EUROASIA
Matematik, Mühendislik, Doğa ve Tıp Bilimleri Dergisi
Journal of Mathematics, Engineering, Natural & Medical Science

Research Article e-ISSN: 2667-6702 https://doi.org/10.5281/zenodo.19218341

Ministered to Sheep in the Late Transition Period on Immune and Metabolic Values and Passive Immunity in Lambs

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Article Info

Received: 25.01.2026
Accepted: 27.02.2026

Keywords
Levamisole
Akkaraman crossbred
Transition period
Passive immunity
Metabolic profile

Abstract: This study aimed to investigate the effects of levamisole administration during the late gestation period in ewes on immune and metabolic parameters during the transition period and on passive immunity in lambs. For this purpose, 60 Akkaraman crossbred ewes with similar characteristics were divided into two groups: Levamisole (Group I, n = 30) and Control (Group II, n = 30). Starting from the 15th week of gestation until parturition, Group I received levamisole at a dose of 2.5 mg/kg subcutaneously on a weekly basis, while Group II was administered a placebo (physiological saline). Blood samples were collected from the ewes before treatment, during the 16th, 17th, and 18th weeks of gestation, within the first 4 hours after parturition, and during the 3rd week of lactation; samples from lambs were obtained within 24–36 hours after birth. Analysis of parameters (GLU, NEFA, BHB, IgG, ALT, AST, etc.) revealed statistically significant differences ($P < 0.05$) between groups in LDL and IgG levels in ewes. In lambs, LDL, TP, GGT, and IgG levels differed significantly between groups. These findings indicate that levamisole administration during late gestation may have beneficial effects on maternal health and passive immunity transfer in lambs.

Introductıon

The cornerstone of sustainability in sheep farming lies in the proper management of pregnancy and parturition processes to ensure the birth of healthy lambs. The transition period, also referred to as the periparturient period, encompasses the final weeks of gestation and the onset of lactation, representing the most critical stage for flock health. Recent studies emphasize that metabolic stress during this period not only affects the dam but also influences the long-term health of the offspring through epigenetic mechanisms (Wang et al., 2021). During this critical phase, negative energy balance (NEB), oxidative stress, colostrogenesis, and abrupt hormonal changes contribute to immunosuppression. Enhancing immune response during late gestation is of great importance for improving colostrum quality and optimizing passive immunity transfer. In ruminants, supporting maternal immunity has been shown to improve the immunoglobulin and cytokine composition of colostrum, thereby reducing neonatal mortality, as demonstrated by recent research (Kessler et al., 2021; Hernandez-Castellano et al., 2021). In this context, levamisole, an anthelmintic agent, stands out for its strong immunomodulatory effects. Although levamisole is known to enhance cellular immune response, this effect has been reported to depend on dosage and frequency of administration. Modern veterinary medicine increasingly focuses on proactive support of immunometabolic health during the transition period, rather than solely on disease treatment (Lopreiato et al., 2020). Therefore, this study aimed to determine the effects of levamisole administered at an immunostimulant dose during the transition period in ewes on maternal health and passive immunity transfer to lambs.

Materıals and Methods

Animal Material and Grouping:

The study was conducted on 60 Akkaraman crossbred ewes confirmed pregnant by ultrasonographic examination, with similar age, parity, and body condition score (BCS). To standardize factors that could affect passive immunity, only healthy ewes with singleton births and their lambs were included; ewes with twin lambs and their offspring were excluded.

The animals were randomly divided into two groups:

Group I (Levamisole, n = 30): Starting from the 15th week of gestation, levamisole (Actipar®, ALKE) was administered subcutaneously (SC) at a dose of 2.5 mg/kg weekly.

Group II (Control, n = 30): An equal volume of placebo (physiological saline) was administered SC.

Applications were repeated once a week from the 15th week of gestation until parturition, for a total of six times.

Sampling Schedule: Blood samples from ewes were collected before the first administration (15th week/baseline), at the 18th week of gestation (beginning of the transition period), at the 19th week (period of intense IgG transfer), at parturition, and during the 3rd week of lactation (end of the transition period). To prevent postprandial variations, all samples were taken 4–6 hours after morning feeding.

To determine passive colostral immunity in lambs, blood samples were collected between 24–36 hours after birth. To ensure equal colostrum intake, all lambs were bottle-fed colostrum at a dose of 200 ml/kg within the first 24 hours after birth.

Laboratory Analyses: Blood samples were collected into tubes with and without anticoagulant (K_2 EDTA) and centrifuged at 3000 rpm for 10 minutes. Plasma and serum samples were stored at –20°C until analysis.

Biochemical Parameters: NEFA and BHB levels were determined spectrophotometrically using commercial kits (Randox, UK). GLU, UREA, UA, CREA, TP, TG, LDL, HDL, CHOL, TBIL, and enzyme activities (AST, GGT, ALT, LDH) were measured using a fully automated analyzer (Mindray BS-120 Vet).

Specific Proteins and Minerals: Serum Amyloid A (SAA), albumin, and IgG levels were evaluated using commercial ELISA kits according to the manufacturer's instructions. Ca, P, and Mg levels were determined by spectrophotometric methods.

Statistical Analysis: Statistical evaluation of the data was performed using the SPSS software package. One-Way Analysis of Variance (ANOVA) and post-hoc tests (Tukey HSD and Duncan) were applied to determine changes over time and differences between groups. Independent Samples t-Test was used to compare data obtained from lambs. Relationships between parameters were assessed using Pearson correlation analysis. Data were presented as mean ± standard error (SE), and a value of $P < 0.05$ was considered statistically significant.

Results

Clinical Findings:

Throughout the study, all ewes in both groups were monitored for mastitis, metritis, and metabolic disorders. Apart from a single case of E. coli-induced diarrhea detected in one lamb from the control group, no pathological findings were observed during the study period.

Biochemical Findings: All biochemical and metabolic data for ewes are presented in Tables 1–6, and data for lambs are shown in Table 7.

Energy and Lipid Metabolism Values

Glucose: In both groups, serum glucose levels reached their highest values at parturition ($P < 0.001$) and showed a significant decrease by day 21 of lactation. No statistical difference was detected between groups.

NEFA and BHB: NEFA and BHB, indicators of negative energy balance, showed an increasing trend in both groups until parturition, peaking at birth ($P < 0.05$). A significant difference in NEFA values was observed between groups at parturition ($P < 0.05$), whereas BHB levels were similar across groups.

Lipid Profile: Cholesterol levels decreased to their lowest point at parturition in both groups and increased again during lactation. LDL cholesterol levels showed a statistically significant difference in favor of the levamisole group at the 3rd, 4th, and 5th sampling times ($P < 0.001$).

Protein Metabolism and Immunity

Total Protein and Albumin: TP and albumin levels decreased in both groups until parturition, reaching their lowest values at birth, and then increased again by day 21 of lactation ($P < 0.05$).

Serum IgG: One of the most striking findings of the study was that IgG levels decreased in both groups until parturition (consistent with colostrogenesis). However, IgG levels in the levamisole-treated group were statistically higher than those in the control group at all sampling times (except baseline) ($P < 0.05$).

Liver Enzymes and Oxidative Stress Markers

Enzyme Activities (ALT, AST, GGT, LDH): Liver enzyme activities generally increased as the transition period progressed, reaching their highest values on day 21 postpartum. No significant differences were observed between groups for these parameters.

NO and PON: Although NO and PON values, indicators of oxidative stress, fluctuated over time, levamisole administration did not result in a significant difference between groups for these parameters.

Minerals and Acute Phase Proteins (APP)

Minerals: Serum Ca and Mg levels dropped to their lowest values at parturition ($P < 0.05$), while P levels showed a decreasing trend throughout the study. No significant differences were found between groups regarding mineral concentrations.

APP (Hp, CRP, SAA): Inflammatory markers Hp, CRP, and SAA increased until parturition and then decreased postpartum. No differences were observed between groups for these parameters.

Biochemical Values in Lambs

Biochemical analysis of lambs at 24–36 hours postpartum revealed statistically significant differences in LDL, TP, GGT, and IgG levels between Group I and Group II ($P < 0.05$). Notably, the differences in IgG and GGT—key indicators of passive immunity transfer and colostrum intake—demonstrate that maternal effects influenced lamb blood parameters.

Conversely, no significant differences were detected between groups for GLU, NEFA, BHB, CHOL, TG, and HDL (reflecting energy metabolism and general health), nor for renal and hepatic function parameters (UREA, UA, CREA, TBIL, ALT, AST, LDH) ($P > 0.05$). Similarly, oxidative stress and inflammation markers (PON, NO, Hp, SAA, CRP, ALB) and essential mineral concentrations (Ca, Mg, P) were comparable between groups and statistically insignificant.

Tablo 1. Energy Metabolism Parameters (GLU, NEFA, BHB)

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
GLU	I	43.21±1.5^{a}	43.56±1.1^{a}	44.44±1.0^{a}	37.29±1.1^{a}	90.07±8.7^{b}	58.24±1.3^{c}	0,001
(mg/dL)	II	45.14±1.0^{a}	47.38±0.9^{a}	52.92±4.9^{a}	39.39±1.5^{a}	92.71±7.7^{b}	56.61±2.6^{c}	0,001
	P	NS	NS	NS	NS	NS	NS	
NEFA	I	0.35±0.01^{a}	0.38±0.01^{a}	0.43±0.01^{b}	0.68±0.01^{c}	0.79±0.01^{dx}	0.47±0.1^{b}	0.05
(mmol/L)	II	0.37±0.01^{a}	0.37±0.01^{a}	0.46±0.01^{b}	0.70±0.01^{c}	0.72±0.01^{cy}	0.47±0.1^{b}	0.05
	P	NS	NS	NS	NS	0.05	NS	
BHB	I	0.41±0.0^{a}	0.44±0.0^{b}	0.49±0.0^{c}	0.74±0.0^{d}	0.84±0.0^{e}	0.48±0.0^{b}	0.05
(mmol/L)	II	0.40±0.0^{a}	0.44±0.0^{b}	0.50±0.0^{c}	0.73±0.0^{d}	0.83±0.0^{e}	0.49±0.0^{b}	0.05
	P	NS	NS	NS	NS	NS	NS	

GLU: Glucose, NEFA: Non-Esterified Fatty Acids. BHB: Beta-Hydroxybutyrate, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 2. Lipid Profile (CHOL, TG, HDL, LDL)

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
CHOL	I	65.07±1.2^{a}	62.92±1.3^{a}	62.72±1.8^{a}	62.86±1.5^{ax}	49.75±1.7^{b}	61.04±1.8^{a}	0,001
(mg/dL)	II	63.77±1.1^{a}	61.65±1.7^{a}	59.96±1.5^{a}	55.49±1.4^{ay}	47.88±1.4^{b}	57.56±1.9^{a}	0,001
	P	NS	NS	NS	0,001	NS	NS	
TG	I	58.65±3.4^{a}	57.33±3.7^{a}	61.74±4.09^{b}	56.5±2.88^{a}	51.00±3.27^{c}	46.24±3.6^{d}	0,001
(mg/dL)	II	49.86±2.94^{a}	48.43±2.7^{a}	57.22±3.01^{b}	56.41±2.92^{a}	54.65±2.4^{c}	45.60±3.3^{d}	0,001
	P	NS	NS	NS	NS	NS	NS	
HDL	I	19.11±0.68^{a}	19.12±0.69^{a}	20.72±1.04^{a}	25.59±1.3^{b}	31.42±2.1^{c}	31.51±2.4^{b}	0,001
(mg/dL)	II	23.17±2.27^{a}	22.44±2.41^{a}	23.10±1.27^{a}	26.55±1.4^{b}	27.99±1.6^{c}	32.71±2.7^{b}	0,001
	P	NS	NS	NS	NS	NS	NS	
LDL	I	22.59±0.52^{a}	21.82±0.42^{a}	21.53±0.82^{ax}	23.08±0.85^{ax}	17.51±0.95^{bx}	17.78±0.62^{b}	0,001
(mg/dL)	II	21.97±0.81^{a}	20.34±0.61^{a}	18.46±0.61^{ay}	19.95±0.68^{ay}	14.83±0.63^{by}	20.94±1.4^{a}	0,001
	P	NS	NS	0,001	0,001	0,001	NS	

CHOL: Total Cholesterol, TG: Triglycerides, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 3. Protein and Immune Parameters (TP, ALB, UA, TBIL, CREA, IgG)

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
TP	I	7.07±0.06^{a}	7.01±0.06^{a}	6.70±0.07^{b}	6.75±0.08^{b}	6.38±0.08^{c}	6.58±0.07^{b}	0,001
(g/dL)	II	7.28±0.07^{a}	7.15±0.07^{a}	6.83±0.06^{b}	6.75±0.08^{b}	6.35±0.08^{b}	6.37±0.11^{b}	0,001
	P	NS	NS	NS	NS	NS	NS	
UREA	I	5.42±0.19^{a}	4.56±0.23^{b}	4.64±0.12^{b}	4.88±0.31^{ax}	5.73±0.21^{a}	6.36±0.34^{c}	0,001
(mg/dL)	II	5.14±0.22^{a}	4.46±0.11^{a}	4.70±0.07^{a}	4.13±0.19^{ay}	5.74±0.41^{a}	6.86±1.3^{b}	0.05
	P	NS	NS	NS	0.05	NS	NS	
UA	I	0.11±0.01^{a}	0.14±0.01^{b}	0.16±0.01^{b}	0.23±0.01^{c}	0.34±0.01^{d}	0.31±0.01^{d}	0,001
(mg/dL)	II	0.13±0.01^{a}	0.16±0.01^{b}	0.16±0.01^{b}	0.25±0.01^{c}	0.35±0.01^{d}	0.32±0.01^{e}	0,001
	P	NS	NS	NS	NS	NS	NS	
CREA	I	1.85±0.04^{a}	1.75±0.07^{b}	1.67±0.03^{b}	1.76±0.03^{ax}	1.76±0.03^{a}	1.54±0.03^{b}	0,001
(mg/dL)	II	1.87±0.02^{a}	1.93±0.02^{a}	1.62±0.02^{b}	1.62±0.02^{by}	1.72±3.5^{c}	1.50±0.03^{d}	0,001
	P	NS	NS	NS	0,001	NS	NS	
TBİL	I	0^{a}	0.0069^{a}	0.0034^{a}	0.0759^{b}	0.2138^{c}	0^{a}	0,001
(mg/dL)	II	0^{a}	0.0033^{a}	0^{a}	0.0567^{b}	0.1833^{c}	0^{a}	0,001
	P	NS	NS	NS	NS	NS	NS	
IgG	I	38.96±1.1^{a}	37.27±1.1^{ax}	34.06±0.93^{bx}	31.97±1.1^{cx}	30.05±7.65^{cx}	35.97±1.4^{bx}	0.05
(mg/dL)	II	37.30±1.0^{a}	35.58±0.85^{by}	27.78±1.0^{by}	21.81±0.7^{cy}	18.11±0.89^{cy}	42.18±10.5^{dy}	0.05
	P	NS	0.05	0.05	0.05	0.05	0.05	

TP: Total Protein, UREA: Urea, UA: Uric Acid, CREA: Creatinine, TBİL: Total Bilirubin, IgG: Immunoglobulin G, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 4. Liver Enzymes (ALT, AST, GGT, LDH)

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
ALT	I	11.23±3.9^{a}	14.73±5.3^{b}	14.75±3.07^{b}	16.98±3.3^{c}	18.37±5.2^{d}	19.57±3.1^{e}	0,001
(U/L)	II	12.66±5.2^{a}	12.94±3.8^{a}	16.52±3.9^{b}	18.21±3.3^{b}	18.45±4.4^{b}	20.70±2.8^{c}	0,001
	P	NS	NS	NS	NS	NS	NS	
AST	I	84.16±2.0^{a}	82.35±2.0^{a}	78.44±2.5^{a}	80.17±2.2^{a}	89.19±1.9^{a}	105.47±2.3^{b}	0,001
(U/L)	II	88.27±2.1^{a}	85.14±2.3^{a}	84.70±1.8^{a}	77.37±1.8^{b}	87.71±2.8^{a}	104.55±2.3^{c}	0,001
	P	NS	NS	NS	NS	NS	NS	
GGT	I	45.27±1.3^{a}	45.09±1.6^{a}	46.46±1.5^{a}	44.50±1.4^{a}	45.34±1.4^{a}	55.50±1.8^{b}	0,001
(U/L)	II	47.95±1.7^{a}	45.41±2.0^{a}	45.67±1.1^{a}	42.44±1.8^{b}	41.84±1.1^{b}	50.39±1.8^{a}	0,001
	P	NS	NS	NS	NS	NS	NS	
LDH	I	255.0±9.4^{a}	254.4±4.5^{a}	251.7±6.4^{a}	215.4±2.2^{b}	95.21±2.9^{b}	126.0±2.5^{c}	0,001
(U/L)	II	260.8±6.3^{a}	259.7±6.6^{a}	255.6±7.9^{a}	213.3±6.4^{b}	92.96±2.6^{c}	126.8±4.5^{d}	0,001
	P	NS	NS	NS	NS	NS	NS	

ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, GGT: Gamma-Glutamyl Transferase, LDH: Lactate Dehydrogenase, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 5. Minerals

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
Ca	I	9.01±0.09[a]	8.85±0.09[a]	8.94±0.07[a]	8.69±0.11[a]	8.06±0.43[b]	8.76±0.10[a]	0.05
(mg/dL)	II	8.91±0.2[a]	8.56±0.2[a]	8.87±0.07[a]	8.66±0.10[a]	8.33±0.31[b]	8.54±0.14[a]	0.05
	P	NS	NS	NS	NS	NS	NS	
Mg	I	4.96±0.1[a]	4.45±0.05[b]	4.39±0.09[b]	3.14±0.1[c]	3.14±0.1[c]	3.51±0.1[d]	0,001
(mg/L)	II	4.83±0.1[a]	4.32±0.09[b]	4.31±0.04[b]	3.29±0.1[c]	3.27±0.1[c]	3.42±0.06[d]	0,001
	P	NS	NS	NS	NS	NS	NS	
P	I	11.90±1.3[a]	10.78±0.8[ab]	9.98±0.7[b]	9.68±0.7[b]	8.70±0.7[b]	7.58±0.4[c]	0,001
(mg/dL)	II	11.49±0.6[a]	11.76±0.8[a]	10.59±0.7[ab]	9.58±0.7[b]	8.70±0.6[c]	8.17±0.5[c]	0,001
	P	NS	NS	NS	NS	NS	NS	

Ca: Calcium, Mg: Magnesium, P:Phosphorusabc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 6. Acute Phase Proteins and Oxidative Stress (PON, NO, Hp, SAA, CER and ALB)

P/U	G	Week 15	Week 16	Week 17	Week 18	Birth	PPD 21	P
Hp	I	0.099±0.004[a]	0.136±0.006[b]	0.174±0.012[c]	0.181±0.013[c]	0.347±0.012[d]	0.185±0.014[c]	0.05
(mg/mL)	II	0.087±0.006[a]	0.138±0.008[b]	0.182±0.016[c]	0.193±0.020[c]	0.307±0.13[d]	0.201±0.013[c]	0.05
	P	NS	NS	NS	NS	NS	NS	
SAA	I	8.23±0.57[a]	8.89±0.57[a]	10.56±0.81[b]	12.83±0.55[c]	24.57±0.44[d]	14.28±0.53[e]	0.05
(µg/mL)	II	8.77±0.54[a]	9.06±0.44[a]	11.44±0.77[b]	12.64±0.61[b]	22.72±0.56[d]	15.26±0.46[e]	0.05
	P	NS	NS	NS	NS	NS	NS	
CER	I	12.75±0.49[a]	14.15±0.72[b]	14.71±0.64[b]	15.42±0.69[c]	17.23±0.94[d]	15.86±0.64[e]	0.05
(mg/dL)	II	12.25±0.56[a]	12.27±0.49[a]	14.01±0.60[b]	14.76±0.66[b]	16.74±1.08[c]	15.74±0.51[d]	0.05
	P	NS	NS	NS	NS	NS	NS	
ALB	I	3.48±0.1[a]	3.53±0.09[a]	3.41±0.1[a]	3.31±0.08[a]	2.73±0.08[b]	3.17±0.09[c]	0.05
(g/dL)	II	3.36±0.1[a]	3.34±0.1[a]	3.27±0.07[a]	3.20±0.56[a]	2.83±0.08[b]	3.07±0.07[c]	0.05
	P	NS	NS	NS	NS	NS	NS	
PON	I	2.55±0.05[a]	2.63±0.04[a]	2.72±0.04[b]	2.73±0.09[b]	5.05±0.07[c]	2.55±0.07[a]	0.05
(U/L)	II	2.64±0.05[a]	2.71±0.04[a]	3.09±0.06[b]	3.02±0.09[b]	4.89±0.05[c]	2.65±0.03[a]	0.05
	P	NS	NS	0.05	0.05	NS	NS	
NO	I	8.24±0.12[a]	8.25±0.20[a]	11.21±0.19[b]	17.14±0.28[c]	14.29±0.22[d]	11.27±0.21[b]	0.05
(µmol/L)	II	8.24±0.14[a]	8.27±0.14[a]	10.93±0.17[b]	17.86±0.29[c]	14.01±0.23[d]	10.96±0.17[b]	0.05
	P	NS	NS	NS	NS	NS	NS	

Hp:Haptoglobin, SAA: Serum Amyloid A, CER:Ceruloplasmin,ALB: Albumin, PON: Paraoxonase, NO:Nitric Oxide, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Tablo 7. Immune and Metabolic Values of Newborn Lambs

P/U	G	Mean	P
GLU (mg/dL)	G 1	98.6755±4.6	P>0.05
	G 2	104.5003±6.8	
NEFA (mmol/L)	G 1	0.3397±0.009	P>0.05
	G 2	0.3153±0.001	
BHB (mmol/L)	G 1	0.42±0.0081	P>0.05
	G 2	0.44±0.0095	
CHOL (mg/dL)	G 1	53.1869±2.04	P>0.05
	G 2	52.5103±2.1	
LDL (mg/dL)	G 1	34.8938±2.7	P<0.05
	G 2	27.156±1.8	
TG (mg/dL)	G 1	146.747±7.4	P>0.05
	G 2	141.181±6.7	
HDL (mg/dL)	G 1	17.5621±1.2	p>0.05
	G 2	19.773±1.4	
TP (gr/dL)	G 1	7.53±1.13	P<0.05
	G 2	7.2±1.26	
UREA (mg/dL)	G 1	12.1003±0.3	P>0.05
	G 2	12.305±0.3	
UA (mg/dL)	G 1	0.31±0.17	P>0.05
	G 2	0.31±0.17	
CREA (mg/dL)	G 1	0.8552±0.05	P>0.05
	G 2	0.98±0.06	
TBİL (mg/dL)	G 1	0.98±0.10	P>0.05
	G 2	0.95±0.12	
IgG(mg/dL)	G 1	39.231±1.4	P<0.05
	G 2	28.52±1.2	
ALT (U/L)	G 1	21.5931±0.8	P>0.05
	G 2	19.6667±0.8	
AST (U/L)	G 1	94.49±5.05	P>0.05
	G 2	98.78±6.1	
GGT (U/L)	G 1	2075.86±134.09	P<0.05
	G 2	1726.35±138.52	
LDH (U/L)	G 1	131.71±6.8	P>0.05
	G 2	147.98±10.0	

GLU: Glucose **NEFA**: Non-Esterified Fatty Acids, **BHB**: Beta-Hydroxybutyrate, **CHOL**: Total Cholesterol, **LDL**: Low-Density Lipoprotein, **TG**: Triglycerides, **HDL**: High-Density Lipoprotein, **TP**: Total Protein, **UREA**: Urea, **UA**: Uric Acid, **CREA**: Creatinine, **TBİL**: Total Bilirubin, **IgG**: Immunoglobulin G,**ALT**: Alanine Aminotransferase, **AST**: Aspartate Aminotransferase, **GGT**: Gamma-Glutamyl Transferase, **LDH**: Lactate Dehydrogenase, abc XY Values represented by different letters indicate statistical significance; NS: no statistical significance.

Dıscussıon and Conclusıon

Due to the metabolic load imposed by the fetus during pregnancy, significant changes occur in the cardiovascular, gastrointestinal, respiratory, genital, and central nervous systems of the dam, as well as in its biochemical, physiological (blood parameters), and immunological functions. In late gestation, the increasing weight and growth of the fetus exert pressure on the rumen, leading to reduced feed intake in the dam. Although some of these changes are compensated by the dam, metabolic, physiological, and anatomical alterations caused by the fetus's increasing demands during the last third of gestation become much more pronounced (Özyurtlu et al., 2007).

Inve Glucose is highly important for revealing energy imbalance in the animal and for maintaining pregnancy and fetal development during late gestation. The decrease in glucose levels during the last stages of pregnancy is reported to be due to the fetus's increasing glucose demand and the reduction in feed intake caused by the pressure exerted on the rumen and uterus as the fetus grows in size. Furthermore, it has been reported that immediately after parturition, glucose levels rise as a result of increased cortisol levels associated with birth stress (Balıkçı et al., 2007; Tanrıtanır, 2010). In our study, although no statistically significant differences were found in blood glucose levels during the prepartum period, a relative decrease was observed.

These findings are consistent with previous reports indicating that blood glucose levels decrease in ewes during late gestation (Purohit et al., 1999; Balıkçı et al., 2007). In our study, serum glucose values measured immediately after parturition were around 90–92 mg/dL, and glucose levels returned to normal by day 21 postpartum, which aligns with earlier findings (Todorovic and Davidovic, 2013; Teama and Gad, 2014). The high value measured at parturition is thought to be associated with birth stress, a situation previously reported and consistent with our results (Todorovic and Davidovic, 2013; Simenew and Wondu, 2013; Teama and Gad, 2014). Since no statistical differences were observed between groups at the same sampling times, we conclude that levamisole administration had no effect on this parameter.

When glucose becomes insufficient to meet the increased energy demand during late gestation, the body compensates by mobilizing fat reserves, which is reported to be the main reason for elevated BHB and NEFA concentrations (Atakişi et al., 2009; Mohammadi et al., 2016). In ewes, BHB concentrations between 0.80 and 1.60 mmol/L indicate negative energy balance (Mohammadi et al., 2016). In our study, BHB values of 0.83 and 0.84 mmol/L obtained within the first four hours postpartum suggest that the animals were at the threshold of negative energy balance during this period. Additionally, the statistically significant increase in BHB values as parturition approached ($P < 0.05$), followed by a return to normal ranges after reaching the peak at birth, is consistent with previous studies (Atakişi et al., 2009). Since no statistical differences were observed between groups at the same sampling times, we conclude that levamisole administration had no effect on this parameter either. Stigating the effects of levamisole administration during late gestation on immune and metabolic parameters in ewes and passive immunity in lambs is important for understanding metabolic changes occurring before and after parturition, enabling early diagnosis of potential disorders, and improving farm profitability. In this study, the effects of levamisole administered during late gestation on immune and metabolic parameters during the transition period and on passive immunity transfer in lambs were evaluated.

In our study, an increase in NEFA values was observed at the 18th week of gestation, at parturition, and on day 21 postpartum, indicating mobilization of fat reserves. The fact that NEFA levels were lower in the levamisole-treated group compared to the control group suggests that fat mobilization was less pronounced in this group. This may be a consequence of the reported negative effect of levamisole on mitochondria and aerobic glycolysis occurring there, a situation that requires further clarification through more comprehensive studies. Additionally, the relatively lower glucose values obtained from the levamisole group may imply that, due to a potential unexplained effect of levamisole on mitochondria, energy was predominantly derived from glucose rather than fat reserves. Based on our literature review, the NEFA values obtained in this study have not been previously investigated by other researchers, making these findings the first of their kind in this field.

Studies conducted on pregnant animals (Nazifi et al., 2002; Yıldız et al., 2005) have reported that HDL and LDL concentrations increase during late gestation and decrease after parturition. In our study, HDL values in both groups increased similarly until parturition, with Group I reaching the highest level at birth, and then decreased by day 21 postpartum. In

contrast, HDL levels in Group II continued to rise until day 21 postpartum. These findings are consistent with previous reports (Nazifi et al., 2002; Yıldız et al., 2005). Although HDL values in Group I were relatively higher than those in Group II, no statistically significant difference was detected between groups. We believe that this relative difference may be attributed to the effect of levamisole used in our study.

In this study, LDL values showed statistically significant differences ($P < 0.05$) between groups at weeks 17 and 18 of gestation and at parturition. This difference, similar to findings reported for other lipid parameters, is thought to be related to the effect of levamisole administered to Group I. Although LDL levels were lowest at parturition, no statistically significant difference was observed compared to prepartum values; however, these results are consistent with previous studies (Nazifi et al., 2002; Yıldız et al., 2005).

Cholesterol and triglyceride levels in ewes have been reported to increase during late gestation by various researchers (Atakişi et al., 2009; Balıkçı et al., 2007). Another study reported that serum triglyceride levels remained stable until parturition but decreased during birth and lactation. In the present study, no statistical difference was found between prepartum cholesterol values of the two groups; however, cholesterol levels dropped to their lowest point at parturition in both groups and then increased significantly ($P < 0.001$) during the postpartum period. Similarly, triglyceride levels followed a pattern comparable to cholesterol, showing a statistically significant decrease ($P < 0.001$) during parturition and the subsequent period. We believe this decrease is due to the high fat content of colostrum and the substantial transfer of fat from serum to colostrum and milk for a certain period after birth. The fluctuations in cholesterol and triglyceride levels observed in our study are consistent with findings reported by Karadaş (2008) and Tanrıtanır et al. (2010).

In our study, serum total protein levels before parturition decreased significantly ($P < 0.001$) until birth, and measurements taken on day 21 postpartum showed a slight relative increase compared to the last prepartum measurements. This downward trend observed until parturition did not result in a statistically significant difference between the two groups. Previous studies (Balıkcı et al., 2007; Tanrıtanır et al., 2007; Tanrıtanır et al., 2010) have reported that total protein levels in pregnant ewes are lower compared to non-pregnant ewes and decrease during late gestation compared to postpartum, due to the increased protein demand, which is consistent with our findings.

Fırat and Özpınar (1996) reported that bilirubin levels were high during late gestation in ewes, whereas Özyutlu et al. (2007) found no statistically significant difference in bilirubin levels throughout pregnancy. In our study, measurements taken during late gestation and at parturition showed statistically significant differences ($P < 0.001$) compared to other sampling times, and bilirubin levels returned to baseline values after birth. These changes in total bilirubin are consistent with previous reports (Balıkcı et al., 2007). Elevated plasma urea levels during pregnancy, along with increased bilirubin concentrations, may be attributed to fetal hemoglobin breakdown or insufficient glucuronic acid synthesis, resulting in additional bilirubin production.

Serum urea, uric acid, and creatinine concentrations are considered indicators of protein utilization in the diet or feeding practices. Changes in these parameters have been interpreted by researchers as seasonal variations rather than effects of reproduction (Yokuş et al., 2007). In our study, significant decreases in these parameters were observed from gestation to parturition. Nazifi et al. (2002) explained these changes as a result of alterations in protein synthesis and increased demand. We also believe these changes may be associated with negative energy balance during late gestation and the mobilization of body protein reserves to meet the needs of the developing fetus.

In ruminants, amino acids are normally not extensively catabolized; however, in females during late gestation and for milk protein synthesis, their utilization may increase, leading to

reduced urea production and decreased plasma urea concentration. In our study, serum urea levels in pregnant ewes showed a decreasing trend until parturition, supporting this information. Similar results were reported by Balıkçı et al. (2007). The reduction in urea during pregnancy may also be associated with pregnancy stress and decreased feed intake.

In our study, the increase in urea levels observed at parturition and on day 21 postpartum differs from the findings of some researchers (Mohammadi et al., 2016). We believe this discrepancy may be due to differences in feeding practices between the two studies.

Decreases in IgG levels during the periparturient period, which are associated with colostrogenesis, have been reported in previous studies (Herr et al., 2011). In our study, IgG levels in both groups decreased significantly ($P < 0.05$) until parturition during late gestation; however, IgG levels in the levamisole-treated group were relatively higher compared to the control group. This clearly demonstrates that levamisole supports immunity in ruminants. The statistically significant differences ($P < 0.05$) observed between groups at all sampling times throughout the study further confirm that immunity is suppressed during late gestation and that suppressed immunity can be enhanced by levamisole without question. Gürbulak and Kılıçarslan (2004) obtained similar results in a study conducted on cattle. We believe these findings indicate that the positive immunostimulant effect of levamisole is responsible for improving immune status during late gestation, supporting the results obtained in our study.

AST and ALT activities are reported to be associated with implantation during pregnancy, maintenance of embryonic life, fetal growth, carbohydrate metabolism in the uterus, and glycogen storage, and all these physiological processes may lead to increases and fluctuations in AST and ALT values (Rao, 1981; Khan, 2002). Enzyme levels play a decisive role in evaluating metabolic activities and physiological conditions. Measuring enzyme activities is also useful for detecting pathological conditions in tissues. Numerous studies have reported that serum enzyme levels change in cases of tissue damage (Liesegang et al., 2007;Tanrıtanır et al., 2010; Kenerman, 2011). Various researchers have reported changes in ALT and AST activities during late pregnancy. In Awassi ewes, AST levels before parturition were found to be higher than postpartum levels, which has been attributed to hormonal changes during pregnancy (Özyurtlu et al., 2007; Tanrıtanır et al., 2010). Yokuş et al. (2006) reported that AST levels varied according to season and reproductive period in Chios-Awassi crossbred ewes.

In our study, no statistical difference was found between ALT and AST values in the control group and the levamisole-treated group, indicating that levamisole administration did not affect these parameters, consistent with previous reports. Measurements of GGT, ALT, and AST enzymes used to assess liver damage showed a statistically significant ($P < 0.001$) increase toward the end of the study in both groups, clearly demonstrating intense metabolic activity in the liver during pregnancy. A positive correlation was observed among these values. We believe that all these changes in enzyme activities are due to the natural effects of pregnancy, parturition, and lactation on the liver.

LDH activity increases when dietary protein intake decreases and muscle mobilization rises. In our study, LDH values measured at weeks 16 and 18 showed a statistically significant difference ($P < 0.001$) between groups, then decreased similarly in both groups until parturition, and rose to the reference range by day 21 postpartum. This suggests that the observed changes in LDH reflect muscle catabolism to meet energy requirements during late pregnancy.

Serum PON levels increased from week 15 onward, peaked at parturition, and returned to normal ranges postpartum. A previous study reported that PON activity changes with lipid metabolism and is clearly affected by negative energy balance. Turk et al. (2013) reported significant decreases ($P < 0.05$) in PON activity in heifers until parturition, which does not align with our findings. Our literature review revealed no other studies tracking PON values during

pregnancy. PON is an HDL-associated enzyme that inhibits LDL oxidation; therefore, its positive correlation with HDL and negative correlation with LDL is expected. In our study, HDL and LDL values were consistent with the classical biochemical behavior of PON.

Nitric oxide (NO) production increases in response to bacterial, viral, parasitic, or fungal infections and plays a role in nonspecific defense mechanisms with antimicrobial, anti-inflammatory, cytoprotective, and cytotoxic effects. It also rises toward the end of pregnancy due to inflammation. NO helps maintain uterine quiescence during pregnancy by increasing production in vascular endothelium and regulates uterine blood pressure throughout gestation. Its level decreases at parturition to allow uterine contractions necessary for labor (Atakişi and Özcan 2005; Yarım et al., 2006). In our study, NO values increased from the beginning of the study until week 18 of gestation, then decreased at parturition and on day 21 postpartum, consistent with previous reports (Karadaş, 2008). No statistical differences were observed between groups, suggesting that levamisole had no effect on NO levels.

Acute phase proteins (APPs) are synthesized by the liver and are known markers of the acute phase response (APR) to tissue damage, inflammation, infection, and immunological disorders. Changes in APP levels, triggered by cytokines released during inflammatory conditions, are useful parameters for disease diagnosis, prognosis, and monitoring treatment (Merhan and Özcan, 2010). In our study, haptoglobin, serum amyloid A, ceruloplasmin, and albumin were evaluated throughout the study. Haptoglobin, serum amyloid A, and ceruloplasmin increased until parturition, peaked at birth, and decreased afterward, while albumin showed an opposite trend. Haptoglobin increases in inflammatory diseases, collagen tissue disorders, trauma, and glomerulonephritis. It has also been reported that haptoglobin decreases in liver degeneration, increases in hepatic lipidosis, and can therefore be used in diagnosing hepatic lipidosis (Humblet, 2006).

In our study, the haptoglobin values obtained were consistent with those reported by other researchers, while the absence of a statistically significant difference between groups suggests that levamisole administration had no effect on this parameter (Nowroozi-Asl et al., 2008; Merhan and Özcan, 2010). Our literature review revealed no studies investigating serum amyloid A levels during pregnancy in ewes; therefore, the results obtained in this study were evaluated based on the general characteristics and trends of acute phase proteins under similar conditions. The statistically significant increase ($P < 0.05$) in serum amyloid A levels from the beginning of the study until parturition, followed by a decrease postpartum, was interpreted as a physiological response similar to inflammation during late pregnancy, with the decline reflecting the resolution of this process after parturition. The absence of a statistically significant difference between groups, despite a slight numerical variation, suggests that levamisole did not influence this parameter during pregnancy.

In our study, albumin levels in both groups gradually decreased as pregnancy progressed, reaching the lowest level at parturition ($P < 0.05$), and then increased significantly by day 21 postpartum. These findings are consistent with previous reports (Irmak et al., 1998; Balıkcı et al., 2007; Mohammadi et al., 2016). Mohammadi et al. (2016) attributed this decrease to nutritional deficiencies, while other researchers suggested that these changes result from protein metabolism and transfer to colostrum during pregnancy.

Calcium levels in animals are influenced by several factors, the most important being nutritional status and hormonal changes during pregnancy (Özyurtlu et al., 2007). In our study, serum calcium levels in both groups remained within normal limits (9–12 mg/dL) before parturition but decreased at birth and postpartum. This decline is known to occur due to the continuous transfer of calcium to the fetus to meet its increasing needs until birth. The lowest level recorded at parturition can also be explained by the high calcium requirement for milk production immediately after birth (Irmak et al., 1998). Our findings are consistent with

classical literature, and based on these results, we conclude that levamisole had no effect on serum calcium levels.

Yokuş et al. (2004) and Özyurtlu et al. (2007) reported that magnesium concentrations in Chios-Awassi crossbred ewes were generally unaffected by physiological changes. However, in our study, serum magnesium levels showed a statistically significant decrease ($P < 0.001$) in both groups at week 18 of gestation and at parturition, followed by a significant increase by day 21 postpartum. This indicates that magnesium undergoes substantial changes during the transition period, similar to calcium, due to its excessive utilization for fetal development, which aligns with previous reports (Irmak et al., 1998; Roubies et al., 2006).

In both groups, serum phosphorus concentrations decreased significantly ($P < 0.001$) throughout the study, consistent with findings from other studies attributing this to fetal growth and the onset of milk production (Roubies et al., 2006; Özyurtlu et al., 2007). The absence of a statistically significant difference between groups suggests that levamisole had no effect on serum phosphorus levels.

In our study, the parameters that showed statistically significant differences between lambs born to Group I and Group II were LDL, TP, GGT, and IgG. All other parameters examined in the lambs GLU, NEFA, BHB, CHOL, TG, HDL, LDL, UREA, UA, CREA, TBIL, ALT, AST, LDH, PON, NO, Hp, SAA, CER, ALB, Ca, Mg, and P remained within accepted physiological limits, and no statistically significant differences were detected between groups. We believe this normality is due to proper care and high-quality feeding of the ewes during pregnancy.

Feeding protocols for lambs were standardized: 50 ml/kg of colostrum was administered by bottle within the first 4 hours after birth, and a total of 200 ml/kg within 24 hours. This likely contributed to most parameters remaining within normal ranges. The statistically significant difference in LDL between groups is thought to result from the high cholesterol and insoluble lipoprotein content in colostrum. Fundamentally, this finding reflects the relative and statistically significant differences in total cholesterol and LDL levels observed in ewes at parturition, which were transferred to lambs via colostrum. To our knowledge, these findings have not been previously reported, making them a novel contribution to the field.

Total protein levels above 6.5 mg/dL within the first 24 hours indicate adequate colostrum intake in lambs (Scott, 2007). In our study, lambs from both groups exceeded this threshold, suggesting strong passive immunity. However, TP values in lambs from the levamisole-treated group were significantly higher ($P < 0.05$) than those in the control group. Similarly, GGT ($P < 0.05$) and IgG ($P < 0.05$) key indicators of passive immunity were significantly higher in the levamisole group, likely due to enhanced maternal immunity during pregnancy. Levamisole administration has been reported to increase immunoglobulin levels in colostrum and newborn calves (Şentürk et al., 2003). Our findings for GGT and IgG in lambs align with results from studies on calves born to levamisole-treated cows (Gürbulak and Kılıçarslan, 2004). A positive correlation was observed among GGT, total protein, and IgG values. This triple relationship is consistent with previous studies reporting that high total protein and GGT levels are associated with elevated IgG concentrations (Krakowski et al., 1999).

In recent years, globally and nationally, research aligned with realistic scientific goals and livestock policies has focused on understanding changes in immunology, biology, and metabolism during the transition period a critical phase for productivity and offspring survival in ruminants. Efforts aim to prevent immunosuppression, oxidative stress, inflammation, negative energy balance (NEB), and physiological phenomena linked to colostrogenesis, which cause dramatic declines in immune parameters. Improving colostrum quality and ensuring strong passive immunity in newborns are essential for reducing disease incidence and severity in dams and offspring, thereby supporting sustainable and profitable livestock production.

This study aimed to evaluate the potential contribution of levamisole a known immunostimulant at low doses administered during the transition period to prevent immunosuppression, oxidative stress, and NEB, and to assess its effect on colostrum quality and neonatal health. Based on our findings, levamisole administration during late gestation did not significantly affect the metabolic profile of ewes but had a clear positive impact on colostrum quality, thereby increasing the likelihood of producing healthy lambs. Lambs born to treated ewes demonstrated stronger passive immunity and a better start to life. We conclude that further comprehensive studies using levamisole and/or other immunostimulants could provide valuable contributions to flock health, productivity, and profitability.

Ş K: Study design, execution of field and laboratory work (blood sampling and biochemical analyses), data collection, statistical analysis, and drafting of the manuscript. E U: Project planning, formulation of the scientific hypothesis, determination of methodology, provision of laboratory facilities, interpretation of findings, academic review of the manuscript, and final approval (Supervision/Consultancy).

Conflict of Interest Statement: The authors declare that there are no financial, personal, or institutional conflicts of interest regarding the research, authorship, and/or publication of this study. This work was conducted strictly within the framework of scientific ethical rules and for academic purposes. This article is derived from the thesis entitled "Effects of Levamisole Administration to Sheep in the Late Stage of Pregnancy on Transition Period Immune and Metabolic Values and Passive Immunity in Lambs".

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