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Colostrum induced passive immune transfer in lambs

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ABSTRACT

During last decades, the production and consumption of small ruminant milk have been increased. As a result of this, sheep and goat farming have been developing and scientists are focused on clinical and feeding strategy researches on these animals. By the evolutionary challenges and adaptations, colostrum has a crucial role in immune complementation for litter. As a result of these challenges and adaptations neonatal life is more important especially in ruminants due to its lifetime effect and the future of livestock. The passive immune transfer is the main mechanism explained by biological evolution between the dam and lamb which is influenced by certain factors related to both dam and litter. Today the importance of passive immune transfer is well known for the future of livestock economy and animal welfare. In the literature, researchers are focused on correlation between colostrum quality (especially immunoglobulin concentration) and blood serum levels of immunoglobulin levels in newborns. The aims of the present review are to discuss data of recent studies and how passive immune transfer occurred in lambs as well as effecting factors and to supply new ideas to researchers.

Keywords: colostrum, passive immunity, sheep, lamb mortality.

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Introduction

The domestication of the sheep is considered approximately ten thousand years ago during the Neolithic age in Central Asia (Zohary et al., 1998). Since that age sheep farming has become an important food and animal-by product resource for human beings. Milk and dairy products of small ruminants are quite important for proper human nutrition where cow milk is not readily available or affordable (Haenlein, 2001).

The placental structure of the sheep is epitheliochorial and due to that structure, maternal antibodies are considered not transferred in utero to the offspring (Agenbag et al., 2021). Thus, colostrum induced passive immune transfer (PIT) is crucial for the whole life of the lamb. Alongside a strong immunostimulant activity of the colostrum, it is a nutrient rich source for the litter. Newborn lambs are born quite limited energy reserves thus they need immediate access to intake colostrum which has enough amount and quality (Nowak and Poindron, 2006). Colostrum has immunological and nutritional composition (Moreno-Indias et al., 2012; Övet, 2023). It also has high magnesium concentration that plays an essential role in peristaltic activation of newborns. Alongside that peristaltic activity, colostrum promotes the removal of meconium and helps avoiding the bacterial colonization in the gastrointestinal tract (Barza et al., 1993). All these properties of colostrum make it a unique life source for the newborn.

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The fetus is well-adapted to the relatively hypoxemic intrauterine environment. The transition from intra- to extrauterine life requires rapid, complex and well-orchestrated steps to ensure neonatal survival (Morton and Brodsky, 2016) and that challenge has combined some influences such as the behavior of the litter and mother after birth (Nowak et al., 2000). According to literature data, passive immunity in ruminant newborns not only ensures prevention against diseases but also accelerates growth performance (Dewell et al., 2006; Yalçın and Temizel, 2010; Gokce et al., 2013a). Neonatal lamb mortality has no one specifical cause (dos Santos et al., 2023); it has a multifactorial issue. Besides its major function of digestion and absorption of nutrients, gastrointestinal tract provides immunological defense against pathogens, endotoxins and antigenic substances (Turner, 2009). In newborn ruminants jejunum is a major intestinal region for IgG (immunoglobulin G) absorption (Nordi et al., 2012; Yang et al., 2019).

Why PIT is Crucial?

Although in some mammals (i.e., human, rabbit, mouse), PIT is completely occurred via placenta during intrauterine life (DuBourdieu, 2019) in ungulates, it is occurred limited or considered not to be occurred (Silva et al., 2022). Due to placental structure, transfer of maternal antibodies occurs via colostrum not only in lambs but also in other neonatal ruminants in 24 hours post partum; thus PIT is related to colostrum quality and its amount intake by the litter. Mechanism of PIT is based on absorption of maternal immunoglobulins via consumed colostrum. That absorption decreases rapidly in 24h postpartum (Loste et al., 2008). Meanwhile digestion of proteins and amino acid catabolism are slightly (Constable et al., 2016).

Failure of PIT causes major economical losses in livestock; it is an important economical concern for producers. Thus PIT is crucial for producers to prevent neonatal mortality and morbidity by monitoring the immune status of lambs (Pekcan et al. 2013; Elitok, 2018). The nature of PIT is an adaptive natural immunity (Figure 1).

Lamb mortality is a key factor influencing the productivity of ewes and the profitability of livestock (Shiels et al., 2021). Mortality rates are variable by different circumstances (such as management, gestational diseases, common infections, failure of PIT and others) and during last decades the average mortality rate of newborn lambs remained relatively constant by 15% around the world. This rate could be to be higher (up to 30%) in small-scale sheep farming systems in developing countries (dos Santos et al., 2023). According to studies, failure of PIT's incidence ranges between 3.4% and 20% and; in Kars province in

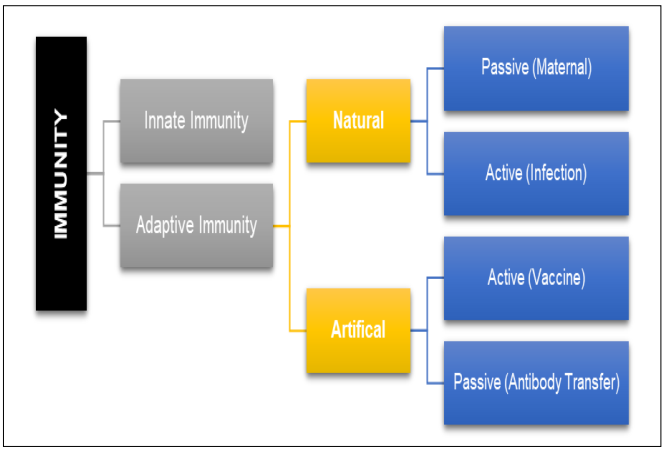

Figure 1. Summarized diagram of immunity.

Turkey mortality rates vary between 45% and 50% and during the first 2 weeks of neonatal life (Erdogan, 2009). Failure of PIT in neonatal lambs has a significant consequence on neonatal mortality and newborn losses of infectious causes are positively correlated with low concentrations of serum Ig (Sallam, 2019; Ibrahim et al., 2020) Several factors cause failure of PIT as follows: **1.** Insufficient concentration of Ig in the colostrum. **2.** Lack of specific pathogen exposure or an inability to respond. **3.** Insufficient intake of colostrum by the litter. **4.** Insufficient production of colostrum by the dam. **5.** Lack of transmural Ig transfer from the neonatal intestine to blood.

Hence, failure of PIT has been related to multiple conditions of lambs, including respiratory disease, diarrhea, septicemia, and commonly omphalophlebitis (Herndorn et al., 2011; Demis et al., 2020). All these conditions and lack of colostrum intake during the first weeks of neonatal life, would affect the litter's whole life (Agenbag et al., 2021). The amount of colostrum is important but also management during the suckling and weaning period; such as stress produced by dam separation, milk quality and suckling frequency, can affect the final immune status of the lambs (Hernández-Castellano et al., 2015).

The gastrointestinal tract of newborn lamb is considered sterile and once it's exposed to microorganisms after birth, development and maturation of the intestinal mucosal immune system start (Wesemann et al., 2013). Although it's not well-explained yet, it is known that the mechanism of passive immune transfer from dam to litter occurs by the high permeability of the intestinal tract of litter to macromolecules to pass through especially immunoglobulins in ruminants. This permeability is highest at the first 6 hours of birth and it decreases in 24 hours (Castro-Alonso et al., 2008; Hernández-Castellano et al., 2014a,b). Pinocytosis of enterocytes also has a role in that maternal antibody absorption by the newborn (Brujeni et al., 2010). PIT is a complex of

reactions by acting together with Toll-Like Receptors, mucins, antimicrobial peptides, and claudins in intestinal defense during the PIT in newborn lambs (Zhu et al., 2020). On the other hand, Fc receptor mediated pathways are key mechanisms in IgG metabolism (Tizard, 2017). However, that high permeability increases also the risk for pathogens enter to the circulation (Fischer et al., 2019).

Effecting factors of the PIT

Factors up to dam: Dam's health is one of the most important factors to produce high-quality colostrum. The healthy udder gland is key to producing high-quality milk in dairy ruminants (Castro et al., 2019). Nutrition is a major contributing factor to the quantity and quality of colostrum (Banchero et al., 2015; McGovern et al., 2015). Sufficient energy to the dam is ingesting and whether that meets its gestational requirements (Banchero et al., 2006; Muñoz et al., 2008). Viola et al. (2022) have indicated that an ewe's diet in the last period of gestation can effect colostral IgG concentration; for instance hazelnut skin in ewe's diet effects positively colostral IgG concentration. Under that condition, colostrum quality is associated directly to the dam's nutrition. In the late gestation, sheep supplemented with oat grain had higher colostral protein and IgG and high IgG concentrations in the blood serum of their lambs (Castellaro et al., 2022).

According to some recent studies, age of dam has no significant effect on growth performance in neonatal lambs (Talore, 2009; Taye et al., 2010; Abegaz et al., 2011; Gokce et al., 2013a). Although data on the effect of parity on colostrum quality in sheep and goats is not numerous, some studies reported that primiparous ewes have higher colostral protein and IgG concentrations (Higaki et al., 2013; Tabatabaei et al., 2013). But in contrast, Sjoberg and Van Saun (2021) reported that parity has no effect on colostral IgG levels. In a previous study, parity influenced characteristics of colostrum in multiparous dams; lambs born from primiparous dams have lower protein, glucose and plasma IgG concentrations than lambs born from multiparous dams (Chniter et al., 2013). Gokce et al. (2012) reported that risk of neonatal mortality and morbidity are higher in dams at first parity than the dams that have higher parities because ewes show mismothering at first lambing. Physiological mechanisms in first pregnancy might play a role in increasing stress in primiparous ewes since; they are still growing and need to partition nutrients to sustain their growth physiology and their fetuses (Chniter et al., 2015). Eventually, parity is one of the important effecting factor on colostrum quality and lamb morbidity-mortality.

In cows, the use of probiotics and prebiotics leads to higher levels of colostral immunoglobulin (Sol Morales et al., 2000; Strusinska et al., 2004). In the sow, dietary probiotics improve colostrum quality and growth performance in piglets (Wu et al., 2023). There is insufficient data on the effects of using probiotics on colostrum quality in sheep nutrition. Nouri et al. (2023) have demonstrated that prepartum and postpartum feed restriction in fat-tailed dairy sheep does not affect colostral IgG or lamb serum IgG concentration. Vaccination has important effects on colostrum quality and PIT in newborns; higher serum antibodies in ewes would effect antibody concentrations in colostrum (Burezq and Khalil, 2022).

Factors up to litter: Not only lambs but also kids and calves need to access colostrum in sufficient amount and quality. In the literature it is controversial the relationship between litter size and colostrum quality. While some studies (Mandal et al., 2007; Turkson and Sualisu, 2005; Yapi et al., 1990) have shown that there is a significant relationship between single and multiple-born lambs, other studies discussed multiple births may increase the risk of neonatal mortality (Holmoy et al., 2012). Alves et al. (2015) have shown that lambs demonstrated the failure of PIT once their a serum IgG concentration lower than 15 mg/mL at the 36th hour postpartum.. Similarly lambs have lower serum total protein (TP) concentration at 24th-hour postpartum show higher morbidity-mortality rates (Gokce and Atakisi, 2019). Management applications and animal characteristics (e.g. singleton or twin, birth weight, gestational diseases in ewes) are also associated with PIT (Gokce et al., 2013b).

Evaluation methods

Nowadays, various methods have been developed and still used to evaluate PIT in newborn ruminants. These methods are mainly divided into direct and indirect methods (Table 1). According to literature data, the most accurate method for evaluating colostrum quality is radial immunodiffusion (RID); Enzyme-Linked ImmunoSorbent Assay (ELISA) is also a reliable method (Lee et al., 2008; Cuttance et al., 2019). However, RID is an expensive laboratory method and requires time for results. Although it is not well-accurate, in farm-practice the best method is brix refractometry to evaluate colostrum quality because it is fastest and easiest method (Agenbag et al., 2023). Another method is Split trehalase immunoglobulin G assay (STIGA) that used in bovine colostrum (Drikic et al., 2018). Besides, the radial gel immunodiffusion

immunodiffusion technique can be used to determine serum and colostral IgG concentration (Castellaro et al., 2022). Total immunoglobulin levels of blood serum and colostrum can be evaluated by Zinc Sulfate Turbidity Test (Vatankhah, 2013). Transmission Infrared Spectroscopy (TIR) is also another direct method to measure colostral IgG concentration (Elsohaby et al., 2016).

Table 1. Common direct and indirect methods to evaluate colostrum quality.

Type	Method
Direct	RID
	ELISA
	STIGA
	TIR
Indirect	Refractometer
	Colostrometer
	Zinc Sulfate Turbidity Test
	Sodium Sulfite Turbidity Test

Capillary electrophoresis (CE) is also utilizable to evaluate colostral IgG concentration and it might be reliable method to evaluate total Ig concentration in sheep colostrum (Lopreiato et al., 2017). CE is suitable for a reliable estimate of IgG in lamb serum (Morittu et al., 2020).

Colostral TP and Ig concentration

The majority of total colostral protein is originated by immunoglobulins, especially IgG in ruminant colostrum. Management, gestational diseases, mastitis, age and parity are factors that affect colostrum quality (Swarnkar et al., 2019). Sufficient amount and quality of colostrum are important factors for the PIT. According to the ELISA method, values between 29.55 and 53.41 are considered high-quality (Alves et al., 2015; Constantin and Sipos, 2021). Brix refractometry can be used in farm practice to evaluate colostral protein and values are changeable (Table 2).

Table 2. Brix values of sheep colostrum in different studies.

Brix Values Range (%)	Breed	Reference
14.4 – 17.1	Awassi	Berge et al. (2018)
13.0 – 23.5	Crossbreed	Constantin and Sipos (2021)
8.6 – 40.0	Santa Inês	de Sousa et al. (2018)
16.8 – 22.6	Lacaune	Torres-Rovira et al. (2017)
15.4 – 40.0	Unknown	Kessler et al. (2021)
21.6 – 44.7	Merino	Agenbag et al. (2023)
16.8 – 27.0	Unknown	Todaro et al. (2023)

Immunoglobulin levels in lamb blood serum

There are different methods to estimate serum Ig levels. Detection of IgG levels by ELISA (Yenilmez et al., 2021) is one of the common methods. Healthy newborn lambs (in 21 days after birth) have significantly higher serum IgG levels than before they consume colostrum; and also their dams have higher colostral TP levels (Gokce and Atakisi, 2019). Laser-induced breakdown spectroscopy method also can be used evaluation of proteins in sheep colostrum (Abdel-Salam et al., 2019). That method is based on spectroscopic detection and analysis of atomic, ionic and molecular emission of a laser produced plasma; it can be used for in-situ and real time measurements (Harmon and Senesi, 2021). Another evaluation method is the Zinc Sulphate Turbidity Test (ZST) which creates turbidity which is proportional to the quantity of gamma globulin in the sample and can be quantified in a calorimeter at 525 nm/Spectrophotometer 460 nm. This method was used for the first time in the 70s to determine gamma globulin levels in calves. According to ZST, neonatal lambs with have total serum level below 12 are considered to indicate failure of PIT (Demis et al., 2020). Enzymatic colorimetric kits can be used to estimate serum TP and albumin concentrations (Alves et al., 2015).

Table 3. IgG, fat and protein concentrations in different breeds of sheep colostrum (Alves et al., 2015; Kessler et al., 2019).

Breed	*Component*		
	Fat (%)	*Protein (%)*	*IgG (mg/ml)*
Merino Land	7.44	22.49	44.2
Brown-Headed Meat	13.64	20.30	35.0
Swiss Charollais	8.05	17.55	28.9
Lacaune Dairy	4.04	14.07	20.2
Santa Inês	7.43	8.24	15.7

Conclusion

According to FAO 2022 report consumers especially in high-income countries, are more interested about what they eat and how their food is produced, processed and transported than undeveloped countries (FAO, 2022). Sheep farmers produce consumable products (meat and milk) and animal-by products (wool and skins) for national and/or international markets (Morris, 2017). These economical changes and feeding preferences lead farmers, governments and researchers to focus on small ruminant practices. Suckling lambs intake non-immunological factors such as nutrients, vitamins,

minerals, hormones, and growth factors alongside colostral IgG (Massimini et al., 2006). Because newborn lambs bore quite limited energy reserves, they need immediate access to intake colostrum that has enough amount and quality (Nowak and Poindron, 2006). Today, most veterinarians use field-based methods in livestock routinely which leads them to make medical decisions on newborns. There are two main reasons to detect PIT in practice: accurate diagnosis and treatment of newborns and ensure better management (Massimini et al., 2006; Pekcan et al., 2013; Elitok, 2018). Immunological differences between species or breeds lead to different strategies on farm-wide or country-wide. There are immunological differences between sheep species; for instance Bighorn Sheep (Ovis canadensis) lambs are more susceptible to Mannheimia haemolytica infections than the other breeds (Herndorn et al., 2011). Although there have been attempts to reduce lamb mortality in recent years (from 1970 to 2014), it hasn't changed significantly and has remained at an average of 15% in many countries (dos Santos et al., 2023). Gokce and Atakisi (2018) have shown that neonatal losses occurred mainly first week of life (84.6% rate). Eventually in nature, newborn mortality is an inevitable case

The major keys of PIT are colostral Ig concentration and absorption by the litter. In the literature, the role of colostral immunoglobulin concentration in passive immune transfer to newborn kids has demonstrated (Castro et al., 2005; Rodríguez et al. 2009). Gokce et al. (2013a) have shown that neonatal morbidity and mortality risks are higher in lambs who have low birth weight than in medium or high birth weight lambs in Kars province in Turkey. The lambing season may affect mortality rates, but some studies in the literature (Mukasa-Mugerwa et al., 2000; Tibbo et al., 2003; Berhan and Van Arendonk, 2006; Swarnkar et al., 2019) claim that season has a significant effect on mortality and some studies (Turkson and Sualisu, 2005; Mandal et al., 2007; Piwczynski et al., 2012) have indicated that birth season has insignificant effect. The influence of gender on neonatal mortality is controversial. While some studies (Vatankhah and Talebi, 2009; Ahmed et al., 2010; Abdelqader et al., 2017) have indicated higher mortality in male lambs compared to female lambs, Turkson and Sualisu (2005) reported higher mortality in female lambs. In a study on the Shaul breed (Brujeni et al., 2010), PIT wasn't affected by sex, litter size, parity and birth weight. Yenilmez et al. (2021) have showed that twin born affects TP and globuline levels in blood serum, but it does not affect IgG levels. Failure of PIT in lambs has a significant effect on neonatal mortality and losses due to infectious causes are positively correlated with low concentrations of serum immunoglobulins (Sallam, 2019; Ibrahim et al., 2020). Lamb's serum IgG levels at post partum 24th hour are between 21.51 and 81.25 mg/mL (Castellaro et al., 2022). Hunter et al. (1977) reported that these concentrations could be in a range of 0 to 102 mg/mL in post partum 24th hour. Increased 24th hour serum immunoglobulin levels have a significant relationship with growth performance in lambs (Gokce et al.,2013a). Eventually, newborn lambs should consume at least 30 g of IgG in the first 24 h postpartum to ensure adequate PIT (Alves et al., 2015).

In conclusion, the importance of small ruminant farming has been increasing especially in developed, high-income countries. Thus in consideration of economical losses, management and animal welfare have importance and lead us to evaluate PIT and new strategies on that aspect. On the other hand, lambs need to utilize enough maternal IgG via colostrum as well as consume high-quality colostrum.

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