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ASSOC. PROF. DR. KEZBAN ŞAHNA

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CONTENTS

CHAPTER 1

AN IMPORTANT CLOSTRIADAL DISEASE IN GOATS: GANGRENIOUS MASTITIS

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INTRODUCTION

Malignant edema, another name for gas gangrene, is a serious clostridial infection that affects all over the world. The primary characteristics of the disease in people and ruminant animals include necrosis in soft tissues, particularly muscles, and abrupt deaths (Silva et al. 2016). The etiology of gas gangrene is linked to several clostridial components, such as *Clostridium septicum, Clostridium sordellii, Clostridium chauvoei, Clostridium perfringens type A,* and *Clostridium novyi type A* (Srivastava et al. 2017). According to Knapp et al. (2010), the disease in animals is brought on by vegetative or spore forms of at least one species of Clostridium entering the body through scratches, scrapes, and wounds created during castration. Small ruminants' soft tissues are where Clostridium agents proliferate, albeit tissue damage is a significant factor. *C. septicum* can readily grow in certain locations without causing tissue stress since it is more aero-tolerant than other species (Gazioğlu et al. 2018).

One or both sides of the mammary glands may be affected by the clinical indications of gangrenous mastitis, which typically surface in the early weeks of breastfeeding. Fever, anorexia, dyspnea, and systemic toxemia are among its hallmarks (Ribero et al. 2007). On the affected side, the breast first feels warm, hurts, and has edema, milky pus, clotted pus, and/or blood. The breast's color changes, cooling, the marking of the afflicted area, the formation of an abscess, and pus leakage are all indicative of the process' progression. According to Anderson et al. (2005), deteriorating physical state, pneumonia, septicemia, and/or toxemia all indicate a fatal clinical course. Hemolytic infections caused by *S. aureus* or *M. aureus*, and gangrenous goat mastitis are typically linked to it. Antimicrobial and anti-inflammatory drugs taken in conjunction with fluid therapy, surgical drainage, debridement, and the removal of necrotic tissue are all part of the treatment (Cable et al. 2004). The current research details a unique instance of *S. aureus*-caused combination infection.

Numerous anaerobic, spore-forming, rod-shaped, gram-positive bacteria belonging to the genus Clostridium can be found in a range of settings, including soil, marine sediments, sewage, decomposing and rusted items, humans, and animals (Cook et al. 2001). Clostridium species infections are particularly significant because they frequently mediate the release of strong toxins in both humans and animals (Stevens et al. 2012; Akkaya et al., 2021). Owing to its widespread distribution, Clostridium infections can arise through spores, infected foods carrying preformed toxin(s), or vegetative cells. According to Zaragoza et al. (2019), deep wounds, lacerations, or burns with an appropriate anaerobic environment are also thought to be entrance points for pathogenic Clostridium. This page provides information on the etiology, clinical and microbiological diagnosis, and risk factors of gangrenous mastitis, a disease that is significant in agricultural animals, particularly dairy goats. Lastly, some technical recommendations on the matter are offered with the goal of reducing any financial losses.

ETHOLOGY

The most severe and challenging type of mastitis to treat is gangrenous mastitis, sometimes referred to as "blue bag," in which necrosis develops in the affected area (Alimi et al. 2020; Abubakar et al. 2024). The breast skin becomes blue after a few hours, indicating ischemia, hence the term "blue bag" (Al Salihi 2018). In the acutely infected mammary gland, pyogenic and saprophytic organisms proliferate quickly in the presence of high humidity and temperature (Abubakar et al. 2020). The virulent microorganism's alpha toxin acts on the endothelium of the mammary veins, causing thrombosis that causes gangrene. This can result in toxemia and the animal's mortality (Tufani et al. 2010; Pilau et al. 2011). According to Kumar et al. (2019), the clinical manifestation of mastitis typically appears in the first few weeks of breastfeeding, either with or without systemic pyrexia, anorexia, dyspnea, and toxemia symptoms.

Clinical evidence of gangrenous mastitis includes a blue-blackish or blue-greenish coloring of the udder skin, coldness to the touch, demarcation of the afflicted tissue, development of an abscess, and pus discharge. Clinical indications of pneumonia, septicemia, or toxemia are noted in the advanced stages of the illness (Abubakar et al. 2020). A radical treatment for gangrenous mastitis typically involves a radical or partial mastectomy because of the potentially fatal effects of toxemia. However, it has been reported that the combination of treatments, such as fluid administration, antibiotics, specific antitoxin therapy (Egwu et al. 2001), debridement in the case of a focal gangrenous area, anti-inflammatory drugs, and preservation and restoration of integrity, is successful in managing the condition and restoring milk production. breast in the management that followed the joke (Dewangan et al. 2020). One or more of the clostridial species *Clostridium cepticum, C. chauvoei, C. novyi type A, C. perfringens type A,* and *C. sordellii* have the potential to cause gas gangrene. These elements are widely present in the environment, and many animal species' gut microbiomes usually contain some of these elements. Additionally, all clostridial organisms might be frequent postmortem invaders. Given that invasion of intestinal tissues starts in the final minutes of life or soon after death, their existence in carcasses warrants a thorough investigation. The five clostridial species listed above produce strong poisons that have an effect on the host (Table 1).

Table 1. *Some characteristics of clostridal species that cause gas gangrene in animals*

Agent	**Toxin**	**Region**	**Mode of action**
C. septicum	Alpa	Plasmid or chromosome	Pore formation
C. chauvoei	Toxin A (CctA)	Chromosome	Pore formation
C. perfringes A	Alpa (CPA)	Chromosome	Phospholipase C/ sphingomyelinase
C. sordelli	Lethal toxin (TesL) haemorrhagic toxin	Chromosome	GTPase inactivation
C. novyi tip A	Alpha	Phage	GTPase inactivation

Source: Oliveira Junior ve ark. 2020

The primary causative agent of braxy in sheep and calves is *C. septicum*. According to Gomez-Martin et al. (2018), it is also the cause of gangrenous or clostridial dermatitis in poultry and gas gangrene in ruminants. Compared to other Clostridium species that cause myonecrosis in humans, *C. ceptum* may be more virulent and aerotolerant, which could explain its fatality (Srivastava et al. 2017). Serious financial losses in the livestock and poultry industries are caused by *C. septicum* infections (Salvarini et al. 2011). According to Navarro and Uzal (2016), malignant edema in agricultural animals has been linked to *C. ceptum* infection of wounds from vaccination, castration, dehorning, and other medical and surgical operations. Conversely, eating pasture that has frozen has been linked to braxy instances. Although *C. ceptum* is known to produce a wide variety of toxins (Kennedy et al. 2005), fatal alpha toxin (ATX) is the primary mediator of its pathogenesis. The csa gene codes for ATX, which is released as a 46 kDa prototoxin before undergoing proteolytic cleavage to become a 43 kDa active toxin (Chakravorty et al. 2015). Cell oncosis is caused by pore-forming ATX, which shares structural similarities with Aeromonas Hydrophila's aerolysis. ETX of types *B* and *D C. perfringens*. Phylogenetically linked to *C. chauvoei, C. ceptum* possesses a similar agrD gene that is recognized for controlling virulence in other pathogenic Clostridium species. Nevertheless, the regulation of ATX production is not the focus of molecular investigations (Prescot et al. 2016).

RISK FACTORS

According to Gouveia et al. (2015), there are a few risk factors associated with the condition that might come from the individual, the environment, the equipment, the milking system, and the practitioner. Below is a summary of each of these.

a. Individual Risk

A risk factor for heightened vulnerability to intramammary trauma and contamination could be the anatomy of the breasts. Furthermore, the udder structure, which is compact, well-supported, and permits full milk deposition with teat cups implanted at the base of the udder cistern, can influence machine milking (Casu et al. 1983). A number of writers have put out some standards for assessing breast features. The genetic enhancement of the breast could be made possible by selection based on these phenotypic traits (Gelasakis et al. 2012). Due to microbial penetration and the growth of pre-existing bacteria, mastitis can arise and persist as a result of keeping milk in the udder cistern and using improper milking techniques (Bergonier et al., 2003). Skin infections after trauma and lesions from pustular dermatitis can accelerate the development of infections, particularly staphylococci-related infections.

b. Hygiene of the environment

According to Silanikove et al. (2014), hygiene is crucial in lowering the bacterial load in the surroundings and so preventing mastitis brought on by external microbes. The microbiological cleanliness of the water used to wash the milking machine and proper litter control are crucial in rural sheep and goat dairy farms. The sanitary and hygienic quality of production is also impacted by good hygiene management practices on the farm. In order to minimize the microbial load and guarantee that the greatest number of germs are eliminated from the environment, proper cleaning is required.

c. The Milking Machine and Routine

Milk quality and udder health are impacted by milking practices. As a result, milking needs to be done under hygienic conditions and according to the right protocols (Romero et al. 2020). Small ruminants are particularly sensitive to stressful events, hence it is best to minimize sudden movements and sounds during milking (Sevi et al., 2009). In order to assess any anomalies in the milk caused by clinical mastitis, it is advised to examine the foremilk. According to Sevi et al. (2012), the milking machine poses a risk for the emergence and spread of udder illnesses since it can injure the teat, induce infections in animals, and function as a conditioning element in the presence of abnormalities. According to Bademkıran and Doğruer (2016), the safety and dependability of a milking machine are contingent upon its proper installation, usage, and management about milking practices, maintenance, and cleaning. When milking machines are not properly cleaned, a lot of bacteria, particularly those that create biofilm, find an ideal growing environment and tend to proliferate, making milking equipment a potential source of illness.

d. Factors Originating from the Practitioner

Drug infusions into the breast during the dry period or during nursing may damage the breast duct and, if not done with good hygiene practices, may make it easier for pathogens to enter the breast duct, particularly *Pseudomonas* and *Aspergillus* (Las Heras Domínguez et al. 2000, Lopez et al. 2000).

PROCEDURES FOR TRANSMISSION

Most cases of gas gangrene begin with the contamination of wounds with spore or vegetative forms of histotoxic Clostridia (Davies et al. 2017). Spore development and the growth of vegetative forms of gas gangrene are facilitated by low redox potential, metabolites of the broken protein, and an acidic pH. The generation of poisons that eventually cause the recognizable lesions and clinical indications of gas gangrene follows this. The idea that some cases of gas gangrene, especially in non-human primates and infrequently in horses, may have a pathophysiology similar to blackleg is supported by the description of cases with no signs of trauma (Springer et al. 2009). After consuming *C. chauvoei* spores, which have had one or more reproductive cycles in the colon, the spores enter the bloodstream and go to different parts of the body, such as the heart and skeletal muscle, where they dormantly dwell for varying lengths of time. The spores germinate, multiply, and generate the disease-causing toxins when blunt trauma or other injuries that do not result in skin or mucosal wounds occur and induce a reduction in redox potential (Stevens et al. 2012). For other clostridial species, a similar pathophysiology has been hypothesized but not proved. When endothelial cells are first affected by clostridial toxins in gas gangrene instances, alterations in circulation ensue, leading to edema, bleeding, ischemia, and local necrosis. The conditions in this ecosystem are perfect for these bacteria to live, grow, and create additional toxins. Collagenases, DNases, hyaluronidases, and neuraminidases are among the enzymes produced by histotoxic clostridia that facilitate the progression of infection by causing tissue damage, early host defense evasion, and nutrition acquisition (Silva et al. 2016). When poisons enter the bloodstream, toxemia develops, which is followed by shock and death. Because gas gangrene agents are found in the blood and different organs, bacteremia is also frequently occurring (Roth et al. 1999). Because CPA and PFO are strongly hemolytic, intravascular hemolysis may also happen in cases of C. perfringens type A.

CLINICAL FINDINGS

Breast or systemic symptoms can be used to make a disease diagnosis. A general evaluation is necessary in the event of a systemic disease (Zaragoza et al. 2019). It takes a clinical examination of the breast to identify anomalies in the mammary gland. Palpation is the sole way to detect hardening and volume increases in the supramammary lymph nodes. Physical alterations in milk secretion are frequently linked to clinical mastitis.

A. Microbiological Diagnosis

Identification of the microorganism causing intramuscular mammitis is necessary to develop disease control plans, track animal health, evaluate the pathogen's susceptibility to antibiotics, confirm the efficacy of treatment, and produce autovaccine (Cannas et al., 2007). A reliable bacterial culture test requires sampling. To avoid unintentional bacterial contamination that could "hide" the growth of the causative infection, the sample should be obtained in an aseptic environment (Carter and Cole, 2012). To replicate the microbial content of the original sample without modifying the culture is the goal of a successful bacteriological test. Improper sampling might lead to microbial contamination, which can complicate the accurate interpretation of the results. Microbiologists should suspect improper sampling if they find contaminated plates. To preserve the microbial composition in the laboratory, samples should be analyzed within 24 hours of collection or frozen until analysis (Cannas et al. 2019).

The coexistence of many etiological agents, which may be present in quantities below the microbiological detection threshold or can be reliably removed by milk, should be considered when calculating the sample size (Contreas et al. 2007).

Sample Types: Single samples of milk from two half breasts are taken; these exhibit lesser sensitivity and specificity than the half-breast sample due to the dilution effect, but may be collected more quickly.

-Half breast pound sample is identified with higher accuracy and decreased possibility of contamination.

-A "tank sample" or group of two animals is taken. This figure may be raised in cases where contamination levels are high. As a screening test, it can also be conducted.

-The only need to sample tank milk in its whole is to look into infectious bacteria. They cannot be regarded as trustworthy for the detection of other environmental microorganisms since they are unable to differentiate between contaminating bacterial flora.

How to Get Samples?: Careful sampling is necessary to avoid contaminating milk with bacteria from the breast, teat, or skin (Dore et al. 2011). The work done in the laboratory could be meaningless if the material is contaminated, necessitating a second run. Costs go up and diagnosis is delayed as a result. It is required to wear disposable gloves when collecting samples.

a. Use paper towels and disinfectant to thoroughly wipe and sanitize the nozzle before collecting a sample. It is necessary to transfer the initial milk sample into a container.

b. When collecting the sample, take care to hold the test tube firmly and to prevent contamination from the animal's udder or the hand of the person collecting the sample. Once the tube is about two thirds full, cap it right away.
c. As soon as the sample is taken, it should be placed in the refrigerator and sent to the laboratory right away.

B. Diagnosis of Molecular Genetics

Mastitis can be diagnosed using biomolecular diagnostic techniques including Real-Time PCR and Polymerase Chain Reaction (PCR). Compared to culture procedures, these techniques are typically faster and more sensitive. The foundation of PCR is the direct amplification of tiny portions of specific DNA sequences from mastitis pathogens in milk samples (Zanetti, 2005). Based on this method, diagnostic kits can identify several causal germs like *Staphylococcus aureus, Streptococcus agalactiae*, and *Mycoplasma bovis*. These kits are primarily designed for species that impact dairy cows. As an alternative, primers found in scholarly publications can be used to develop customized PCR assays for particular sheep mastitis infections. Nonetheless, it is frequently challenging to discriminate between groups of related bacterial species (Waminal et al. 2019). Consequently, only situations where it is crucial to confirm or rule out etiological agents that are already known to exist in the herd should warrant the use of molecular testing. In order to avoid false positive results in traditional culture, biomolecular methods (PCR) offer a response time of less than a day, the ability to analyze milk samples from treated animals or milk that has bacteriostatic substances added to extend shelf life, and the ability to analyze milk samples contaminated with ubiquitous microorganisms. (Yasser et al., 2014). It should be noted, nevertheless, that one of the PCR method's drawbacks is that it is "targeted," meaning it can only identify the pathogen for which the test is intended; Furthermore, the detection of bacterial DNA carries a risk of false positive interpretation because no information regarding the survival of the DNA is known.

DISEASE CONTROL AND PREVENTION

Since gas gangrene is typically an acute condition, treatment options are frequently limited (Mişlnes and Platter, 2003). This is particularly true for animals raised intensively and for species not under careful observation (Silva et al. 2005). On the other hand, therapy can be attempted in horses if an early diagnosis is discovered. High doses of antibiotics, preferably beta-lactams like narrow-spectrum penicillin, should be administered to affected animals whenever possible. These medicines have a high level of activity against the agents that cause gas gangrene and have minimal effects on the normal microbiota (Aldape et al. 2018). When feasible, use potassium or sodium penicillin instead of procaine penicillin because of the volume and frequency required, which can cause irritation. This therapy has very little effect on ruminants (Gazioğlu et al. 2018). It has been recommended that horses receive large doses of antibiotics, anti-inflammatory drugs, hydration therapy, and either a fasciotomy or myotomy during the first 24 hours following hospitalization (Power, 2003). 32 horses with 37 incidences of gas gangrene had fasciotomy or myotomy treatment. The effectiveness of treatment for gas gangrene in wild animals is not well-documented (Islam et al. 2011).

TREATMENT METHODS OF GAS GANGRENE IN GOATS

Goat gas gangrene is a serious medical condition that needs to be treated by a veterinarian very once (Najeeb et al. 2013). Treatment frequently consists of;

a. Veterinary Examination and Diagnosis: The first step involves the veterinarian assessing the goat's health and making the diagnosis of gas gangrene. A physical examination, blood tests, ultrasounds, or x-rays are examples of diagnostic instruments that the veterinarian can use to ascertain the ailment.

b. Eliminating Gas: The veterinarian has several techniques at his disposal to get rid of any gas that has built up in the goat's digestive system. This could involve techniques like moving the goat around or massaging the anus to expel gas or along the goat's digestive tract.

c. Fluid and Electrolyte Therapy: Since dehydration is a common side effect of gas gangrene, it's critical to give the goat fluid and electrolyte support. Fluid and electrolyte administration or intravenous therapy are two possible methods for doing this.

d. Antibiotic Treatment: The veterinarian may advise antibiotic treatment if gas gangrene develops as a result of an infection or if an infection is possible. This procedure aids in infection control.
e. Painkillers: To aid in the goat's relaxation and a peaceful recuperation, the veterinarian may prescribe painkillers.

f. Nutrition and Care Modifications: By making adjustments to feeding and herd management techniques, the veterinarian may attempt to promote the health of the goat's digestive system. This could entail taking steps like improving feeding practices, lowering stress levels, and offering high-quality feed.

Goats with gas gangrene have a dangerous illness that, if neglected, can be fatal. As a result, it's critical to keep a careful eye on the goats' health and seek veterinarian assistance.

STRATEGIES TO BLOODY GANGRENE IN GOATS

Veterinarians and company owners alike need to know how to treat bloody gangrene in goats (Bedruddin, 2023). The list of tactics that have been used for this aim is provided below.

Vaccination and Treatment: Immunizations have been created to prevent diseases like bloody gangrene. Regular vaccinations can stop the spread of disease in goats. Additionally, in order to cure afflicted goats and alleviate symptoms, veterinarian assistance is crucial.

Quarantine: To stop the transmission of disease, quarantine measures must be put in place before any additional animals are brought onto the property. One of the most crucial steps in safeguarding the current herd is to quarantine new animals for a minimum of several weeks and conduct health examinations.

Cleanliness and Hygiene: Farm hygiene is crucial. The danger of illness transmission can be decreased by routinely cleaning goat shelters, sanitizing tools, and paying attention to worker hand hygiene.

Herd Monitoring and Early Diagnosis: It's critical to keep a close eye on the goat herd in order to spot illness symptoms early on. An early diagnosis can help control the disease's progress and improve the effectiveness of treatment.

Herd Isolation: It is imperative to keep a sick or sickly-looking goat apart from other goats. By doing this, the herd's ability to contract diseases may be reduced. Several of the above-mentioned tactics can be useful in the fight against blood gangrene. To identify the best tactics, it's crucial to enlist the assistance of veterinarians and other specialists, as each company and area is unique.

SUGGESTIONS

The spores of many common clostridial species are incredibly resistant to environmental changes. This complicates the disease's eradication. Animal vaccinations against the disease and stringent hygienic measures are critical to its prevention. Aseptic procedures and appropriate carcass handling are required during wound-inducing activities in order to minimize Clostridium contamination. In domestic animals, gas gangrene is still a prevalent disease that can afflict individual mammals or entire populations. Veterinarians can lessen the impact of the disease in animals by identifying risk factors and implementing preventative measures with the support of up-to-date information on the topic. Therefore, it is important to remember that giving sheep and goats with gangrenous mastitis a single dose of the mastitis vaccine at the start of their treatment will enhance standard clinical treatment procedures and increase the milk production of the vaccinated animals.

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CHAPTER 2

IDENTIFICATION AND PREVALENCE OF SOME IMPORTANT PATHOGENS PLAYING A ROLE IN NEONATAL CALF DIARRHEA IN DIFFERENT REGIONS OF TURKEY

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INTRODUCTION

Diarrhea; It is a symptom that occurs due to infectious and non-infectious causes and is characterized by the volume of the stool, the amount of liquid it contains, and the increase in the frequency of excretion. This problem poses a significant challenge to cattle farming enterprises, especially with neonatal calves; It has high morbidity and mortality rates and can negatively impact businesses economically (Khan and Khan, 1991; Hall *et al.,* 1992; Radostits *et al.,* 1994; Lorenz *et al.,* 2011a; Renaud *et al.,* 2019). Diarrhea in newborn calves is a major health problem associated with dehydration, and weight loss. The severity of the diarrhea may depend on the causative agents, which contain a number of enteropathogens (bacteria, viruses, fungi, protozoa, and helminths), and their interaction with other factors such as environment, other etiologic agents, management, and host factors (i.e., immunosuppression, malnutrition, and stress (Hoet *et al.,* 2003; Ganapathy *et al.,* 2023). During pregnancy, ruminants do not transfer immunoglobulin from mother to fetus. For this reason, calves are usually born hypogammaglobulinemic or agammaglobulinemic and receive the necessary immunoglobulins through colostrum and milk after birth (Arda, 1994; Yılmaz and Akgül, 2014). Calves start producing their own immunoglobulin on the 10th day after birth and reach normal plasma immunoglobulin levels when they are 60 days old. This may cause infectious diarrhea to be common in neonatal calves (Çakıroğlu *et al.,* 2010; Yılmaz and Akgül, 2014). During the first 28 days of their lives, enteropathogens such as *Bovine rotavirus* (BRV) Bovine coronavirus (BCV), *Escherichia coli* (E. coli) and *Cryptosporidium* (Crypto) are common factors that cause diarrhea in neonatal calves, either alone or as mixed infections (Kozat, 2000). Among these enteropathogens, it has been reported that *Bovine rotavirus* (BRV) is the most common viral agent in neonatal calf diarrhea, along with *Bovine coronavirus* (BCV) (Snodgrass *et al.,* 1986; Clark, 1993; Schaefer, 2000). Among bacterial factors, *E. coli* is an important enteropathogen in neonatal calves. Additionally, *Cryptosporidium* spp. The prevalence and zoonotic importance of parasitic agents such as *Giardia* and Giardia are increasing day by day. In addition to viral, bacterial and parasitic factors, non-infectious factors such as unfavorable shelter conditions, animal breeders with low education levels, insufficient colostrum intake and neglect of umbilical cord care are also effective in neonatal calf diarrhea (Kozat, 2000).

In Turkey, important studies are carried out to obtain healthy calves and protect them from diseases. In this context, it has been observed that research on the causes and factors that cause diarrhea, especially in calves, has increased rapidly in recent years (Kozat, 2000; Özkan and Akgül, 2004; İçen *et al.,* 2013). Effective control and prevention of calf diarrhea is based on a detailed understanding of various enteropathogens, complex pathogen combinations, environmental variables and care-nutrition factors.

In this review, we aim to provide insight into which factors are most frequently detected in which regions in Turkey, using data from studies on the specific enteropathogens and their prevalence in diarrhea occurring in neonatal calves in neonatal period, and to provide veterinarians with a guide on prevention and control strategies.

Animal Material

The scope of this research; In Bursa province in the Marmara region of Turkey, in Burdur province in the Mediterranean region, in Ankara province in the Central Anatolia region, in Elazığ, Erzurum, Kars, Van, Bingöl and Muş provinces in the Eastern Anatolia region, in Tokat in the Central Black Sea region, in Manisa and Aydın provinces in the Aegean region and in Sivas province of the Central Anatolia region. It consists of data obtained from research conducted in seven different regions. For this research, detailed information has been given about the rate of presence of enteropathogens that cause diarrhea in the neonatal period, the distribution of pathogens in the regions and the methods of identifying pathogens. Within the scope of the research, studies on calves with neonatal diarrhea from 1984 to 2023 were examined. For this review, data from 18 scientific studies were examined and evaluated.

Detection of diarrhea factors from stool samples

They used different techniques and methods to detect enteropathogens in calves used in research. While some studies identify the causative agent using rapid diagnostic test kits, some studies do not identify the causative agent; They detected the agent using the Carbol-fuchsin technique, ZnCl+NaCl centrifugal flotation technique, RT-PCR Test and Modified acid fast staining method.

Statistical Analysis

The obtained data were used to determine the rate and frequency of occurrence of the factors for descriptive statistics. SPSS (version-21) statistical package program was used in the calculations.

Biochemical Findings

Within the scope of this research, data obtained from 18 studies conducted so far on 1795 calves with diarrhea were examined. In these data, the distribution, prevalence and occurrence rates of enteropathogens were compared on a regional basis. According to data analysis, while the Bovine rotavirus agent was at the highest rate in Tokat and Ankara provinces of Turkey, it was determined that the Bovine coronavirus was at the highest rate in Turkey's Muş province. The highest rate of *Cryptosporidium* spp. was detected in Burdur province and its surroundings with 26.04% and in Aydın province with 55.09%. The results of studies on the prevalence of enteropathogens in many regions in Turkey regarding calves with neonatal diarrhea are summarized in Table 1.

Table 1.: *Some studies and findings regarding the prevalence of infectious agents in calves with neonatal diarrhea in Turkey.*

Researchers	Number of materials	Region /Province	Infectious factors					
			Seyir	BTV (%)	BCV (%)	*Crypto* (%)	*E. coli* (%)	*Giardia* (%)
Burgu (1984)	56	Karacabey (Bursa)	Mono			26.7		
Alkan *et al.* (1992)	97	Ankara	Mono	26.8				
Burgu *et al.* (1995)	78	Muğla Kırklareli Tekirdağ Samsun, Denizli Ankara Muş Bursa	Mono	33.6				
Alkan (1998)	83	Bursa Şanlıurfa Konya Denizli Samsun Ankara	Mono	44.57	9.63			
			Mono+ co-infection	53.01	18.07			
Erdoğan *et al.* (2003)	104	Kars	Mono	26.9	0.96			
Sahal *et al.* (2005)	109	Ankara	Mono			35.8		
Çabalar *et al.* (2007)	89	Van	Mono	17.97	1.12			
Sarı *et al.* (2008)	189	Erzurum	Mono			22.8		
Al and Balıkçı (2012)	30	Elazığ	Mono	30	13.33	0	16.66	
			Mono+ co-infection	36.66	16.66	0	20	
Altuğ *et al.* (2013)	51	Van	Mono	21.56	1.96	3.92	21.56	
			Mono+ co-infection	27.45	1.96	5.88	27.45	
Kaya and Coşkun (2018)	107	Tokat	Mono	30.84	0	1.87	1.87	12.15
			Mono+ co-infection	44.86	9.35	11.21	7.48	16.82
Bal (2019)	100	Manisa	Mono	2	3	23	26	
			Mono+ co-infection	14	12	35	40	
Kuliğ and Coşkun (2019)	138	Sivas	Mono	7.24	3.62	3.62	23.18	
			Mono+ co-infection	21.73	9.42	5.79	26.08	
Taş and Kozat (2023)	96	Muş	Mono	10.41	25	5.2	7.29	
			Mono+ co-infection	37.5	52.08	5.2	7.29	
Çelik an Kozat	98	Burdur	Mono	11.45	7.29	26.04	12.5	6.25
Balıkçı *et al.* (2023)	167	Aydın		37.13	19,76	55.09	5.39	%7,19
Güreli and Kara (2023)	80	Kırkale	Mono	10	25	10	15	3.75
			Mono+Mik	23.75				
Keçeci *et al.* 2023	120	Bingöl	Mono	16.81	9.16	11.67	17.50	3.33
	1795							

Mono-infection: Infection in which the infectious agent occurs alone, **Co-infection:** Infection or co-infection in which the infectious agent occurs simultaneously with other enteropathogens

It is a fact that calf diarrhea still causes economic losses in cattle farms, despite modern veterinary practices. In addition to diarrhea treatments, determining etiological factors and taking preventive measures is becoming increasingly important. Diarrhea caused by infectious and non-infectious factors in newborn calves worldwide and digestive system disorders caused by diarrhea are the main reasons contributing to calf deaths (Alimirzaei and Nikkhah, 2022). As stated by Walker (1998), the fact that diarrhea in newborn calves causes high morbidity and mortality constitutes a serious problem in the cattle industry. Worldwide, one of the main causes of calf deaths and financial losses to the cattle industry is losses due to diarrhea (Von Buenau et al., 2005; Wudu *et al.,* 2008; Kozat, 2019). It is stated in the literature that various factors play a role in the emergence of diarrhea and that environmental factors, the effects of infectious agents, nutrition and many factors affecting the immune system interact in a complex manner (Waltner-Toews *et al.,* 1986).

Precautions taken starting from the pregnancy period are of great importance to reduce the frequency of calf diarrhea (Şahal *et al.,* 2018). It has been emphasized in many studies that taking the right precautions in cases of diarrhea, especially giving colostrum on time and sufficiently, plays a critical role in strengthening the immune system of calves (Göncü, 2013; Şen *et al.,* 2013). In addition to colostrum, improving the housing conditions of enterprises and ensuring hygiene can make significant contributions to the growth of calves in a healthier and more disease-resistant manner (Kozat, 2000). When the scope of research on calves with neonatal diarrhea is evaluated; It is stated that diarrhea cases are less common in enterprises where the dry period is applied during pregnancy and protective vaccination is applied during the dry period during pregnancy (Taş, 2022, Çelik, 2023). It has been determined that adequate colostrum intake, as well as appropriate shelter conditions and balanced nutrition, are of great importance in raising healthy and disease-resistant calves during the neonatal period.

This situation causes calves to decrease in their resistance to diseases and to the emergence of health problems such as diarrhea, as calves are not raised in a hygienic environment and proper care is not provided (Waltner-Toews et al., 1986; Göncü, 2013; Şen et al., 2013; Kozat, 2000; Kozat and Tuncay, 2018).

According to statistics, the rate of diarrhea cases in newborn calves is over 50%, and the calf mortality rate varies between 1.5 and 8% depending on these cases (Frank and Kaneene, 1993).

Similarly, in Turkey, calf diarrhea is accompanied by high levels of morbidity and mortality; This situation still continues to be an important problem today due to reasons such as high treatment costs, poor performance and death causing economic losses (Uzlu et al., 2010; Taş and Kozat, 2023).

Bovine rotavirus is the most recognized pathogen causing acute diarrhea in calves under one month of age worldwide (Geletu *et al.,* 2021). Bovine rotaviruses cause the destruction of enterocytes during their journey from the oral tract to the small intestine, causing shedding in the intestinal cavity (Kozat 2000). As a result of the replication of these viruses, disruptions occur in the digestion and absorption mechanisms (Saklı, 2017). Microorganisms such as *Bovine rotavirus, Bovine coronavirus*, *E. coli, Cryptosporidium* spp. and *Giardia* are stated as the most important causes of calf diarrhea (Khan and Khan, 1991; de La Fuente *et al.,* 1998; *Langoni et al.,* 2004; Lorenz *et al.,* 2011b).

It is emphasized that there is no single cause of neonatal calf diarrhea; instead, multiple factors play a role, and regular and accurate fluid-electrolyte treatment is as important as an effective chemotherapy treatment to reduce high mortality rates due to diarrhea (Cho and Yoon, 2014). When the data of studies in Turkey were examined, it was revealed that the enteropathogens detected in neonatal calves with diarrhea were similar to the infectious agents identified by previous researchers (Khan and Khan, 1991; de La Fuente *et al.,* 1998; Langoni *et al.,* 2004; Lorenz *et al.,* 2004). al., 2011; Cho and Yoon, 2014).

It was determined that in addition to providing appropriate hygiene conditions, taking into account multiple etiological factors plays a critical role in the control and prevention of diarrhea. Many studies indicate that a holistic approach is required to effectively manage cases of calves with diarrhea. Diarrhea occurring in neonatal calves significantly affects milk production losses and calf mortality rates. Therefore, it is of great importance to quickly identify the factors that cause diarrhea and apply effective treatment methods in order to reduce diarrhea-related losses and alleviate its effects (Murat and Balıkçı, 2012; Kozat and Tuncay, 2018).

For this purpose, rapid diagnostic test kits are widely used (Al and Balıkçı, 2012; Kozat and Tuncay, 2018; Bal, 2019). Immunochromatographic ready-made diagnostic kits help to quickly and effectively to detect the causes of diarrhea in newborn calves, thanks to their ability to obtain rapid results under field conditions, low cost, easy applicability, and ability to analyze multiple factors (Kozat and Tuncay, 2018). In recent years, rapid diagnostic test pantries have been widely used in Turkey to detect *Bovine rotavirus*, *Bovine coronavirus*, *Cryptosporidium* spp., *E. coli K99* and *Giardia lamblia* from fresh stool samples in a short time such as 5-10 minutes. Many studies have been conducted on *Bovine rotavirus*, which causes diarrhea in newborn calves in Turkey. In a study by Burgu et al. (1995), the *Bovine rotavirus* rate was determined as 33.6%. In Al and Balıkçı's (2012) research, this rate was found to be 30%. In a different study, Alkan (1998) and his team detected 53% *Bovine rotavirus* in Ankara. In another study conducted in Ankara, Alkan et al. (1992) found the Rotavirus rate to be 26.8%. In the study conducted by Erdoğan and his team (2003) in Kars, this rate was found to be 26.9%. In a study conducted in Manisa, the rate determined by Bal (2019) was reported as 14%. In the study conducted in Van, Çabalar and colleagues (2007) detected *Bovine rotavirus* at a rate of 17.97% (Çabalar *et al.,* 2000; Bal, 2019).

Bovine rotavirus infections can often occur as mixed infections (Garcia *et al.,* 2000). In the research conducted in Turkey's Burdur province and its surroundings, mixed Bovine rotavirus infection was detected in 26 of 96 calves (27.08%) in total. The single infection rate was found to be 11.45%.

Additionally, it has been determined that the stool in diarrhea due to *Bovine rotavirus* infection is generally yellow and watery. These findings emphasize that *Bovine rotavirus* infection may begin at an early age in neonatal calves and that the risk of disease continues at young ages (Rodger et al., 1982; Walker *et al*., 1998; Çelik 2023). *Bovine coronaviruses* cause diarrhea due to decreased absorption and digestion, resulting in water and electrolyte loss (Clark, 1993). Diarrhea caused by *Bovine coronaviruses* has a more severe course compared to *Bovine rotaviruses*. In many studies conducted on Bovine Coronavirus in Turkey, different rates were obtained in different regions. While Al and Balıkçı's (2012) study in Elazığ determined the *Bovine coronavirus* rate as 13%, in Altuğ et al.'s (2013) study in Van, this rate was found to be 1.96%. In other studies, *Bovine coronavirus* rates are as follows: 7% in the study conducted in the Siirt region (Kozat and Tuncay, 2018), 9.35% in the Tokat region (Kaya and Coşkun, 2018), 9% in the Manisa region (Bal, 2019), 9% in the Sivas region (Kuliğ and Coşkun, 2019), 25% in the Muş region (Taş and Kozat, 2023).

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In the research conducted in Burdur province and its surroundings, Coronavirus was detected alone in 5 of 96 neonatal calves with diarrhea aged 1-28 days, and the number of infected calves reached 12 with the mixed ones. In this context, it is stated that while the coronavirus's single occurrence rate is 5.20%, its mixed prevalence rate is 12.5% (Çelik 2023). These results show that geographical differences and climatic conditions in Turkey may affect the spread of *Bovine coronavirus*. Different rates have been obtained in studies conducted around the world. Coronavirus rate in calves with diarrhea in Scotland is 3.6% (Snodgrass *et al.,* 1986), 16.5% in the southwestern region of France (Bendali *et al.,* 1999), 10.7% in Spain (Garcia *et al.,* 2000), Switzerland. It was detected at a rate of 7.8% in calves with diarrhea aged 1-21 days (Lanz Uhde *et al.,* 2008), and 3.17% in 126 calves with diarrhea in Iran (Mayameei *et al.,* 2010).

Cryptosporidium species are zoonotic protozoans that cause gastrointestinal infections in various species (Guerrant, 1997*). Cryptosporidium* spp.is transmitted to animals via the fecal-oral route (Olson *et al.,* 1997). Infected calves expel oocysts along with their feces. Oocysts cause villous atrophy, degeneration and subsequent inflammatory changes, causing diarrhea (Sanford and Josephson, 1982). In particular, *Cryptosporidium parvum* is considered one of the main causes of calf diarrhea and is important as a potential zoonotic factor (Chalmers *et al.,* 2011; Grabbe *et al.,* 2023). In studies conducted in different regions in Turkey, *Cryptosporidium* spp. Data on the prevalence have been obtained

Many studies on *Cryptosporidium* spp. have been conducted in Turkey. According to the results of these studies, *Cryptosporidium* spp. is 26.7% in Bursa's Karacabey Farm (Burgu, 1984), 7% in Sivas (Kuliğ and Coşkun, 2019), 5.12% in Siirt (Kozat and Tuncay, 2018), 10.7% in Aydın (Özlem *et al.,* 1997), 7.2% in Elazığ (Özer *et al.,* 1990), 25.7% in Kars (Arslan *et al.,* 2003), 27.33% in Konya (Sevinç *et al.,* 2003), 35.8% in Ankara (Sahal *et al.,* 2005), 22.8% in Erzurum (*Sarı et al.,* 2008), 20.7% in Nevşehir (Şimşek *et al.,* 2012), 11.21% in Tokat (Kaya *et al.,* 2012). Coşkun, 2018), 5.12% in Muş (Taş and Kozat, 2023). While only Cryptosporidium infection was detected in 13 (13.54%) of 96 calves with neonatal diarrhea aged 1-28 days in Burdur province, 38 (39.58%) were found to have other factors along with Cryptosporidium infection.

It is reported that *Cryptosporidium* spp. may be effective alone or may cause diarrhea in combination with other factors (Çelik 2023). In a study conducted in Aydın province, the prevalence of the factors that cause diarrhea, regardless of whether they are mono- or co-infected, is *Cryptosporidium* spp. (55.09%), Rotavirus (37.13%), Coronavirus (19.76%), *Giardia* spp. (7.19%) and E. coli K99 (5.39%). Co-infections include Cryptosporidium spp. It was determined as the most common combination with + *Bovine rotavirus* (16.77%). According to calf health scores, the highest score (6.5) was *Cryptosporidium* spp. + In the combination of *Rotavirus* + *Coronavirus*, the lowest score (4) is *Cryptosporidium* spp. + Giardia spp. They were found to be in combination (Balıkçı *et al.,* 2023).

In a study conducted in Kırıkkale and surrounding provinces, they tested the feces of 80 calves with diarrhea for *Bovine rotavirus*, *Bovine coronavirus*, *Cryptosporidium* spp, *Giardia lamblia* and *E.coli K-99* with an immunochromatographic ready-made diagnostic kit. They found that no enteropathogen was found in 10 of the 80 calves with neonatal diarrhea included in the study, and a single enteropathogen was detected in 51 of the remaining 70 calves, and more than one enteropathogen was detected in 19 of them. They reported that they detected mono or mixed infection in the etiology of the calves included in the study: *E.coli K-99* in 18, *Bovine rotavirus* in 24, *Bovine coronavirus* in 34, *Cryptosporidium* spp. in 18 and Giardia lamblia in 3 (Gureli and Kara, 2023).

In studies conducted in other countries around the world, different rate of *Cryptosporidium* spp. have been obtained regarding its prevalence. 47.9% in newborns in Spain (Castro-Hermida *et al.,* 2002), 17.9% in France, 33.5% in Vietnam (Nguyen *et al.,* 2007), 13% in Canada, 27.9% in England (Brook *et al.,* 2008), 35% in America (Santin *et al.,* 2004) and 11% in Sweden (Lefay *et al.,* 2000; Björkman *et al.,* 2003; McAllister *et al.,* 2005). *Cryptosporidium* spp. It is stated that there are many risk factors that affect its prevalence. Factors such as the number of animals in the farm, the age of the animals, whether they are diarrheal or healthy, shelter type, suckling status, litter type and water source can have an impact on the prevalence of Cryptosporidium infections (Brook *et al.,* 2008; Trotz-Williams *et al.,* 2008). When we look at Cryptosporidium infections in Turkey and around the world, we see that the prevalence rates are different. It is thought that the reasons for these differences may be related to the geographical and climatic characteristics of the region where the studies were conducted, animal breeding practices, isolation of sick animals and the effect of environmental factors. Considering these risk factors on the prevalence of Cryptosporidium is important for protecting animal health and preventing zoonotic diseases. In the study, it was stated that Cryptosporidium infection had been seen in certain enterprises before, but the disease was prevented by the use of the drug called halofuginone. Although Cryptosporidium infection has been seen in calves between the ages of 3 and 20 days, it has generally been observed that the calves are between the ages of 7-15 days. These findings show that Cryptosporidium infection can be seen in neonatal calves in the first week and is more common in calves in the first week or two.

Escherichia coli infections are considered one of the leading causes of calf diarrhea, which usually occurs within 2-10 days after birth, and can rarely be seen within the first 24 hours after birth (Bilal, 2007). This infection, which is frequently encountered in the neonatal period, especially in 1-7 day old calves, stands out as one of the main causes of diarrhea worldwide (Rodostitis *et al.,* 2007). It has also been stated that enteropathogenic *E. coli* can be seen in neonatal calves within the first 30 days (Rodostitis *et al.,* 2007). E. coli K99 rates vary around the world, for example, 0.3% in Switzerland (Torsein *et al.,* 2011), 2.6% in Germany (Bartels et al., 2010), 16.1% in India (Suresh et al., 2010). 2015). In a study conducted in Spain, the mixed ratio of *E. coli K99* and *C. parvum* was found to be 27.8% (De la Fuente, 1998).

E. coli infection rates also vary in studies conducted in Turkey (Table 1). For example, in a study conducted in Siirt and its surroundings, the incidence of *E. coli* alone was reported as 6%, while the incidence rate in mixed was reported as 18% (Kozat and Tuncay, 2018). In a study conducted in the Tokat region, the rate of *E. coli* in calves with diarrhea was found to be 7.48% (Kaya and Coşkun, 2018). In Elazığ, the prevalence of *E. coli* in calves with diarrhea was determined as 16.66% (Al and Balıkçı, 2012). In the Van region, it was found to be 27.45% (Altuğ *et al.*, 2013). In a study conducted in Burdur province and its surroundings, it was observed that there were other factors along with E. coli infection, and it was stated that while the rate of *E. coli* alone was 12%, the rate of coexistence with other enteropathogens was 15.62% (Çelik 2023).

Research was conducted to reveal the prevalence of the most common pathogens that cause diarrhea using rapid diagnostic test (HTT) kits, standard diagnostic methods and RT-PCR tests in 120 calves with 0-30 days of diarrhea in Bingöl and its surroundings. According to this research data, the infectious agents that cause diarrhea in calves are proportionally; They detected eimeria 20.83%, *Escherichia coli* 17.50%, rotavirus 16.81%, *Clostridium perfringens* 13.27%, *Cryptosporidium* spp 11.67%, *Bovine* coronavirus 9.16% and giardia 3.33% (Keçeci et al., 2023).

Giardia infection usually occurs at the end of the neonatal period and usually causes acute diarrhea (O'Handley and Olson, 2006). Giardia lamblia is becoming increasingly important as it causes growth retardation in farm animals, reduces feed utilization and causes economic losses by causing diarrhea (O'Handley *et al.,* 2003). *Giardia lamblia*, which causes significant economic losses in calf diarrhea in Turkey, is among the etiological factors that are generally ignored in some studies (Ayan *et al.,* 2016). In one study, the presence and prevalence of Giardia was evaluated in the feces of 10,672 cattle aged 1-730 days, and Giardia was identified in 1,236 feces. It was determined that Giardia agents continued to spread as cysts in 1,184 of the animals in which Giardia was detected (Mark-Carew *et al.,* 2010).

In studies conducted in Turkey, Göz *et al.* (2006) detected Giardia at a rate of 14.7% in 231 newborn and young calves aged between 1 day and 8 months in Van. Kaya and Coşkun (2018) detected Giardia at a rate of 16.82% in 107 neonatal calves with diarrhea in Tokat. In the study in Burdur province, Giardia mono infection was detected in 6 of 96 1-28 day old neonatal calves with diarrhea, and it was reported that Giardia infection and other factors were present in 2 of them. While it is stated that the rate of Giardia alone was 6.25%, the rate of mixed calves was 8.33%.

In this review, the data of some important enteropathogens that caused diarrhea and were detected in cases of diarrhea in newborn calves in Turkey were evaluated collectively. When these data were examined, it was concluded that diarrhea in newborn calves in different regions of Turkey constitutes a significant problem for the cattle industry, causing high mortality and productivity losses. A difference was observed between the rates of occurrence of these factors alone and in mixed forms.

According to research data, it has been revealed that enteropathogens that play a role in neonatal calf diarrhea vary between regions. Considering that these factors can be seen in the first two weeks of the neonatal period, the importance of preventive measures in the emergence of diarrhea in neonatal calves was emphasized.

It was also observed in the research results that the shelter conditions and hygiene of the enterprises are of critical importance, especially in the emergence of diarrhea. As a result, in order to control diarrhea cases in newborn calves and reduce economic losses in cattle farms in Turkey, the factors should be identified quickly and accurately and effective treatment methods should be applied. In addition, according to the data obtained in the studies examined, it was concluded that producer training, animal care and nutrition, standardization of shelter conditions and taking protective measures are important in order to raise healthy and productive animals in the cattle industry.

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CHAPTER 3

THE IMPORTANCE OF FISH-BORNE PARASITIC AND BACTERIAL ZOONOTIC DISEASES FOR PUBLIC HEALTH

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1. INTRODUCTION

In recent years, people have been paying attention to their nutrition and therefore take care to consume healthy foods.Among these foods, seafood has the most important place.Aquatic products are essential for a healthy and balanced diet and are an important food source with their high protein value. It constitutes 17% of the animal protein consumed worldwide and 6.5% of all protein sources **(Naylor et al., 2000; Cabello, 2006; Maqsood et al., 2011; Reverter et al., 2014).**

According to the report published by the United Nations Food and Agriculture Organization (FAO) in 2022, world aquaculture production was announced as 182.8 million tons, and the highest increase compared to the previous year was in Ecuador with 24.8%.

When evaluated on a country basis; It has been stated that aquaculture production is not distributed homogeneously, and especially the countries in the Asian continent are ahead of other countries in aquaculture production. China is the leader with 64.2 million tons of aquaculture production, accounting for 35% of the total production.China is followed by India, Indonesia, Vietnam and Peru. According to FAO data, world aquaculture production is expected to reach 202 million tons in 2030 **(FAO,2023).**

The increasing prevalence of aquaculture creates disease problems caused by various viruses, bacteria, fungi and parasites that put the sustainability of the sector at risk **(Soler-Jiménez et al., 2017; Soares et al., 2017a, 2017b).** Excessive stocking density, negative changes in water quality, etc. Factors cause bacterial and parasitic diseases to be common.When these diseases cannot be treated, reasons such as slowing of growth and fish deaths can cause great economic losses in commercial enterprises.In addition, some of these diseases negatively affect human health due to their zoonotic character **(Bjöklund & Bylund, 1990)**.

Some diseases are transmitted from animals to humans or from humans to animals, and these types of diseases are called zoonotic diseases. Infections transmitted from fish to humans are defined as Ichtyozoonosis (fish zoonoses) **(Babu, 2000; Nemetz &Shotts, 1993).**

The report "Asia Pacific strategy: 2010" suggests that approximately 60% of human infections are zoonotic, and among these pathogens, more than 70% originate from wildlife species **(Rahman et al., 2020).**

Especially, non-compliance with hygiene conditions, stock density and animal reservoirs cause increases in such contamination.Factors such as environmental factors, climate change, unconscious drug use, formation of resistance to drugs and economic factors also lead to an increase in the severity of the problem.Factors such as healthier eating habits and preference for raw/

exotic fish dishes lead to an increase in the consumption of aquatic products and an increase in the incidence of diseases caused by these products **(Shamsi et al., 2018).**

Fish-borne zoonotic diseases worldwide cause significant problems in human health. With the developing aquaculture sector and fish trade, the risk of environmental contamination and the spread of fish-borne zoonotic diseases in humans also increases. Incidence of fish zoonoses; In countries where fish dishes are widely eaten, the increase in raw fish consumption has increased significantly due to reasons such as the widespread consumption of dishes prepared with raw or minimally processed fish, such as sushi and sashimi **(Lima dosSanto & Howgate, 2011)**.

2. Parasitic Fish Zoonoses

Parasites are extraordinarily diverse in aquatic ecosystems, which are likely the environments where parasitism first emerged. In this diversity; Cestodes, monogeneans, trematodes and myxozoans are among the most well-known parasites **(Adlard et al., 2015).**

While fish can be the intermediate host or final host of parasites, other creatures (birds, dogs, humans) can be the final host **(Quiazon, 2015).**

However, some of these parasites can also occur in other living species through aquaculture and advanced transportation and distribution systems.

It is stated that especially as a result of travel and migration, exotic diseases can be seen as well as infections caused by highly resistant protozoa that can be carried by water **(Dorny et al., 2009).**

Some parasites detected in fish (diphyllobothriidean tapeworms, anisakid nematodes, opisthorchid liver flukes and intestinal heterophyid) are considered to be among the most important foodborne parasites all over the world **(Cong & Elsheikha, 2021).**

Among zoonotic fish parasites, the helminth families Opisthorchiidae and Heterophyidae (Class Trematodea,Digenea sub. spp.), Anisakidae and Gnathostomidae (Phylum Nematoda) and Diphyllobothridae (Class Cestoda) come to the fore due to their high incidence. People acquire these fish-borne parasites by consuming infected raw, undercooked or improperly stored fish **(Lima dosSantos & Howgate, 2011)**.

More than 50 helminth species originating from aquaculture have been found to cause infection in humans worldwide. **(Bardhan, 2022)**.

2.1. Protozoa with Zoonotic Character

Zoonotic protozoans *Cryptosporidium* spp., *Giardia duodenalis* and *Toxoplasma gondii* are found in aquatic environments and mostly in shellfish

(Moratal et al., 2020). *Giardias* are considered to be one of the most common causes of diarrhea in humans and animals **(Caccio & Ryan, 2008)**.

Cryptosporidium spp. It is also considered a fish-borne zoonotic risk to humans. Different *Cryptosporidium* species have been identified in freshwater, marine and aquarium fish around the world.Infection can occur by consuming raw or undercooked fish contaminated with oocysts of the parasite or by consuming water contaminated with oocysts shed by fish feces **(Robertson et al., 2019).**

Diarrhea, vomiting, nausea, loss of appetite and cramps are common clinical symptoms of cryptosporidiosis **(Ryan et al., 2016; Ryan et al., 2018).**

Toxoplasma gondii is a prozoan species that has been isolated from almost all homoiotherm animals, including humans, livestock, and marine mammals. Infection in humans is usually asymptomatic and may show mild flu-like symptoms **(Zhang et al., 2014).**

Although fish are not considered the main biological hosts for *T.gondii*, it has been determined that they can be infested with oocysts that enter the marine environment through freshwater streams (such as sewage discharges, soil floods) and thus act as mechanical carriers **(Marino et al., 2019).**

T.gondii transmission to humans occurs through consumption of raw or undercooked contaminated fish **(Moratal et al., 2020).**

It is known that amoebic dysentery, caused by the intestinal protozoan parasite *Entamoeba histolytica*, affects 500 million people worldwide every year and causes the death of more than 55,000 people.

It is an important public health problem, especially in countries with inadequate sanitation and hygiene. It has been classified as a fish-borne parasitic zoonosis due to recent outbreaks in Southeast Asian countries.

Although it is mainly transmitted to humans through contaminated food and water (carrying cysts and trophozoites), consumption of raw fish obtained from rearing environments where sewage or wastewater is mixed and the application of traditional cooking techniques can be the main source of outbreaks. Clinical symptoms include abdominal pain, bloody diarrhea, dysentery and dehydration. **(Bardhan, 2022)**.

2.2. Zoonotic Trematodes

While trematodes use snails and fish as intermediate hosts, they use creatures such as humans, dogs and cats as definitive hosts **(Mahdy et al., 2021).**

The number of people infected with fish-borne trematodes is estimated to exceed 18 million worldwide. Moreover, it is thought that the number of people at risk, including those in developed countries, exceeds 500 million. Of the 33 digenic trematode species recorded to be transmitted to humans through the consumption of fish, crustaceans or molluscs, only a few pose serious threats.

Chlonorchis sinensis, *Clinostomum complanatum*, *Heterophyes heterophyes*, *Metagonimus yokogawai*, *Metorchis conjunctus*, *Nanophyetes salminicola*, *Opisthorchis viverrini* and *Paragonimus* spp. are considered the most important species among trematodes in terms of public health **(Chai et al., 2005; Ljubojevic et al., 2015; Bardhan, 2022).**

It is stated that there are 13 genera and 29 species of fish-borne heterophid (Heterophyidae) trematodes that infect humans **(Chai & Jung, 2017)**.

The best-known members of the Heterophyidae family are *Heterophyes heterophyes* and *Metagonimus yokogawai*.People become infected by consuming raw, marinated or undercooked fish. These digenic trematodes can cause inflammation, ulceration and necrosis in the small intestines.

In addition, it can cause severe and long-lasting infestations such as cholangitis, hepatomegaly, and cholecystitis, as well as gallbladder enlargement **(Ljubojevic, 2015)**.

Clinostomum complanatum (Rudolphi, 1814) is also a digenic trematode from the Clinostomidae family. *C. complanatum* is a zoonotic parasite that causes Halzoun syndrome and poses a threat to public health due to consumption of raw or undercooked fish. In human infestations, *C.complanatum* adheres to the mucosal membrane of the throat and often causes acute pharyngitis and laryngitis **(Menconi et al., 2020; Hajipour et al., 2022)**.

The Opisthorchiidae family consists of many opisthorchiid trematodes that infest the bile ducts, gallbladder and liver of predominantly mammalian and avian hosts. An estimated 45 million people in Europe and Asia are infested with these liver flukes.

It has also been determined that these liver trematodes cause bile duct cancer or cholangiocarcinoma **(Chai et al., 2005; Saijuntha et al., 2021)**.

2.3. Zoonotic Nematodes

Anisakidosis is a zoonotic parasite belonging to the Anisakidae family. Nowadays, it is reported that there is an increase in the cases of gastrointestinal infestations accompanied by allergic reactions caused by *Anisakis simplex* and *Anisakis pegreffii*. *Anisakis simplex*, raw, undercooked; After consumption of salmon, cod and mackerel, *A. simplex* larvae can settle in the stomach or intestinal mucosa in humans and cause abscesses or eosinophilic granulomas **(Aibinu et al., 2019).**

2.4. Zoonotic Cestoda

Cestodes are very common and are also called tapeworms. They are different from trematodes and are taller than tremadotes. *Diphyllobothriosis*, caused by "fish tapeworms" of different genera of the order Diphyllobothriidea, is an important fish-borne parasitic zoonosis responsible for the infestation of more than 20 million people worldwide. One of the most common agents of human diphyllobothriosis is *Dibothriocephaluslatus* (Cestoda: *Diphyllobothriidea*), formerly known as *Diphyllobothrium latum* **(Ziarati, 2022).**

The life cycle of this tapeworm includes two intermediate hosts (crustaceans and fish) and one definitive host.Humans are thought to become infected after consuming raw or undercooked fish fillets that contain plerocercoids, the infective larval stage **(Radacovska et al., 2019)**.

3. Fish Originated Bacterial Zoonoses

Table 1. *Fish bacterial zoonosis agents are reported by Austin & Austin (1999) as follows;*

Pathogen	**Disease**
Aeromonas hydrophila	Diarrhea and septicemia
Clostridium botulinium type E	botulism
Edwardsiella tarda	Diarrhea
Eryspelothrix rhusiopathiae	Erysipeloid
Mycobacterium fortuitum	Atypical Mycobacteriosis
Pseudomanas aeroginosa	Pneumonia
Plesiomonas shigelloides	Gastroenteritis
Streptecoccus inia	Endocarditis, Meningitis and Arthritis
Vibrio vulnificus	Septicemia and Wound infections

3.1. Aeromonas sp.:

Aeromonas are facultative anaerobic, oxidase-positive, Gram-negative bacteria found in the normal fauna of the aquatic environment.They are divided into two groups: motile (*Aeromonas hydrophila*, *Aeromonas sobria*, *Aeromonas caviae*, etc.) and immotile (*Aeromonas salmonicida*, *Aeromonas achromogenes*, *Aeromonas masoucida*). Dormant species are of little concern as human pathogens **(Quehl, 1993)**.

Aeromonas that cause disease in humans can occur with many different infections such as septicemia, wound infection, meningitis, peritonitis and liver dysfunction. Especially, it can cause infections such as bacterial gastroenteritis, septicemia, peritonitis and respiratory diseases **(Lau et al., 2000)**. Most of the diseases caused by *Aeromonas hydrophila* are associated with the consumption of seafood or long-term frozen ready made foods **(Daskalov, 2006).**

3.2. Clostridium spp.:

Members of the genus Clostridium, an anaerobic spore forming bacterium, exist as commensal organisms in the intestinal systems of freshwater and marine fish. Clostridium species cause serious infections in humans. Especially *Clostridium perfringens* and *Clostridium botulinum* are two important species that cause botulismus disease as a result of consuming contaminated fish **(Quehl, 1993).** It is reported that type E toxin is responsible for many disease cases that occur in humans associated with fish consumption **(Gauthier, DT. 2015).**

3.3. Edwersiella spp.:

Edwardsiella genus is a member of the Enterobacteriaceae family, and the species in this genus are Gram-negative, generally motile, facultative anaerobic microorganisms. *Edwardsiella tarda* causes diarrhea in humans **(Piersimoni & Scarparo, 2009).**

3.4. Erysipelothrix spp.:

Erysipelothrix species include *E. rhusiopathiae*, *E. tonsillarum* and *E. inopinata*. While the disease caused by *E. rhusiopathiae* in animals is known as "erysipelas", in humans the disease is called "erysipeloid" **(Gauthier, 2015**.This agent causes itching and burning in the fingers and wrist of the infected person. In addition, edema, septicemia, endocarditis, anemia and meningitis may also be observed in patients. It has been reported that zoonotic transmission to humans (fish handlers disease) caused by *E. rhusiopathiae* occurs among workers in the fishing industry. It is an occupational disease that particularly harms fishermen and workers in fish processing factories **(Babu, 2000; Nemetz et al. 1993).**

3.5. Mycobacterium spp.:

Mycobacterium infections are among the most common bacterial infections transmitted by fish **(Boylan, 2011).** It mostly affects people working in tanks and aquariums in aquaculture **(Chomel, 2015).** *M.marinum* and *M. fortuitum* are species that can pass from sick fish to humans **(Frerichs & Roberts R.J. 1989).** These bacteria, which are especially common in swimming pools, aquarium walls and ornamental fish, are transmitted to humans through skin wounds and cause granuloma infection.

The lesions develop on the ands and feet, first in a blue-purple color and then as granulomatous ulcers **(Bilgehan, 1995).**

3.6.**Pseudomonas sp.:**

Pseudomonas are Gram-negative aerobic rods, some of which produce pigments while others produce toxins **(Bergan, 1981)**. These pathogens are commonly found in water and soil throughout the world **(Gauthier, 2015**.

Pseudomonas aeruginosa is known to cause pneumonia in humans **(Lederman & Crum NF. 2004)**.

3.7. Plesiomonas shigelloides:

P. shigelloides infection is thought to be mostly caused by ingestion of contaminated seafood such as undercooked or raw fish, scallops and shrimp, or by drinking water containing Plesiomonas **(Janda & Abbott, 1993)**. It is an important pathogen that causes mainly intestinal diseases in humans, as well as more common extraintestinal diseases such as sepsis and meningitis, which have a high mortality rate **(Stock, 2004)**.

3.8. Streptococcus spp.:

Streptococci are Gram-positive, non-motile, sporeless, non-encapsulated and aerobic microorganisms **(Arda et al.2005)**. Although *Streptococcus iniae* is common in both freshwater and marine fish **(Janda & Abbott, 1999; Weinstein et al., 1997)** defined *S. iniae* as a zoonotic infection in a disease outbreak in Toronto. It causes endocarditis, meningitis and arthritis infections in people who consume raw fish.

3.9. Vibrio spp.:

Vibrio species are very common in the marine environment **(Roberts et al. 2009)**.Vibrios, belonging to the Vibrionaceae family, are Gram-negative, facultative anaerobic, generally motile microorganisms in the form of straight or slightly curved rods **(Arda et al. 2005)**. *Vibrio vulnificus*, *Vibrio parahaemolyticus*, *Vibrio cholerae* and *Vibrio damsela* **(Haenen et al.2003; Austin, 2010).** Among these bacteria, *Vibrio vulnificus* is the most common Vibrio species transmitted from fish to humans **(Lowry & Smith, 2007).** Symptoms of the disease caused by this factor are fever, memory loss, ecchymotic hemorrhages and pain in the extremities. At the same time, the disease is characterized by edema, hemorrhage and extensive tissue necrosis. In humans, *Vibrio vulnificus* infection is generally associated with consumption of fish, shellfish and seawater contamination **(Nemetz et al. 1993)**.

3. CONCLUSION

Considering the consumption of aquatic products, fish are the creatures with the highest infestation in humans. This risk is increasing day by day, especially due to the increasing popularity of raw fish dishes. For this reason, studies on preventing fish-borne diseases are becoming more important day by day. Systems and effective regulations for the control of zoonotic diseases of aquaculture origin are among the activities that can eliminate the negative effects of these diseases on public health.

The most important risk factor for the spread of fish-borne zoonotic diseases is the consumption of raw or undercooked fish. Due to the multifaceted interactions between host, pathogen and environment in the aquatic environment, a serious challenge is required to control zoonotic fish diseases. Unfortunately, advances in transportation, technology, and food processing increase the risk of the spread of these diseases. Fish consumption habits need to be changed to prevent dangers to human health, especially due to zoonotic and other pathogens. The most important issue in controlling fish-borne zoonoses is complete hygiene and constant awareness among people. Proper education, adoption of personal hygiene, proper cooking, use of clean water for drinking and bathing are the most important aspects involved in the control of fish-borne zoonotic diseases worldwide.

In the fight against fish-borne zoonotic infections, countries have an important role to play in raising public awareness, especially about healthy food consumption and health education, and as much as possible to make the society understand why these are so important through the media and relevant institutions.

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CHAPTER 4

THE SIGNIFICANCE OF DYSTOCIA IN SHEEP PRODUCTION AND ITS REASONS

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1. REASONS OF DYSTOCIA

Dystocia is defined as an abnormality in the ratio of the fetus's size to that of the mother's pelvis, resulting from the disproportion between the two. This can happen in successive lambings and is frequently associated with high birth weight lambs. The length of labor and the frequency of dystocia in many breeds of sheep are negatively correlated with the size of the pelvis (Balasopoulou et al., 2022). The ringed cervix structure, which is characterized by the cervix not fully opening six hours after the fetal membranes first show in the vulva, is another significant concern. The cervix typically has an opening that is 3 to 5 cm in diameter, making it impossible for more than two or three fingers to pass through (Basher, 2006). Uterus: Obstacles to fetal birth, uterine torsion or inguinal hernia, and vaginal prolapse can all result in maternal dystocia (Baria et al., 2023). A ringed cervix indicates that the cervix's opening is not fully opened, which could lead to complications during childbirth or dystocia. In addition, obstruction from insufficient cervix dilatation has been linked to cervical injury, uterine lethargy, vaginal prolapse, and other lamb malbirth complications (Mostefai et al., 2019). During a clinical examination, inadequate cervical dilation might be mistaken for uterine torsion in sheep, despite the latter being an uncommon disease. Injured lambs are more prone to cold shock, malnourishment, and mismothering in their early days of life. However, this isn't always the case because dystocia has a major impact on the mortality rate of lambs in all litter sizes. The optimal birth weight varies depending on the race and type of birth. Dystocia is more common in lambs born with extremely low or exceptionally high birth weights. Low birth weight appears to be linked to an increased risk of multiple pregnancies (Scott, 2011).

1.1. Dystocia Due to Dam

Two subheadings—sheep or lamb origin—can be used to analyze dystocia (Table 1). This condition is taken into consideration jointly since the fetus and mother may share the discrepancy between the breadth of the pelvis and the size of the cub (Noakes et al., 2001). Although maternal dystocia's causes are consistent with certain research (Cloete et al., 1998), they might not be consistent with other research (Mostefai et al., 2019). According to Ennen et al. (2013), breech presentation is also the cause of the majority of these issues, even if fetal dystocia accounts for 36% to 75% of them.

Table 1. *Causes of dystocia due to dam and fetus*

Maternal dystocia	**Fetal dystocia**
Fetus-pelvis disproportion	Abnormal presentations
Insufficient dilation of the cervix	Fetal disease and death
Vaginal prolapse	Congenital defects
Partial or complete obstruction of the uterus	
Inguinal hernia	
Regeneration of the uterus	

Source: Jacobson ve ark. 2020

Uterine laziness, which is the incapacity of the uterus to remove the fetus, is another crucial problem on the topic (Balasopoulou et al. 2022). It mostly affects sheep when uterine contraction is diminished or impaired. It can also result in endocrine disorders like estrogen-rich alfalfa consumption, metabolic diseases like hypocalcemia and pregnancy toxemia, or physical injuries like abdominal wall rupture or abdominal or umbilical hernia (Barbagianni et al. 2015). Stress during lambing may also decrease uterine activity and subsequent labor. Stress, loss of uterine rigidity, misalignment of the cub's entrance, extended labor, and myometrial exhaustion can all contribute to secondary uterine laziness (Baria et al. 2023).

1.2. Fetus-Induced Dystocia

According to research that focuses on the need for intervention from birth, neck, shoulder, or wrist flexions are among the most common aberrant presentations in at least 50% of instances of dystocia (Cloete et al. 1998). Nevertheless, the simultaneous arrival or rearing of lambs can potentially result in dystocia. The fetus may malform as a result of congenital abnormalities that lead to fetal malformations. While fetus-pelvis disproportion is unusual in sheep, congenital abnormalities such as increased spinal fluid, large offspring, buildup of water in the tissue and body cavities, and hydrops fetalis can occur (Basher, 2006).

1.3. Mismatch Between Fetal and Pelvic Measurements

Dystocia is the result of an incompatibility between the mother's and the fetus's pelvic dimensions; it can happen in consecutive lambings. Fetal-pelvis disproportion puts single-born children at significant risk and is typically linked to high birth weight in lambs. The fertility records of 3224 Merino or mixed breed lambs born in Australia during a four-year period were examined by Brown et al. (2014). He discovered a negative correlation between fore-aft length at a specific birth weight and certain kinds of dystocia-related mortality that were positively connected with lamb breast circumference, which was derived from birth weight. In contrast, at a given birth weight, the probability of birth damage was positively connected with fore-aft length and negatively correlated with chest circumference. This implies that the occurrence and effects of dystocia may not be lessened by genetic selection favoring taller and slimmer lambs. Although they are uncommon in sheep, congenital abnormalities such as hydrocephalus, wild animals, and hydrops fetalis can also manifest as fetopelvic disproportion (Basher, 2006). In sheep, the length of labor and the prevalence of dystocia in several breeds are negatively correlated with the conjugate diameter of the pelvis and pelvic area. Recommendations for mitigating the risk of fetus-pelvis disproportion include mating ewes when large enough, preventing obesity in ewes, and selecting rams carefully (Ali, 2011).

1.4. Anatomical Problems

Cervical blockage, vaginal prolapse, uterine torsion, or inguinal hernia can all cause dystocia caused by sheep. A “ringed cervix” is a result of the cervix not softening and dilating enough during childbirth as a result of regular physiological processes failing. According to reports, this illness has a major role in maternal dystocia outside of Australia (Ennen et al. 2013). Further research is necessary because, despite the lack of a clear definition, the frequency of dystocia in sheep in Australia may differ seasonally for many causes. In lambs, failure of cervical dilatation may be seen in conjunction with breech lambing, cervical injury, vaginal prolapse, uterine immobility, and various malpresentations (Menzies, 2006). Because of a decrease in the reproductive tissues’ resistance to stretching or an increase in intra-abdominal pressure, vaginal prolapse can happen either before or during lambing. A history of vaginal prolapse, advancing age and parity, bigger litter sizes, malnourishment, metabolic disorders, and extended recumbent posture with concomitant bladder distension are among the risk factors. Uterine torsion is a rare condition in sheep but may be confused with incomplete dilatation of the cervical cervix during clinical examination (Scott, 2011).

1.5. Other Causes

Failure to start labor and subsequent fetal mortality in the uterus can result in dystocia (Jackson, 2004). A number of factors, including compromised placental function, infection, exposure to toxins, metabolic disorders, stress, and congenital abnormalities, can cause intrauterine death. Dead cubs’ autolysis and emphysema can harm the uterus and raise the possibility of vaginal or uterine injury during delivery (Menzies, 2006).

2. DYSTOCIA AND THE SURVIVAL IN LAMBS

Extended labor and dystocia, regardless of the cause, increase the risk of hypoxia and circulatory impairment, which can result in lesions and edema of the central nervous system. According to one study, up to 33% of neonates suffered from severe hypoxia, and twins had a fifteen-fold increased risk compared to singletons (Dutra and Banchero, 2011). Dystocia-related mortality has been linked to hypoxia, which is characterized by bleeding and blockage in the CNS meninges. More recently, the central nervous systems of every lamb that was necropsied had hypoxic ischemic lesions, which are indicative of an oxygen shortage, according to Dutra et al. (2007). Lesions often develop prior to or during delivery, however if the lungs do not fully inflate, postnatal lesions may develop. Lambs with dystocia showed greater cell loss in the dentate gyrus of the hippocampus compared to lambs that died from barbiturate overdose (Lashley et al., 2014). Large lesions may also arise in the absence of neuronal degeneration, along with blood vessel dilatation and hemorrhaging of the central nervous system (Robertson et al., 2020). The probability of dying is also correlated with the degree of lesions, and Barlow et al. (1987) proposed that more research is needed to determine how mothers contribute to the mortality of newborn lambs through intrapartum hypoxia and decreased placental efficiency.

2.1. Birth Injury in Lambs

Although the etiology of birth injury in lambs is not fully understood, the severity of these birth injury lesions is associated with the risk of death. Barlow et al. (1987) proposed that more research is needed to determine how maternal factors, such as intrapartum hypoxia and decreased placental efficiency, contribute to neonatal lamb mortality. In comparison to controls delivered by cesarean section, lamb mortality was 15% higher and the incidence of meningeal lesions was nine times greater in an experimental dystocia model including peri-vaginal sutures to prolong labor time in sheep (Jakkali et al. 2022). This implies that birth injuries are influenced by the intensity and length of labor. Using immunohistochemical staining, it was possible to detect a higher rate of neuronal death in the dentate gyrus of the hippocampus in lambs who died from dystocia as opposed to lambs who died from starvation-absence or barbiturate overdose (Lashley et al., 2014).

2.2. Dystocia, Hunger and Mismothering

Over the past fifty years, the process for identifying dystocia as the cause of death at autopsy has changed. McHugh et al (2016) described necropsy lesions used to determine the time of lamb death based on the time of birth. This method was devised by Holst (2004), who separated deaths from dystocia into three groups. Refshauge et al. (2016) reported these later. The category referred to as dystocia Lambs with subcutaneous edema in A were capable of breathing and walking (Table 2). Based on the central nervous system lesion score and the presence of substantial edema, lambs are critically placed into one of three dystocia classes. This classification scheme suggests that, aside from central nervous system abnormalities, symptoms consistent with birth damage may be present in cases of hunger and inability to locate the mother. Main, preterm or intrauterine death, main exposure, infection, misfortune, or undiscovered illnesses are additional kinds of mortality in this method. While this classification is now well established, the assessment of lesion scores in the central nervous system is arbitrary. The assessor's bias and experience have a major role in classifying lambs into death categories. For instance, lambs that pass away on cold days seem to be more likely to have been exposed to the elements of cold exposure, whereas lambs that are predated are typically classified as primary predation, even in the absence of evidence to the contrary.

Table 2. *Classification of lamb deaths due to dystocia or starvation and inability to find the mother, introduced by Holst (2004) and later redeveloped by Refshauge et al (2016).*

Features	**Dystocia A (Holst, 2004)**	**Dystocia A (Refshauge ve ark. 2016)**	**Dystocia B (Stillbirth)**	**Dystocia C (Birth injury)**	**Hunger and not finding the mother**
Edema *	+	+	-	-	-
Central nervous system lesion score	>2	>2	>3	>3	>2(no lesion)
Walk	-	+/-	+/-	+/-	+
Respiratory	-	+/-	+/-	+/-	+
Metabolic fat stores	-	-	-	+	+

*: subcutaneous edema of the head or shoulders.

** Central nervous system (cranial, spinal) lesion score scale 1-5 (1 = no lesion; 5 = severe bleeding, significant blood clots, and obstruction).

*** Pericardial and perirenal fatty deposits are metabolized.

+ existence of observation.

- lack of observation.

+/- observation is sometimes available.

According to Holst et al. (2002), the brain tissue of deceased lambs had large lesions. Dutra et al. (2007), although classifying 49% of lambs as starvation-inability to find the mother and 40% as dystocia, stillbirth, and birth injury, concluded that these lesions accounted for most of the deaths at birth and within 6 days of birth. Other research on this topic revealed that 20–60% of lambs also had severe birth trauma in the form of injuries to their central nervous systems (Knight et al. 1988).

2.3. Survival of Liveborn Lambs

According to Dutra and Banchero (2011), lengthy and challenging births are linked to a decline in sheep behavior; in other words, they are crucial for forming the attachment between the lamb and the dam and for the lambs' low survival rate. For instance, in sheep, the frequency of bleating causes a decrease in postnatal low-pitched vocalization. As a result, the ewe licks the lamb less frequently and is more likely to exhibit rejection behavior after a challenging birth (Dwyer et al., 2003). Weak lambs in their first hour of life have a lower chance of surviving. Although it has been determined that lambs have lower viability in prolonged births, including delayed standing or sucking behavior (Fonsêca et al. 2014), there is also a study saying the opposite is true. Other significant behavioural traits found in lambs that received assistance at delivery include delayed standing movement emergence, decreased sucking capacity, and suppression of neonatal activities. Immunoglobulin availability and absorption in colostrum are also adversely affected by reduced suckling ability (Hinch and Brien, 2014).

Dystocia-affected lambs are susceptible to the cold, which can lead to dehydration in hot weather. Lambs with poor sucking habits also consume less energy and liquids. Inadequate placenta or hypoxia may also hinder the lamb's ability to produce heat. According to Darwish and Ashmawy (2011), it may be linked to severe hypoxia and significantly decreases heat production for up to 72 hours after delivery. Dystocia-induced hypothermia can be caused by acute hypoxemia from a brief blockage of the umbilical cord (Eales and Small, 1985) or persistent hypoxemia from placental insufficiency (Mellor and Stafford, 2004). Breastfeeding alters the production of heat, even if subacute CNS damage linked to dystocia is not necessarily lethal. The lamb's life may end because it is extremely difficult for it to survive without human assistance, particularly in extremely hot or cold weather. Very few artificially produced lambs die from infectious diseases when they are kept warm after delivery, fed correctly, and risks are managed; nonetheless, lambs with low birth weights can survive with the right care (Greenwood et al. 1998).

2.4. Dystocia and Sheep Health

Effects associated with dystocia in sheep: may result from trauma, bleeding and septicemia (Mavrogianni and Brozos, 2008). Studies on the prevalence of problems during parturition in high-intensity sheep production systems and their effects on ewe mortality and lamb yield are scarce. According to Roger (2009), trauma related to dystocia and/or obstetric intervention may cause organ prolapse, hemorrhage, or infection in the wake of the incident. Ruptures of the cervix, vagina, vulva, or rectum are a few examples of injuries that can happen during dystocia.

In sheep, the risk of infection increases with dystolic delivery. Sheep who have dystocia-related conditions are more likely to develop metritis, which can cause septicemia and even mortality (Tzora et al. 2002). Antimicrobial agents such as oxytocin and non-steroidal anti-inflammatory drugs (NSAIDs) that do not negatively impact fertility are commonly used to treat metritis in sheep. According to Lewis (2007), clostridial infections can cause severe necrotizing myositis, toxemia, and even mortality. These infections can also result in postnatal gangrene after trauma during delivery or obstetric intervention. after lambing, good hygiene lowers the likelihood of metritis, particularly in cases where help is provided after birth. Vaccinating expectant ewes and practicing proper hygiene during lambing also lower the chance of clostridial illness problems.

3. PHYSIOLOGICAL REASONS OF DYSTOCIA

3.1.Lamb Birth Weight and Fertility

Dystocia is one of the important causes of lamb deaths in sheep, although it varies depending on the number of offspring at birth (Kenyon et al. 2019). When a correction is made for birth weight, the difference in dystocia between offspring number groups decreases, but this problem does not disappear (Brown et al. 2014). In this case, dystocia is one of the contributing causes to high birth weight, but it is not the only one. Lamb conformation, for instance, is another significant factor influencing dystocia. According to Brown et al. (2014), who looked at a few causes of death from dystocia, there is a positive correlation between birth weight and lamb chest circumference and a negative correlation between head-anus length in lambs at a particular birth weight. On the other hand, at a given birth weight, the risk of birth damage is positively connected with fore-aft length and negatively correlated with chest circumference. Therefore, selecting longer and thinner lambs for breeding may reduce the incidence of dystocia and related problems. Dystocia in lambs delivered with multiples is more commonly caused by lethal roaming in the fetus, improper delivery technique, and prolonged birth process (Dwyer and Bünger, 2012).

3.2. Live Weight and Body Condition Score in Sheep

There is contradictory data in research about the association between dystocia and ewe live weight or body condition score. Live weight is a combination of both frame size and condition, but the body condition score has the advantage of being an objective metric since it is not reliant on frame (skeleton) size. According to Hall et al. (1994), ewes' body weight at mating had no bearing on the incidence of dystocia. Conversely, Horton et al. (2018) found that sheep live weight and body condition score had favorable correlations with the probability of dystocia for both low and high birth weight. They also noted a favourable correlation between the probability of low and high birth weight dystocia and the live weight of the sheep at 60 and 90 days of pregnancy.

Live weight gain in the last six weeks of pregnancy was reported by Scales et al. (1986) was found to be positively associated with increased rates of dystocia in singles but decreased rates in twins. However, the percentage of ewes in need of help was not significantly impacted by the ewes' body weight just prior to lambing. According to research by Horton et al. (2018), there is a positive correlation between sheep live weight and the risk of dystocia on day 120 of pregnancy; however, a high condition score on the same day was linked to a lower risk of low birth weight and a tendency toward lower rates of high birth weight. Holst et al. (2002) observed higher central nervous system lesion scores in offspring of fatty ewes and concluded that a 'major condition coefficient' exists where ewes with high fat levels are prone to dystocia, fetal birth injury and increased lamb mortality. Holst et al. (2002) found higher central nervous system lesion scores in the offspring of fatty ewes. Additionally, overnutrition during specific pregnancy "windows" raises gestational age, according to Holst (2004). Lambs may grow somewhat as a result, which raises the possibility of dystocia. Dystocia is also associated with low condition scores at lambing and loss of body condition in ewes throughout pregnancy. Behrendt et al. (2019) found a higher incidence of dystocia, birth injury, and dystocia in lambs born to ewes that managed to reach a body condition score of 2.4 or 2.8 at lambing, compared to lambs born to ewes that managed to reach a body condition score of 3.2 or 3.6, lower rectal temperature was observed.

3.3. Birth Time

The time of lambing influences the weight, condition score, and birth weight of the lambs based on the nutrition of the ewes. Because pregnant ewes graze primarily in seasonal settings, the availability and consumption of feed fluctuate according to the timing of mating and lambing. Studies comparing the risk of dystocia in various nations are scarce. There is, however, some indication that the timing of lambing has changed (Oliver et al. 2001).

3.4. Lactation Order and Age in Sheep

The rate of dystocia and birth injury to lambs has historically been reported to be highest in first-born ewes, with little or no difference (McHugh et al. 2016). It has been noted that in ewes, the difficulty of lambing decreases with age, but increases only to 4.5 years. Lambing becomes more difficult beyond this age. According to Horton et al. (2018), the incidence of dystocia rose with the age of the sheep; nevertheless, the lambs born in triplets and with low birth weight were the majority of older ewes with dystocia. This showed that the possible increased risk was specific to low birth weight dystocia. It was discovered that the age groups of sheep had a more equitable distribution of high birth weight dystocia (Horton et al., 2018). Compared to adult ewes, young sheep have been seen to require greater assistance during childbirth and to give birth more slowly (Matheson et al., 2012). While age and lactation order are sometimes misconstrued, smaller, younger ewes having a smaller ewe-to-lamb ratio are widely thought to be the cause of the correlation between dystocia and younger age. The correlation between ewe live weight and pelvic dimensions is positive, indicating that higher pelvic conjugate diameter is linked to a lower incidence of dystocia and higher lamb survivability. Some researchers have reported that rates of labor difficulties do not differ among first-lactation order ewes that lamb at approximately one or two years of age (McHugh et al., 2016). According to Prasad et al. (2014), overfeeding pregnant sheep causes the mother to expand quickly at the expense of the gravid uterus's nutritional needs. Normal mechanical and endocrine delivery processes may be impacted by subsequent food deprivation in the uterus and feto-placental unit (Wallace et al. 2005).

3.5. Fetal Viability and Prediction of Dystocia

Various methods have been developed to determine whether the fetus is alive or not. Fetal heart sounds and ultrasounds are two aspects of the prenatal period and abdominal motility in sheep. While the fetus is inside the uterus, ultrasonographic detection of the heartbeat appears to be the most trustworthy parameter. But while the fetus is in the delivery canal, it might be challenging to determine with accuracy whether or not it is alive. Unless much time has passed since the fetus appeared in the birth canal, veterinarians should try to avoid positive comments about the viability of the fetus (Kenyon et al. 2019). When pressed by hand, the fetus in stressed pregnant ewes does not move; yet, this condition may become active after birth. According to Lashley et al. (2014), radiographic examination might be a useful method for determining the number of fetuses in goats, however it's unclear how well it works to predict dystocia based on the size of the fetal skull.

Prenatal radiographic pelvimetry used to measure pelvic outlet seems to have minimal predictive value for the amount of pelvic outlet present at delivery. Although maternal estrone sulphate levels have shown some promise in predicting pregnancy, fetal viability, and fetal numbers in sheep, their clinical usefulness is less definite (Illera et al., 2000). Research on serum haptoglobin in dystocia-affected ewes has revealed that ewes that have given birth to living lambs have considerably lower serum haptoglobin concentrations than ewes that have given birth to deceased lambs in utero. Sheep with serum haptoglobin values greater than 1.0 g/l may not be good candidates for surgery, according to some evidence. However, such diagnostic indicators are of limited value because obstetrician veterinarians have little choice but to choose caesarean section over sheep euthanasia due to the smaller trial and the potential issue that animals are often presented to referral centers after sufficient delay (Scott, 1989). This is why prenatal prediction in small ruminants appears to be challenging. The length of dystocia is correlated with fetal death (Brounts et al. 2004). When twin lambs are diagnosed prenatally, prompt delivery help is guaranteed.

4. GENETIC APPROACHES TO THE PROBLEM OF DYSTOCIA

The search for high-yielding breeding animals may cause some characteristics to be overlooked. Longer births are the result of domestication and strong selection. According to Dwyer et al. (2003), this strategy has had a negative impact on the development or molding of less favorable maternal behavior in sheep. Stated differently, the goal of achieving quick development in lambs has led to an increase in selection intensity. Lamb strength can decrease and delivery difficulty can increase with muscle building, ideal fat content, using larger sires, and keeping ewe and ram lambs in the flock for extended periods of time due to dystocia (Dwyer and Bünger, 2012). The positive genetic correlation between yearling fatty fleece weight and Dystocia A, B and C and the positive genetic correlation between yearling fatty fleece weight and Dystocia A and C provide further evidence of negative genetic correlations with some production traits. The heritability of delivery assistance was determined by Matheson et al. (2012) to be 0.26, but the genetic association with lamb power and the requirement for breastfeeding aid was reported to be 0.68 and 0.54, respectively. This indicates that selection systems can employ these qualities to lower the rates of dystocia (Brown et al., 2014). Combining indicator features (e.g., lamb size, weight at birth, and conformation) with additional traits related to lamb vigour and ewe-raising capacity may allow for the selection of dystocia, according to reported relationships. Lamb birth weight was found to have a moderate heredity (0.32 to 0.43) by Everett-Hincks et al. (2014), however lamb ease was found to have a low heritability (0.09) by Brien et al. (2010). According to Lashley et al. (2014), there is a weak genetic association between gestation length (0.24) and lambing ease and birth weight (0.31).

Dystocia is characterized by ease of lambing, lamb breast circumference, lamb head-rump length, lamb fleece and birth weight at one year old. Of these, ease of lambing had the highest genetic correlation with dystocia, up to 0.45, followed by lamb breast circumference, up to 0.44. All animals in a group should ideally score for easy lambing points (ELP), as with all qualities. However, the ease of lambing needs to be noted within 24 hours of lambing or in the order that the lambs were born in order for them to obtain ELP points. Many ewes and lambs will not be examined during the lambing event, even on twice-daily lambing rounds, but they will typically be observed within 24 hours following lambing. Therefore, even if the delivery is not directly observed, if daily birth checks are carried out, a score of 1 to 5 should be assigned for ease of lambing.

Table 3. *Easy lambing scoring of lambs*

Point	Description
1	**There is no help.** The birth occurred without any assistance or difficulty.
2	**Easy towing.** Little intervention may be required
3	**Pulling with difficulty.** Helping the birth too much
4	**Breech presentation**
5	**Veterinary intervention**

5. HORMONE, NUTRITION AND METABOLIC RELATIONSHIPS WİTH DYSTOCIA

As a result of regular and accurate checks during pregnancy, all information about the cub at birth will be more accurate. According to Dutra and Banchero (2011), sheep typically choose to give birth at a specific time of day or at a good birth site. The fetus experiences growth and developmental changes during the gestational period, preparing it for the smooth transition from intrauterine to extrauterine existence at delivery. The placenta secretes progesterone, which is the main hormone in sheep during pregnancy. It is frequently referred to as the "pregnancy hormone" due to its several functions in the fetus's development. One of these functions is to stop the uterine myometrial activity in order to stop the fetus from being expelled too soon. Therefore, this hormone inhibition must be removed in order to promote myometrial contraction, which is necessary to eject the fetus during birth. One example of placental endocrine activity is the eradication of progesterone dominance, at least in sheep.

The biochemical alterations in the cervix's connective tissue that occur before uterine contractions set off a series of events that culminate in the cervix dilatation necessary for the fetus to be expelled. In order to trigger the necessary physiological, hormonal, and biochemical changes, the fetal hypothalamic-pituitary-adrenal (HPA) axis must be activated, which starts a neurohormonal cascade that is critical to this process (Challis, 2013). A good birth depends on the uterine rim remodeling occurring in a timely manner and on uterine contractions. According to some research, dystocia—which typically manifests as the cervix not fully dilatation or interfering with uterine contractions—may be caused by hormonal imbalances brought on by the activation of the fetal HPA axis (Brein et al. 2010). Because of the development and ongoing activation of the fetal HPA axis towards the end of pregnancy and at the onset of birth, fetal The concentration of corticosteroids in plasma has increased (Horton et al. 2018). Although there is a significant hereditary component to the chronological timing of this, both internal and external influences can influence it to some degree. Additionally, overfeeding during specific "windows" of pregnancy lengthened the duration of the pregnancy, but only marginally (a few days longer), according to Holst et al. (2002). Due to fetal enlargement, prolonged pregnancy may raise the chance of dystocia. Nonetheless, there isn't much concrete proof of this in sheep, maybe because the length of the gestation period observed in the aforementioned research is so minor.

Increased fetal HPA axis activity during late pregnancy is a common trait of the hormonal maturation of the fetus in various species (Challis et al., 2001). This axis is activated in response to changes in the intrauterine environment, such as hypoxemia (Braems et al., 1996), which puts the fetus under stress. Adrenocorticotropic hormone (ACTH) and adrenal corticosteroid (cortisol in sheep) levels in the fetal blood are elevated throughout HPA development (Challis, 1995). Prostaglandin (PG) synthase expression is elevated by the placenta as a result of elevated cortisol hormone levels. Greater paracrine/autocrine stimulation of PG efflux and enhanced local cortisol generation from cortisone are the results of increased PG synthesis, which also increases the activity of enzymes in fetal membranes (Challis, 2013). Elevated fetal cortisol starts the series of events that lead to delivery and aids in the maturation of organ systems like the lungs, which are critical for the lamb's postnatal survival in the extrauterine environment (Challis, 2013). As a result, the degree of fetal HPA activity plays a crucial role in both dictating the length of the pregnancy and preparing the fetus for life beyond the uterus. The possibility that changed prenatal HPA activity influences the probability of dystocia in sheep has not received much attention.

Two modifications to the sheep's reproductive system are required for birth. First of all, the uterus must be transformed from an immobile structure into a contracting organ. To transfer the contraction-initiated stimulus to the hypothalamus during this metamorphosis, gap junctions between myometrial cells must form. The second alteration is that in order for the fetus to pass through the uterus, the cervical smooth muscle and connective tissue must be able to expand. All of these lead to the synchronization of myometrial activity and an increase in uterine contraction frequency and width in the last stages of pregnancy (Horton et al. 2018). Now when the fetus is pressing on and through the cervix, the mother's pituitary gland releases oxytocin as a neurohormonal reflex, intensifying contractions and bringing on the expulsion phase of labor. The shift from progesterone to estrogen dominance, an enhanced oxytocin response through the activation of myometrial oxytocin receptors, and an increase in progesterone synthesis in the uterus are all associated with these alterations. increased calcium influx into myocytes, a decrease in nitric oxide activity, and the development of myometrial gap junctions all contribute to an increase in myometrial activity (Kenyon et al. 2019).

6. ENVIRONMENT AND STRESS MANAGEMENT DURING LAMBING

Environmental perturbations that elicit fear or anxiety can impact numerous mammalian uterine motility in two different ways: negatively or positively. According to Noakes et al. (2001), stress stimulates the sympathetic nervous system, which leads to the release of adrenaline as well as other catecholamines and glucocorticoids like cortisol. Adrenaline has been shown to both promote and inhibit uterine function in vitro tests. On the other hand, little is known about how environmental stress affects sheep dystocia occurrence. According to a study examining the underlying hormonal mechanism, stress and exogenous adrenaline both reduced sheep uterine motility, although this effect was limited to high levels of endogenous plasma estrogen (Mavrogianni and Brozos, 2008). Adrenaline is known to block the release of oxytocin during the lactation stage in many species during the neurohormonal reflex of milk secretion. Less is known, though, about how stress (adrenaline) during delivery affects oxytocin release and how it contributes to sheep dystocia. The sensitivity of the Hypotamasu-Pituitary axis to stress factors gradually decreases in the late stages of pregnancy and remains suppressed during birth in other species (Ennen et al. 2013).

Cold stress and lamb survival have a known association (Greenwod et al. 1998). Threats to energy balance, such as being in the cold, typically cause the HPA axis to become activated. This causes the release of adrenal hormones, which aid in the mobilization of energy substrates and support energy homeostasis. In this instance, hormonal shifts may cause difficulties in giving birth. It has been reported that under limited feeding, weak sheep's stress response to acute cold threat is reduced. This implies that sheep's ability to momentarily adapt their physiology to the threat of cold is compromised. It's important to consider how climate change may impact fetal development and birth outcomes due to heat stress (Mellor and Stafford, 2004). According to Prasad et al. (2014), sustained heat stress in late pregnancy in sheep may be linked to intrauterine growth limitation, which may result in fetal dystocia due to anomalies in development. There is little research on the subject, even though heat stress does not appear to affect the time of birth in sheep (Wallace et al. 2005).

7. MACROMINERALS, VITAMINS AND UTERINE ACTIVITY

For two centuries, ruminant animals have been known to suffer from acute hypocalcemia, which, if untreated, results in the demise of both the fetus and pregnant sheep. Transient acute or subclinical hypocalcemia is less well understood but has effects on the labor process and maternal dystocia. Increased intracellular calcium in the uterus, brought on by intracellular calcium mobilization and Ca influx from the extracellular area, stimulates myometrial contractions (Fonseca et al. 2014). Low calcium levels permit sodium (Na) to enter nerve cells, escalating irritation and resulting in fasciculations and spontaneous spasms (Basher, 2006). In dairy cattle, subclinical hypocalcemia raises the incidence of retained placenta, uterine prolapse, and dystocia. Regarding secondary consequences in sheep, less is known. Older ewes in commercial production systems are more prone to hypocalcemia, which occurs more frequently up to roughly six weeks prior to lambing. While the induction of hypocalcemia through the infusion of the disodium salt of ethylene-diamine tetra acetic acid causes a decrease in uterine activity, the correlation between dystocia and calcium may not be as strong as it could be (Tzora et al. 2002). The endocrine system's inability to react to the elevated calcium need is the main cause of hypocalcemia. There is uncertainty regarding the role of mineral and vitamin intake in reducing susceptibility in sheep (Friend et al., 2020). A supply of calcium, magnesium (Mg), potassium (K), phosphorus (P), sodium (Na), vitamin D, and ration cation-anion difference is typically uneven when sheep are on pasture during the calving period (Masters et al. 2019). In pastures, low Mg, vitamin D, and high P, decrease Ca absorption or mobilization, while high K and low Na restrict Mg absorption and result in hypomagnesemia. For grazing ruminant animals, hypomagnesemia is a risk factor for hypocalcemia.

8. SUGGESTIONS

Numerous inherited and environmental variables are involved in the development of dystocia. Stress is one of the most significant environmental elements that affects nutrition and herd management techniques. Factors associated with nutrition include body condition score, live weight of sheep and lambs, and muscle deficiencies in minerals and glycogen. Dystocia also has a hereditary component. The disparity between the birth weight of the cubs and the mother's rump width and depth helps to explain this condition, at least in part. A larger ram breed used on a smaller ewe will probably result in dystocia. Domestication and intense selection have led to longer labor, increased muscle mass, and less positive maternal behavior. Despite the hereditary component, dystocia is still a major concern because of its low heritability, which allows direct selection to quickly reduce it, as well as some indication features like ease of lambing. is troublesome. Therefore, additional research is required to fully understand dystocia in intense or semi-intensive industries.

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