Serum IgG threshold values associated with increased risk of diseases in preweaned lambs

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Abstract

Serum IgG cut-off points associated with increased risk of septicemia, fatigue anorexi syndrome (FAS), diarrhea and pneumonia in preweaned lambs was investigated in this study. The study involved 347 Akkaraman crossbred lambs born on two farms in Kars, Turkey. Blood samples were collected 24±1 h after birth and serum IgG concentration was measured by ELISA assay and cut-off values for each disease were determined. Neonatal lambs with diarrhea, FAS and septicaemia had statistically significantly lower IgG concentrations compared to healthy lambs ($P<0.05$). Critical SIgGC-24 cut-off values for increased risk of diarrhea, FAS and septicaemia in neonatal lambs were <800, <1000 and <200 mg/dl. In post-neonatal period, SIgGC-24 (mg/dL) was lower in only lambs with pneumonia compared to healthy lambs ($P<0.05$). The risk of developing septicaemia (IgG<200 mg/dL vs IgG>200 mg/dL), diarrhoe (IgG<800 mg/dL vs IgG>800 mg/dL), FAS (IgG<1000 mg/dL vs IgG>1000 mg/dL) and pneumonia ((IgG<1000 mg/dL vs IgG>1000 mg/dL) was 203, 6, 18 and 12 times higher, respectively. A threshold vaule of IgG<998 mg/dL and IgG<193 mg/dL were determined for neonatal morbidity and mortality, respectively. An appropriate colostrum management may help to maintain the health of pre-weaning lambs, thereby improving the productivity and profitability of sheep farms..

Keywords: *Colostrum, IgG cut-offs, lamb health, passive immunity*

INTRODUCTION

The first three months of life (before weaning), which includes the neonatal period, is the most important period, when morbidity and mortality in lambs is highest, resulting in a loss of future production capacity, since the main objectives of lamb rearing are health, growth, and profitability (Dwyer et al., 2016; Gokce and Erdogan, 2009). Transfer of passive immunity to preweaning lambs via colostrum is an important predictor of lamb health and should be evaluated regularly (Aganbeg et al., 2021; Demis et al., 2020; Sawyer et al., 1977).

Despite significant advances in genetics, nutrition and management, high preweaning morbidity (20-50 %) and mortality (15-20%) remain a global problem affecting lamb welfare and farm productivity (Berge et al., 2016; Dwyer, 2008, Gokce et al., 2013b). Hypothermia, starvation, diarrhoea, septicaemia and pneumonia have been reported to be the most common diseases in pre-weaning lambs (Gokce and Erdogan, 2008; Gokce and Erdogan, 2009; Herndon et al., 2011). Many of these diseases are preventable and the primary predisposing factor is inadequate amount of good quality colostrum (Berge et al., 2016; Demis et al., 2020). Therefore, the first step in addressing these problems is to ensure adequate passive transfer of immunity as lambs are born agammaglobulinemic due to synepitheliochorial placentation (Gokce et al., 2013a; Gokce et al., 2013b; Massimini et al., 2006a).

Colostrum is the main food that protects lambs against diseases and this is defined as passive transfer of colostral immunity (PTCI) (Campion et al., 2019). The peak concentration of IgG in the serum of newborn ruminants is reached at 24 hours after birth. For adequate immunity, colostrum should be given as soon as possible after birth, as the concentration of colostral IgG decreases by 3.3 mg/kg/hour after birth (Bond, 2020; Kessler et al., 2019).

Lambs receiving 30g/L of IgG in colostrum are considered to have adequate PTCI, and below this value is regarded as failure of passive transfer (FPT) (Alves et al., 2015). However there is no internationally accepted threshold value for IgG associated with PTCI or FPT. In neonatal calves, serum IgG levels below 1,000 mg/dL have been associated with an increased risk of morbidity and mortality but a cut-off point between hypogammaglobulinemia and normal serum IgG levels in neonatal lambs has not been universally accepted. Therefore, there is no single IgG cut-off point for FPT and research-based recommendations range from 6 to 16 IgG mg /mL in lambs (Britti et al., 2005).

FPT has been associated with several diseases in ruminants, including respiratory diseases, diarrhea, septicemia, and omphalophlebitis in the first few months of life (Andres et al., 2007; Gokce et al., 2013a; Herndon et al., 2011; Turquino et al., 2011). FPT has been associ-

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ated with an increased risk of morbidity and mortality in lambs (Dwyer et al., 2016; Kessler et al., 2019) but the postcolostral IgG threshold values in lambs that increases or predicts the risk of selected diseases such as fatigue-anorexia syndrome, suspected septicemia, pneumonia, and diarrhea is unknown. This may be because disease detection, health examination, and observation require longer periods of time. Studies on passive immunity in lambs are usually related to risk factors affecting colostrum quality (Alves et al., 2015; Campion et al., 2019; Castro et al., 2011). For a profitable lamb rearing, there needs to be a better understanding of the relationship between common early life diseases and IgG concentrations, particularly disease-related cut-off values so that appropriate measures can be taken to prevent losses in preweaned lambs.

The aim of this longitudinal study was to investigate the relationship between post-colostral [24th hour (±1)] IgG concentrations and selected diseases such as suspected septicemia, fatigue-anorexia syndrome, diarrhea and pneumonia in preweaning lambs. This will also identify SIgGC-24 cut-off values that increase the risk of diseases of concern.

MATERIALS and METHODS

The study was approved by the Kafkas University Institutional Ethics Committee for Animal Experimentation and Use (KAU HADYEK code:2008-23)

Animals

The details of the study design are described elsewhere (Gokce et al., 2014, Gokce et al., 2024). This was a longitudinal study that covered 301 ewes and 347 intensively reared Akkaraman cross lambs born to them on two neighbouring farms in Kars, Turkiye, with similar management practices and feeding regimes, agreed to take part in the study. Ewes were only dewormed and vaccinated against clostridial disease, and no drugs or other compounds were administered during pregnancy. Lambing took place under farmer observation in winter (December to February) or spring (March to May). Only lambs determined as healthy at 24 hours after birth were included in the study. Plastic ear tags were attached to both ears of the lambs shortly after birth and the lambs were then allowed to suckle their mothers naturally. Lambs and their mothers were kept in individual pens for seven days and then moved to groups. Lambs were allowed to suckle twice a day (in the morning and evening) and were fed hay only for three weeks after the first week of life and straw and commercial growth feed (Bayramoglu AS, Turkey) in addition to hay for three months. No vaccines, drugs or other compounds were administered to the lambs during the study period.

Sampling

Blood samples were collected from all healthy lambs at 24 ± 1 h after birth by jugular vein puncture into an 8.5-mL serum clot tube (BD Vacutainer, BD, Franklin Lakes, NJ). Serum was harvested by centrifugation at 4000 rpm for 30 minutes and stored at -20°C until analysed.

Serum IgG Assays

Serum IgG concentrations in lambs were measured directly using a commercially available ELISA kit (Bio-X Competitive ELISA Kit for Ovine blood serum IgG Assay-BIO K 350, Bio-X Diagnostics, Belgium). The assays were performed and the result were interpreted according to the manufacturer's instructions.

Clinical Examination

The health of each lamb was monitored daily during the neonatal period and every two days after the neonatal period until weaning. A routine clinical examination was used to describe each clinical entity. Lambs with one or more of the following signs on clinical examination: poor suckling reflex, anorexia, depression, lethargy, fever, nasal discharge, abnormal lung sounds and high respiratory and heart rates, coughing, diarrhea or watery faeces, at least two signs of dehydration (skin elasticity, sunken eyes etc) and died from causes other than trauma at necropsy were considered sick. Disease groups were classified as diarrhea (watery stools for more then 12 hours, dehydration requiring treatment, weakness, fever, sudden death, bloodstained stools), pneumonia (abnormal lung sounds, dyspnoea, labored breathing, nasal discharge, fever or no fever, anorexia, weakness), suspected septicemia (absent or weak suck reflex, impaired ability to stand or recumbency, full sclera, marked or severe hyperemia, cyanosis or anemia, mucosal or subscleral hemorhage/petechie or presence of hypopyon, prolonged capillary refill time or low urine output, and weakness or depression), fatigue-anorexia syndrome (difficulty in standing, anorexia, partial or complete loss of sucking reflex, depression, incoordination, staggering, pain and starvation at necropsy), and others or unknown according to the previously reported procedure (Gokce and Erdogan, 2009).

Statistical Analysis

Data were entered into a database (Microsoft Access). Data were first tested for normality using the Kolmogrov Smirnov test. Mean ± SE values for serum IgG concentrations were calculated, since the data show a normal distribution. The results of clinical examination were categorized according to the period of life as the neonatal (the first four weeks of life after birth) and postneonatal (the period from 5 to 12 weeks of life after birth). Lambs were categorized as healthy, sick, and dead based on the clinical examination. Independent samples T-test was used to compare SIgGC-24 and different categories of healthy status in both periods. Disease-associated IgG cut-off values were based on the formula: number of lambs diagnosed with a particular disease at that cut-off value/ (total number of lambs at particular threshold value - total number of lambs with other diseases). Chi-square for trend test was used to determine the critical SIgGC-24 cut-off associated with increased risk of diarrhea, pneumonia, FAS, and suspected septicemia. Receiver operating characteristic (ROC) curve analysis was used to find the optimal cut-off point associated with diseases so that to understand the relationships between sensitivity and specificity of measurements. In this study, the Area Under Curve (AUC), Positive Predictive Value (PPV), Negative Predictive Value (PPV), sensitivity, specificity, and diagnostic accuracy statistics were used to evaluate the diagnostic performance of the cut-off values obtained. The AUC can be considered as an index of discriminatory power of a test. An AUC value of 0.50 or less is considered as unsuccessful, 0.6-0.7 is adequate, 0.7-0.8 is good, 0.8-0.9 is very good and 0.9-1.0 is excellent (Simundic, 2009). A value of $p < 0.05$ was considered significant. In this study, IBM SPSS Statistics 26 (academic license) and R 4.4.1 with RStudio were used for statistical analyses and diagnostic test evaluations.

RESULTS

Health Status

A total of 347 lambs were evaluated in this study. The proportion of lambs that developed disease and died in the neonatal period was 17.3% (60/347) and 3.7% (13/347) respectively. Diseases diagnosed in lambs during the neonatal period were diarrhea (9.2%, 32/347), pneumonia (1.7%, 6/347), suspected septicemia (3.2%, 11/347) and fatigue-anorexia syndrome (FAS) (3.2%, 11/347). In lambs with FAS, mistmothering (n=7), starvation (n=2) and hypothermia (n=2) were observed. Nine of the neonatal deaths were due to suspected septicemia in the first week of life. The proportion of diseased and dead lambs during the period of 5-12 weeks were 32.4% (109/334) and 3.9% (13/334) respectively. The most common health problems in lambs in the post-neonatal period were diarhoea (18.6%, 62/334), pneumonia (7.5%, 25/334), suspected septicemia (1.2%, 4/334) and others/unknown causes (5.4%, 18/334) and the number of lambs that died during this period was 15. Of the 47 lambs that were neonatal patients, 26 became ill again in the post-neonatal period and 6 of these died.

The mean SIgGC-24 in all lambs studied was 2162±167 mg/dl. The distribution of SIgGC-24 in different diseases is shown in Table 1. Lambs with suspected septicaemia (354 mg/dL), diarrhea (1890 mg/dL) and fatigue-anorexia syndrome/FAS (1006mg/dL) had significantly lower SIgGC-24 than healthy (2338 mg/dL) lambs in the neonatal period (P<0.001, P<0.05 and P<0.01, respectively). In the postneonatal period, only lambs with pneumonia (1655 mg/dL) had significantly lower SIgGC-24 (P <0.05) than healthy lambs (2294 mg/dL) (Table 1). Mean serum IgG concentration was significantly lower in lambs that died in the neonatal period (n=13, 318±186.9 mg/dL) compared to healthy lambs (n=287, 2337±64.2 mg/dL) (P<0.001). However, no significant difference (P>0.05) was found between the healthy (n=225, 2409±74.2 mg/dL) and deceased lambs (n=16, 2311±326.8 mg/dL) in the postneonatal period.

It was found that an IgG level <800 mg/dL at 24 hours after birth in the neonatal period increased the risk of diarrhea in lambs by approximately six times. In addition, the risk of exposure to FAS (mismothering, starvation, hypoglycaemia) in the neonatal period was found to be approximately 18 times higher in lambs with a postcolostral IgG level <1000 mg/dl than in lambs with a higher level. A postcolostral IgG level <200 mg/dl was found to dramatically increase the risk of sepsis in newborn lambs by 203-fold (Tables 2 and 4). The appropriate cut-off points for the postcolostral (24 hours after birth) IgG in predicting postneonatal pneumonia appeared to be <1000 mg/dL. Lambs with low IgG levels were approximately 12 times more likely to develop postneonatal pneumonia than lambs with higher IgG concentrations (Tables 3 and 4).

Table 1: *Serum IgG concentration (mg/dL) in relation to diseases diagnosed in neonatal and postneonatal period.*

Clinical Diagnosis	Period: Neonatal (first 4 weeks after birth)		Period: 5-12 weeks after birth	
	SIgGC-24	Morbidity (%)	IgG	Morbidity (%)
Diarrhoea	1890 ±179 *	9.2% (32/347)	2055 ± 141	18.6% (62/334)
Suspected Septicaemia	354 ± 213***	3.2% (11/347)	1833 ± 564	1.2% (4/334)
Pneumonia	2031 ± 637	1.7% (6/347)	1655 ± 211*	7.5% (25/334)
FAS*	1006 ±156**	3.2% (11/347)	-	-
Other	-	-	2212 ± 203	5.4% (18/334)
Healthy (n)	2337 ± 64 (n=287)	-	2294 ± 77 (n=238)	-

FAS*=Fatigue-Anorexia Syndrome (Mismothering, hypotermia and starvation) * P<0.05, ** P<0.01, *** P<0.001 significantly different from healthy lambs.

Figure 1 shows the ROC curve for neonatal diarrhoea, FAS, suspected sepsis, and post-neonatal pneumonia. In addition to this figure, Table 5 provides descriptive information on confusion matrices, AUC, PPV, NPV, sensitivity, specificity, and diagnostic accuracy results based on threshold values.

For neonatal diarrhoea, the AUC value was 0.540, indicating that the model had low capability in distinguishing between diseased and healthy individuals. The Positive Predictive Value (PPV) was 81.3%, while the Negative Predictive Value (NPV) was 94.6%, demonstrating the model's effectiveness in identifying negative cases. The sensitivity was 18.7%, reflecting the low ability to correctly identify positive cases, and the specificity was 94.6%, showing strong performance in recognizing negative cases The overall diagnostic accuracy was 93.4%. In the confusion matrix, for <800 mg/dL, there were 6 true positives (correctly identified as Diarrhoea) and 17 false negatives (Diarrhoea cases incorrectly identified as non-Diarrhoea), while for >800 mg/dL, there were 26 false positives (non-diarrhoea cases incorrectly iden-tified as Diarrhoea) and 298 true negatives (correctly identified as non-diarrhoea) (Table 5).

The AUC value was 0.932, indicating high discrimination ability of the model for neonatal FAS. The PPV was

Table 2. *Morbidity and mortality due to various conditions associated with defined categories of serum IgG concentrations at 24 hours after birth in neonatal lambs*

IgG Cut-off (mg/dl)	Diarrhoea				Pneumonia				Suspected Septicemia				FAS*				Total			
	Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality	
	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n3/n4	%	n3/n4	%
<200	1/1	100	1/1	100	0/0	0	0/0	0	9/9	100	9/9	100	1/1	100	1/1	100	11/11	100	11/11	100
201-500	4/4	100	0/4	0	1/1	100	0/0	0	0/0	0	0/0	0	1/1	100	0/1	0	6/6	100	0/6	0,00
501-600	1/2	50	0/2	0	0/1	0	0/1	0	0/1	0	0/1	0	1/2	50	0/1	0	2/3	66,7	0/3	0,00
601-800	0/3	0	0/3	0	0/3	0	0/3	0	0/3	0	0/3	0	0/3	0	0/3	0	0/3	0,0	0/3	0,00
801-1000	0/11	0	0/11	0	0/11	0	0/11	0	0/11	0	0/11	0	3/14	21,4	0/14	0	3/14	21,4	0/14	0,00
1000-1500	4/60	6,7	0/60	0	3/59	5,1	1/59	1,7	1/57	1,8	0/63	0	3/59	5,1	0/59	0	11/67	16,4	1/67	1,49
1501-2000	9/85	10,6	0/85	0	0/76	0	0/76	0	0/76	0	0/76	0	2/78	2,6	0/78	0	11/87	12,6	0/87	0,00
2001-2500	4/41	9,8	0/41	0	0/37	0	0/37	0	1/38	2,6	1/38	2,6	0/37	0	0/37	0	5/42	11,9	1/42	2,38
>2501	9/112	8	0/112	0	2/105	1,9	0/105	0	0/103	0	0/103	0	0/103	0	0/103	0	11/114	9,6	0/114	0,00

n^1= Number of lambs sick or dead, n^2= Total number of lambs - number of lambs in other diseases, n^3= Total number of lambs sick or dead n^4=Total number of lambs. FAS*=Fatigue-Anorexia Syndrome (Mismothering, hypotermia and starvation).

Table 3. *Morbidity and mortality in lambs due to various diseases associated with defined categories of serum IgG concentrations at 24 hours after birth in the post-neonatal period.*

IgG Cut-off (mg/dL)	Diarrhoea				Pneumonia				Suspected Septicemia				Other or Unclasssified				Total			
	Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality		Morbidity		Mortality	
	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n1/n2	%	n3/n4	%	n3/n4	%
<200	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00	0/0	0,00
201-500	0/2	0,00	0/2	0,00	4/6	66,7	0/4	0,00	0/2	0,00	0/2	0,00	0/2	0,00	0/2	0,00	4/6	66,7	0/6	0,00
501-600	1/2	50	0/3	0,00	0/1	0,00	0/0	0,00	1/2	50	1/3	33,3	0/1	0,00	0/2	0,00	2/3	66,7	1/4	25,0
601-800	2/3	66,7	0/3	0,00	0/1	0,00	0/1	0.00	0/1	0,00	0/1	0,00	0/1	0,00	0/1	0,00	2/3	66,7	0/3	25,0
801-1000	3/11	27,3	0/13	0,00	3/11	27,3	2/13	15,4	0/8	0,00	0/10	0,00	0/8	0,00	0/10	0,00	6/14	42,9	2/14	14,3
1001-1500	17/55	30,9	0/57	0,00	8/46	17,4	2/48	4,2	1/39	2,6	1/41	2,4	1/39	2,6	3/41	7,3	29/67	43,3	3/67	4,5
1501-2000	1/79	21,5	1/81	1,2	2/64	3,1	0/66	0,00	0/62	0,00	0/64	0,00	6/68	8,8	1/69	1,4	25/87	28,7	2/87	2,3
2001-2500	7/34	20,6	0/35	0,00	4/31	13	0/32	0,00	1/28	3,6	1/29	3,4	3/30	10	1/29	3,4	15/42	35,7	2/42	4,8
>2501	15/101	14,9	1/107	0,9	4/90	4,4	1/97	1,0	1/87	1,1	1/97	1,0	6/94	6.4	2/98	2,0	26/112	23,2	5/114	4,4

n^1= Number of lambs sick or dead, n^2= Total number of lambs - number of lambs in other diseases, n^3= Total number of lambs sick or dead n^4=Total number of lambs. FAS*=Fatigue-Anorexia Syndrome (Mismothering, hypotermia and starvation)

***Table 4**. Postcolostral (24 hours after birth) IgG (mg/dl) cut-off values that increase the risk of various diseases*

Clinical Diagnosis	Period	Grouping (IgG Cut-off)	Morbidity Rate	X2	P value	OR	95%CI
Diarrhoea	Neonatal	IgG>800	11.1% (26/324)	6.35	0.011	4.05	1.46-11.14
		IgG<800	26.1% (6/23)				
	Post-Neonatal	IgG>800	18.3% (59/322)	0.042	0.84	1.48	0.39-5.65
		IgG<800	25.0% (3/12)				
Pneumonia	Neonatal	IgG>1000	1.6% (5/310)	0.00	1.00	1.69	0.19-14.91
		IgG<1000	2.7% (1/37)				
	Post-Neonatal	IgG>1000	5.8% (18/308)	12.49	0.000	5.93	2.20-15.95
		IgG<1000	26.9% (7/26)				
FAS*	Neonatal	IgG>1000	1.6% (5/310)	18.45	0.000	11.80	3.40-40.92
		IgG<1000	16.2% (6/37)				
	Post-Neonatal	-	-	-	-	-	-
Suspected Septicemia	Neonatal	IgG>200	0.60% (2/336)	203.2	0.000	751.5	94.9-5948.4
		IgG<200	81.8% (9/11)				
	Post-Neonatal	IgG>600	0.98% (3/325)	1.48	0.22	13.42	1.25-143.43
		IgG<600	0.92% (1/9)				

FAS* (mismothering, starvation, hypoglycaemia), OR: Odds Ratio, CI: Confidence Interval

low at 45.5%, but the NPV was high at 90.8%, showing good performance in identifying negative cases. The sensitivity was 54.5%, indicating moderate performance in detecting positive cases, and the specificity was 90.8%, demonstrating strong negative case identification. The overall diagnostic accuracy was 89.2%. The confusion matrix shown 6 true positives and 31 false negatives for <1000 mg/dL, and 5 false positives and 305 true negati-ves for >1000 mg/dL (Table 5).

Neonatal suspected epticemic lambs had the AUC of 0.851, showing good model performance. The PPV was 81.8%, NPV is 99.4%, and diagnostic accuracy was 98.8%, indicating high accuracy in distinguishing both positive and negative cases, with excellent performance particularly in negative predictions. The sensitivity was 81.8%, reflecting the strong ability to detect positive cases, and the specificity was 99.4%, showing the outstanding ability to identify negative cases. The confusion matrix shown 9 true positives and 2 false negatives for <200 mg/dL, and 2 false positives and 334 true negatives for >200 mg/dL (Table 5).

For post-neonatal pneumonia, the AUC value was 0.663, indicating moderate discrimination ability. The PPV was 83.3%, NPV is 89.4%, and overall diagnostic accuracy was 89.4%, reflecting high accuracy in positive predi-ctions and effective identification of negative cases, de-monstrating overall good performance. The sensitivity was 16.7%, showing a lower ability to detect positive cases, while the specificity was 89.5%, indicating strong negative case identification. The confusion matrix shown 1 true positive and 36 false negatives for <1000 mg/dL, and 5 false positives and 305 true negatives for >1000 mg/dL (Table 5).

AUC 75%, PPV 37.7%, NPV 95.1%, and diagnostic accuracy 85.1% were determined (P<0, 05) for the threshold value of IgG <998 mg/dL that increases the risk of neonatal disease in lambs (Figure 2A). As for the threshold value of IgG <193 mg/dL that increases the risk of neonatal mortality in lambs, AUC 91.5%, PPV 84.62%, NPV 100%, and diagnostic accuracy 96.72% were determined (P<0.01) (Figure 2B).

DISCUSSION

The first few months of a lambs' life are critical due to inability to overcome unfaviourable conditions and incomplete immunity to fight infectious diseases when the risk of exposure to disease is relatively high. Therefore, good farm management parctices, including colostrum management, are of paramount importance in the pre-weaning period (Gokce et al., 2013b; Gokce et al., 2021).

Colostrum is a vital source of nutrients and immunoglobulins for the neonate, and an adequate supply of colostrum significantly increases the chance of survival to weaning (Agenbeg et al., 2021; Banchero et al., 2004; Dwyer et al., 2016). It has been reported that lambs with FPT or low antibody titers are at high risk of disease (Altiner et al., 2005; Herndon et al., 2011). Defining the success or failure of passive transfer is not a clear-cut process. It requires the identification of a threshold that addresses multiple objectives: a threshold above which increasing serum IgG concentrations no longer increase the risk of morbidity or mortality, or a threshold that predicts the greatest effect on a particular outcome, or a statistically defined threshold. The optimal threshold of serum IgG concentration defined for FPT has been recommended as <6 mg/ml (Gokce et al., 2019), <8 mg/ml (Sawyer et al., 1977), <15 mg/ml (Turquino et al., 2011; Alves et al., 2015), <16 mg/ml (Massimini et al., 2006a). In our study, low IgG was specifically associated with increased susceptibility to diarrhoea, pneumonia, FAS and suspected septicaemia in young lambs, and critical SIgGC-24 threshold values that increased the risk of developing neonatal diarrhea, FAS, septicemia and post-neonatal pneumonia were determined as <800, <1000, <200 and <1000 mg/dL, respectively. The AUC

Table 5. *Performance results by threshold values for neonatal diarrhoea, neonatal fas, neonatal septicemia, and post-neonatal pneumonia*

Neonatal Diarrhoea (Figure 1A)									
IgG (mg/dL)	Positive	Negative	Total	AUC	PPV	NPV	Sens.	Spec.	Diagnostic accuracy
<800	6	17	23						
>800	26	298	324	0.540	0.813	0.946	0.187	0.946	93.4%
Total	32	315	347						
Neonatal FAS (Figure 1B)									
IgG (mg/dL)	Positive	Negative	Total	AUC	PPV	NPV	Sens.	Spec.	Diagnostic accuracy
<1000	6	31	37						
>1000	5	305	310	0.932	0.455	0.908	0.545	0.908	89.2%
Total	11	336	347						
Neonatal Septicemia (Figure 1C)									
IgG (mg/dL)	Positive	Negative	Total	AUC	PPV	NPV	Sens.	Spec.	Diagnostic accuracy
<200	9	2	11						
>200	2	334	336	0.851	0.818	0.994	0.818	0.994	98.8%
Total	11	336	347						
Post-Neonatal Pneumonia (Figure 1D)									
IgG (mg/dL)	Positive	Negative	Total	AUC	PPV	NPV	Sens.	Spec.	Diagnostic accuracy
<1000	1	36	37						
>1000	5	305	310	0.663	0.833	0.894	0.167	0.895	89.4%
Total	6	341	347						

PPV: positive predictive value, NPV: Negative predictive value, Sens.: Sensitivity, Spec.: Specificity

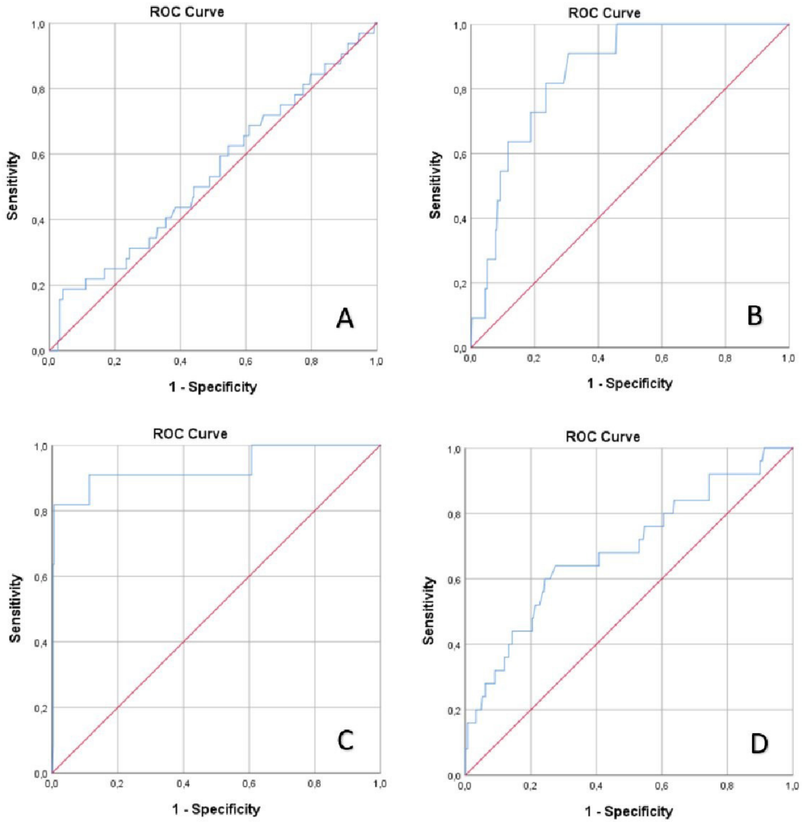

Figure 1. *ROC Curve for A) Diarrhoea, B) FAS, C) Septicemia and D) Pneumonia*

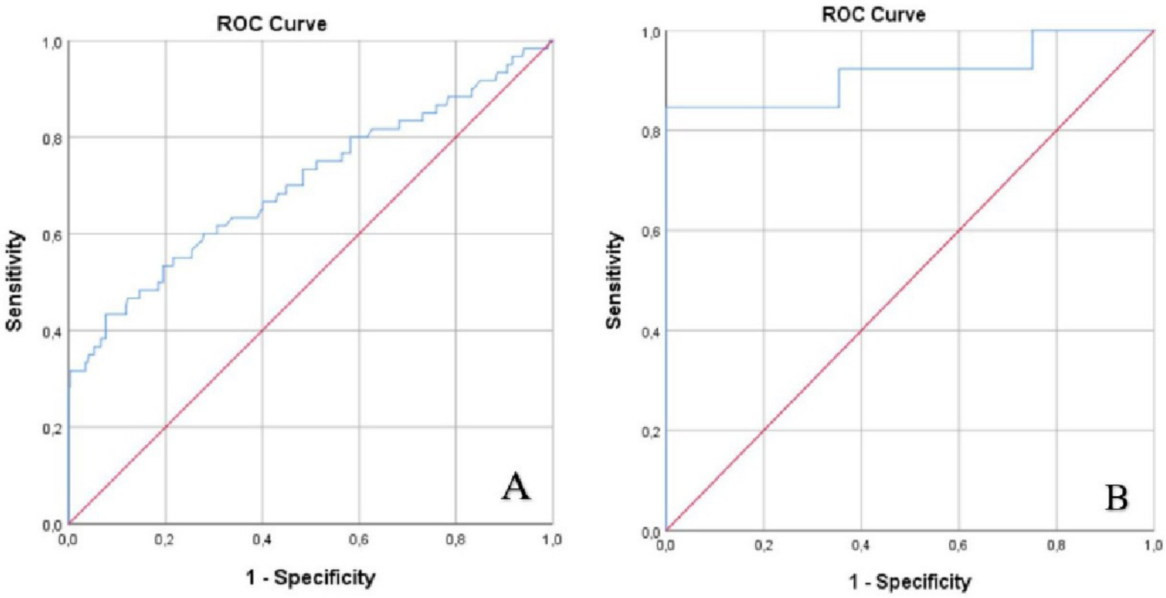

Figure 2. *ROC Curve for A) neonatal morbidity, B) neonatal mortality*

for the respective cut-offs were 56.7%, 72.7%, 90.6% and 60.9%, while the diagnostic accuracy was 87.61%, 89.63%, 98.85% and 88.92%, respectively. The cut off value of IgG <998 mg/dL and the value of IgG <193 mg/dL correctly identified neonatal morbidity and neonatal mortality as the AUC was 75% and 91.5%, respectively. However, it is difficult to compare our results as there are no studies investigating the relationship between SIgGC-24 threshold values and selected diseases in lambs.

In our study, about half of the lambs with neonatal disease relapsed in the postneonatal period, suggesting that precautions should be taken in advance. Identifying these lambs in advance, based on their post-colostral IgG levels, will allow the caretaker to provide adequate passive transfer or desing a therapeutic protocol in advance (Pesca et al., 2020). This timely management of such lambs will lead to rational use of antimicrobials, which is an important concern.

Colostrum is rich in energy sources such as glucose. Therefore, inadequate intake due to mismothering can lead to starvation and hypoglycaemia (Dwyer et al., 2016), namely FAS. Consumption of 100 ml/kg of colostrum within the first 6 hours is recommended to prevent starvation (Bond, 2020) and consequently FAS. Adequate post-colostrum IgG levels also indicate adequate energy intake from colostrum (Dwyer et al., 2016). In our study, lambs with <1000mg/dl SIgGC-24 were 18 times more likely to develop FAS than those with >1000mg/dl. This finding supports the fact that good quality colostrum reduces the risk of FAS as mentioned above. In cases of FAS, adequate colostrum intake can be ensured by management measures such as feeding with another mother or pre-frozen colostrum, and ensuring the mother-offspring relationship (Dwyer, 2008; Dwyer et al., 2016).

An important factor in the susceptibility of the newborn to pathogens is the permeability of the immature gut, which results in the passage of initial immunoglobulins as well as an increased risk of pathogen entry. FPT has been associated with disease in the first two weeks in ruminants. Gram-negative septicaemia is an important cause of mortality and FPT has been positively correlated with sepsis (Altiner et al., 2005). However, colostrum ingestion itself accelerates the process of intestinal closure; thereby it is also preventing the route of neonatal infection (Agenbag et al., 2021; Dwyer, 2008; Fischer et al., 2019). Therefore, the risk of diarrhea and septicemia is high in the first week of the neonatal period. This was also the case in our study where lambs with suspected septicemia died in the first week of life and had FPT, serum IgG below IgG<200mg/ml. Timely administration of colostrum with adequate IgG and low bacterial burden is necessary to prevent these diseases. Monitoring maternal immune and nutritional status and the success of PTCI is also important to prevent diarrhoea (Andres et al., 2007; Gokce et al., 2019).

Respiratory diseases account for 5.6% of all diseases in small ruminants and are an important economic issue in the industry (Kumar et al., 2014; Pesca et al., 2020). In calves, low postcolostral IgG and total protein levels and feeding of mastitic colostrum were found to be associated with a higher risk of pneumonia (Pardon et al., 2015). It has also been reported that preventing pneumonia increases daily gain (Virtala et al., 1996). Our study showed that a low post-colostral IgG concentration was associated with increased risk of pneumonia in lambs, and the cut-off value was determined to be a post-colostral IgG level <1000 mg/dl, as those lambs with a level below this value had approximately 12 times risk when compared to those with IgG >1000 mg/dl. The low proportion of respiratory disease cases observed in the neonatal period was not surprising, as calves and lambs under 30 days of age typically suffer from diarrhea, while respiratory disease is more prevelant in older animals (Gokce and Erdogan, 2008; Lora et al., 2018). This is mainly due to the presence of sufficient antibodies in colostrum against bacterial and viral pathogens in newborn lambs. Interestingly, Smith et al., (1976) also proposed that a small amount of colostrum IgG, once absorbed, diffuses into the nasal and lacrimal secretions of lambs and this may play a role in preventing respiratory infections prior to local production of IgA and IgM at the 2-3 weeks of age (Smith et al., 1976)

This study demonstrated the critical role of sufficient IgG uptake in protecting lambs from pneumonia, diarrhoea, septicaemia and FAS. This effect is maintained until weaning. Lambs born to vaccinated ewes may have protective antibodies for the first 1-2 months. After this period, the lamb's passive immunity appears to decline dangerously, which can lead to the development of infectious diseases (Pesca et al., 2020). Considering the significant economic losses due to disease In preweaning lambs, it is necessary to adopt useful preventive tools for the benefit of the whole sheep industry. Passive immunisation or immunoglobulin products have a clear role to play in modern animal production as a means of controlling infectious diseases, especially with a very low risk of causing the development of bacterial resistance, thus constituting a real and widely applicable alternative to antibiotics.

In conclusion, the effect of IgG concentration on several diseases during the first 3 months in lambs has been demonstrated. We identified the post-colostral IgG thresholds that increase the risk of neonatal diarrhoea, FAS, septicaemia and post-neonatal pneumonia to be <800, <1000, <200 and <1000 mg/dL respectively. These findings may suggest that appropriate colostrum management may help to maintain the health of pre-weaning lambs, thereby improving the productivity and profitability of sheep farms. Lambs at risk of morbidity and mortality based on postcolostral IgG levels can be carefully monitored and treated early. Further studies are also required to use these results as epidemiological data in details.

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Conflict of Interest

Authors declare no conflicy of interest

Ethical Statement

The study was approved by the Kafkas University Institutional Ethics Committee for Animal Experimentation and Use (Protocol number:2008-23).

Author Contributions

EG: Collection of data, writing – original draft, PC: Writing – original draft, statistical analysis, visualizing, OA: Biochemical analysis, AHK: Collection of data, HME: Collection of data, writing – original draft and editing. All authors have read and agreed to the published version of the paper.

Availability of Data and Materıal

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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