceptibility of ewes to GIN infections in the peripartum period are determined by the interaction of various factors:

Genotype or breed:

The resistance of some genotypes depends largely on conditions of environmental origin (Alba-Hurtado & Muñoz-Guzmán, 2013)

Table 1. References related to peripartum rise in ewes by breed, type of infection and main topic attended, as well as the variable response studied.

Breed	N	Infection	Preg - Lact	Topic	FEC	PV	HV	Cells	Igs	Horm	Sp	Author
Cross	18	Nat	Preg-Lact	Season	X							Procter (1968)
Merino	61	Nat	-150 to 60	Season	X						W	O'Sullivan and Donald (1970)
Utah	14	Nat		FEC	X							Van Geldorp and Van Veen (1976)
Mules	20	Nat	-42 to 42	FEC	X	W,I	Hg,P				W	Thomas and Ali (1983)
Florida Native, SC, Barbados, Ram, FD	64	Nat	-21 to 56	R-S	X							Courtney <i>et al.</i> (1984)
Florida Native	76	Nat	-21 to 70	R-S	X		H					Courtney <i>et al.</i> (1986)
Merino	70	Nat	-	Season	X						L3	Gibbs and Barger (1986)
West African Dwarf	40	Nat	Preg-Lact	Season	X						W	Agyei <i>et al.</i> (1991)
Greyface ewes (BL x SBF)	28	Einf	-84 to 21	R-S	X				A,G,M	Pe		Jeffcoate <i>et al.</i> (1992)
Merino	395	Nat	0-42	R-S	X						L3	Woolaston (1992)
Crosses	44	Nat	-14 to 21	R-S	X							Romjali <i>et al.</i> (1997)
Mens, Horro	2786	Nat	-60 to 84	Season	X							Tembely <i>et al.</i> (1998)
Greyface	30	Nat	-42 to 42	Nutrition	X	I	P	T		Al,Pe	W	Houdijk <i>et al.</i> (2000)
Barki	18	-	Preg-Lact	Hemat	X		W,P,Hg			Al,Ur,Cr		El-Sherif and Assad (2001)
Coopworth	96	Nat-Exp	-30 a 84	R-S	X	W,I						McAnulty <i>et al.</i> (2001)
SBF	200	Nat	Lact	Genetic	X	W,I				Min		Bishop and Stear (2001)
Hamp, Rom, WF	27	-	0 to 47	Hormonal						Lep		Mcfaadin <i>et al.</i> (2002)
Merino	120	Nat	-52 to 97	Nutrition	X	W,I						Kahn <i>et al.</i> (2003)
Dorper	40	Nat	NE	Season	X							Ng'ang'a <i>et al.</i> (2004)
BL x NZR	120	Nat	-56 to 48	Nutrition	X	W			T,A			Xie <i>et al.</i> (2004)
Santa Inés, IDF	22	Nat	-150 to 60	R-S	X	W	H,P	E			L3	Rocha <i>et al.</i> (2004)
Rom x Aragonesa	32	Exp	-42 to 21	Nutrition		I	H,Hg	E		Lep	W	Valderrábano <i>et al.</i> (2006)
Martinik	120	Nat	-50 to 50	Curve	X		H					Mahieu and Aumont (2007)

Boutsiko, Chio, cross	33	-	-18 to 15	Cells				Ma,Ne			Theodorou <i>et al.</i> (2007)
Mules	72	Exp	-56 to 24	Nutrition	X	W	P		Al,Ur,Pe		Kidane <i>et al.</i> (2009)
Merino	128	Exp	-50 to 42	R-S	X			E,W,T		W	Beasley <i>et al.</i> (2010)
SBF x BFL		Exp	-24 to 32	Nutrition	X	W,I			Al,Ur,Pe		Kidane <i>et al.</i> (2010)
Merino	144	Nat	-35 to 21	R-S	X					L3	Williams <i>et al.</i> (2010b)
Santa Inés, IDF	120	Nat	-35 to 49	Nutrition	X	W	H,P	E			Rocha <i>et al.</i> (2004)
Santa Inés, IDF	120	Exp	-35 to 49	Nutrition	X	W	H,P	E			Rocha <i>et al.</i> (2011)
Merino	2500	Nat	56 to 68	Curve	X					L3	Goldberg <i>et al.</i> (2012a)
Merino	748	Nat	58 to 68	Genetic							Goldberg <i>et al.</i> (2012b)
Merino	83	Exp	-50 to 40	Nutrition	X	I		E,W,T	Lep	W	Beasley <i>et al.</i> (2012)
Mules	24	Exp	-56 to 31	Nutrition	X	W,I			Pe,Ur,Al		Sakkas <i>et al.</i> (2012)
Red Engadine	78	Nat-Exp	-13 to 29	Nutrition	X	I				L3	Werne <i>et al.</i> (2013)
SC, Dorset x Finnsheep x Ram	20	Exp	-21 to 21	R-S	X		H	A			Bowdridge <i>et al.</i> (2013)
Texel	10	No infection	-42 to 14	Hormonal			H,P,Hg				Zárate Frutos <i>et al.</i> (2014)
Katahdin x Pelibuey	46	Nat	-150 to 90	Sel-Treat	X	W	H				González-Garduño <i>et al.</i> (2014)
Col creole, Romney, Hamp, Corriedale	43	Nat	-150 to 60	Drug	X	W					Vargas-Duarte <i>et al.</i> (2015)
Santa Inés	45	Nat		Nutrition	X		H,P,Hg	W			David <i>et al.</i> (2015)
Texel	72	Nat	-75 to 50	Immun	X	W				A,G	Nisbet <i>et al.</i> (2016)
Criollo, Suffolk	53	Exp	-28 to 42	R-S	X	W	H	E			Romero-Escobedo <i>et al.</i> (2016)
Pelibuey	54	Nat	0-75	Sel-Treat	X		H				Arece-García <i>et al.</i> (2017)
Katahdin	931	Nat	-20 to 80	Curve	X						Notter <i>et al.</i> (2017)

Not specified	240	Nat	0 to 90	Sel-Treat	X				L3	Westers et al. (2017)
Blackbelly	25	Nat	-150 to 90	R-S	X	H _i P	E	A	L3	González-Garduño et al. (2017)
Bergamasca	70	Nat		Nut-Imm	X	H _i P		T		Basseto et al. (2018)
Blackbelly	51	Nat	-150 to 90	R-S	X		E,W	A	L3	González-Garduño et al. (2018)
Exlana	112	Nat	Peak	R-S	X					Vineer et al. (2019)
Texel, IDF	36	Nat	-28 to 56	R-S	X	H _i P				Gasparina et al. (2019)
Mule, Cheviot, SBF, Texel	1750	Nat	Preg-Lact	Season	X				L3	Hamer et al. (2019)
Crioula Lanada	18	Nat	-30 to 120	R-S	X	H _i P	E	G	L3	Pereira et al. (2020)
German Blackhead	23	Nat	-30 to 30	Citometry	X		E,W			Ahmed et al. (2020)
Pelibuey	91	Nat	0 to 75	Sel-Treat	X					Aguirre-Serrano et al. (2020)

Breed: SC: St. Croix, Ram; Rambouillet, FD: Finnsheep x Dorset, BL: Border Leicester, SBF: Scottish Blackface, Ham: Hampshire, Rom: Romanov, WF: White Face, NZR: New Zealand Romney, IDF: Ile de France, BF_L: Blue-faced Leicester, Col creole: Colombian creole, Mules: BFL x SBF, N: Number of ewes, **Infection:** Nat: By grazing, Exp: Experimental infection. **Prg to Lact:** Days from pregnancy to lactation. **Topic:** R-S (Resistant-Susceptibility), Sel-Treat: selective treatment. **FEC:** Faecal egg count. **PV:** Productive variables: W: Live weight, I: Feed intake, **HV:** Hematological variables: H: Hematocrit or packed cell volume, P: Total plasma protein, Hg: hemoglobin. **Cells** T: Tissue cells, E: Eosinophils, W: White blood cells, Ma: Macrophages, Ne: Neutrophils. **Igs:** Immunoglobulins: A: IgA, G: IgG, T: Total antibodies. **Horm:** Hormones: Cor: Cortisol, Al: Albumins, Pe: Pepsinogen, Ur: Urea, Ch: Cholesterol, Min: minerals, Cr: creatinine. **Sp:** nematode species, L3: infective larvae, W: Count of worms.

and flock management. Generally, native genotypes such as Red Maasai (Wanyangu *et al.*, 1997), Santa Inés (Rocha *et al.*, 2004; Albuquerque *et al.*, 2019), Crioula Lanada (Bricarello *et al.*, 2004), Barbados Blackbelly (Yazwinski *et al.*, 1981; Zaragoza-Vera *et al.*, 2019), Florida Native (Courtney *et al.*, 1984, 1986; Díaz-Rivera *et al.*, 2000), Castellana (Gómez-Muñoz *et al.*, 1999), Pelibuey (Morteo-Gómez *et al.*, 2004; Palomo-Couoh *et al.*, 2017), and Mexican creole (Alba-Hurtado *et al.*, 2010) are more resistant to *H. contortus*. Native genotypes, which for many years have thrived in unfavourable environments with poor zootechnical management and without exposure to anthelmintic treatments have proven to be more resistant (Alba-Hurtado & Muñoz-Guzmán, 2013). The use of genetically resistant animals can optimise the use of anthelmintics and delay the resistance capacity of nematodes against anthelmintics (Bricarello *et al.*, 2004). In the same way, the selection of sheep resistant to GIN in the peripartum period would favour a decrease in the contamination of the pasture.

Nutrition:

In the peripartum period, ewes present an imbalance of nutrients that they require to maintain the final third of gestation and prepare the mammary gland for the next lactation (Barger, 1993; Jones *et al.*, 2012). Since nutritional status is an important factor influencing the parasite–host relationship and the pathogenesis of infections (Valderrábano *et al.*, 2006) and affecting the productive behaviour in ewes (Macarthur *et al.*, 2014), adequate nutrition is a control measure, specifically in the critical stages of the final third of pregnancy and during lactation (Macarthur *et al.*, 2014), that can improve the immune response of sheep (Houdijk *et al.*, 2006; Kyriazakis & Houdijk, 2006). Protein supplementation favours a greater presence of inflammatory cells in the abomasum mucosa, increasing the immune response and the animal's resistance and resilience to infection (Kyriazakis & Houdijk, 2006; Rocha *et al.*, 2011). Physiologically, it has been found that when supplementing with protein sources, hyperplasia occurs in the abomasum with a greater quantity of leukocytes and mast cells; after antigenic stimulation the mucosal mast cells release their content, making their function effective 21 days after the start of protein supplementation (Houdijk *et al.*, 2006). Another important aspect of protein supplementation is that eosinophils are benefited, as they are a type of granulocyte related to the response to cells that contain protein-rich cytoplasmic granules (Hayward, 2013). However, supplementation can increase food costs (Davies *et al.*, 2005). Results of a sheep-based meta-analysis suggested an important interaction between parasitism and dietary energy and protein consumption (Méndez-Ortiz *et al.*, 2019). Infected animals require more energy to maintain a live weight gain similar to that of non-infected animals. An energy supply in addition to protein is required for the development of immune mechanisms (Toscan *et al.*, 2017).

Feed consumption:

Infections in ruminants with GIN are characterised by a reduction

in weight gain from 6 to 30% caused, in part, by a decrease in feed consumption (Kahn *et al.*, 1999; Beasley *et al.*, 2012). In parallel, nutritional requirements are increased up to six-fold compared to sheep outside this stage (Houdijk, 2008), which causes a decrease in gastrointestinal motility and a reduction in gastric acid secretion (Louvandini *et al.*, 2006). This low consumption can cause significant protein losses, mainly in infections by blood-sucking nematodes such as *H. contortus*. According to estimates, in sheep infected with *Trichostrongylus colubriformis* the losses are around 20 to 125 g of protein depending on infection level (Kahn *et al.*, 1999; Angulo-Cubillán *et al.*, 2007). All this favours the establishment and reproduction of the GIN with repercussions on the growth, productive efficiency and survival of the lambs.

Age:

Adult animals are able to respond better than younger ones (Goldberg *et al.*, 2012a). Young animals' susceptibility is a consequence of their inability to develop a satisfactory immune response (Kahn *et al.*, 1999; Emery *et al.*, 2000; Getachew *et al.*, 2007). They do not acquire effective immunity before 6 or 12 months of age (Williams *et al.*, 2010a), but this improves as age progresses (Miller & Horohov, 2006; Goldberg *et al.*, 2012a). After puberty, females show differential resistance compared to males. Adult sheep tend to have a higher resistance capacity due to the simple fact that they have lived with parasites for a longer time (Courtney *et al.*, 1984; Torres-Acosta & Hoste, 2008) and with constant exposure to parasites and repeated infections, which is demonstrated by the high number of leukocytes (Miller & Horohov, 2006), except when they are in the peripartum period when their immunity is reduced and when they cause greater contamination of the grazing area (Bishop & Stear, 2001).

Type of birth:

There is some controversy regarding the effect of the type of birth because with the same feeding plan, lambs from single births have lower EPG values compared to those from a double birth; this is evident from the different related nutritional requirements with the number of products in gestation (Houdijk, 2008). Gruner *et al.* (1992) and Goldberg *et al.* (2012a) found that the type of birth had a significant effect, with mothers with multiple births showing higher EPG values than those with single delivery. Woolaston (1992) indicated that those ewes that lost their lambs during lactation had low EPG values. In other study, >90% of the triplet-bearing ewes needed treatment, demonstrating the high treatment risk among ewes with large litter sizes (Aguirre-Serrano *et al.*, 2020).

Season:

Under grazing management, the environmental conditions of the season influence the prevalence and relative dominance of some parasite species (Torres-Acosta & Hoste, 2008), as well as the number of infective larvae (L3). The first studies related to the peripartum period reported that the increase in FEC was due

to the high humidity in the grasslands being accentuated in the rainy season; in this season is common to find greater amounts of *Trichostrongylus* sp and *Haemonchus* sp, and this coincides with the time when ewes are lactating (Van Geldorp & Van Veen, 1976). Later studies indicated that the parasitic eggs remain inhibited during the dry season and are reactivated in the rainy season, causing infection in the sheep when it coincides with the period of low immune response (Ng'ang'a *et al.*, 2004).

Hypobiotic state of the parasite:

The hypobiotic state refers to an adaptation phenomenon of the parasite and the host interacting with the environment, particularly with temperature and humidity (Gibbs, 1982). Nematodes in their L4 larval stage enter a period of arrested development or hypobiosis (Miller & Horohov, 2006; Angulo-Cubillán *et al.*, 2007; Getachew *et al.*, 2007), an adaptive mechanism to enable them to survive during extreme environmental conditions and is considered a defence mechanism. There is evidence that, in some regions with extreme temperature conditions, *H. contortus* worms can survive (Sargison *et al.*, 2007) and increase their longevity, remaining in the host for up to 50 weeks (Getachew *et al.*, 2007). When ewe's lactation coincides with the hypobiotic state of the parasites, it favours the development of the larval stages, providing a suitable environment for the development of the larval stages of the parasites. When ewe lactation starts, hypobiotic larvae resume development, as a consequence of which worm numbers increase and there is a rise in FEC (Taylor *et al.*, 2016). It is quite probable that the impact of the phenomenon of hypobiosis in tropical and subtropical regions has a lesser effect than in temperate regions, as it is not well documented in those areas.

Production system:

Obviously, when sheep are under a grazing system, the degree of infection is higher than when they remain in stable. However, Silva *et al.* (2011) compared the peripartum behaviour of goats kept under a conventional system or in stables with goats under grazing conditions, and they didn't find significant differences between the two production systems. This similar behaviour was attributed to controlled management in both cases, whereas under extensive grazing and with little control the infection could be higher. However, under the same production system, management differences result in different parasitic behaviour (Vineer *et al.*, 2019), which causes each farm to adopt different forms of control, giving priority to sustainable control in order to reduce anthelmintic resistance (Vande *et al.*, 2018).

Conclusions

The genetic selection of resistant individuals is dependent on the heritability (h^2), which is moderately inheritable and highly repeatable for FEC. The physiological, immunological and genetic effects that influence the resistance or susceptibility of sheep to GIN infec-

tions in the peripartum period are in turn determined by the interaction of various factors, such as genotype or breed, nutrition, age, type of birth, time of year and production system, among others.

Conflict of Interest

Authors declare no conflict of interest.

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