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Original article

Influence of melatonin on reproductive performance and some blood parameters in rabbits

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Abstract

Melatonin not only regulates circadian rhythms in animals but also supports reproductive health through its potent antioxidant properties and immunomodulatory effects. In this study, the effects of exogenous melatonin administration on blood total antioxidant status (TAS), total oxidant status (TOS),Immunoglobulin G (IgG),Immunoglobulin M (IgM), and prolactin (PRL) concentrations, as well as on pregnancy rates and litter size, were investigated in rabbits. A total of 26 New Zealand rabbits were divided into two groups for the study. Melatonin implants were administered subcutaneously (SC) to group 1 (n=13) (MEL). Saline injections were administered to group 2 (n=13) (CON). Samples were collected from all rabbits before mating, on the 15th day of gestation and after parturition from the ear marginal vein and TAS, TOS, IgG, IgM, PRL concentrations and hemogram parameters were analyzed. Pregnancy rates were 77% and 92.3% in the CON and MEL groups, respectively, while litter sizes were 5.2 and 6 in the CON and MEL groups, respectively. TOS levels were found to be statistically lower ($p<0.05$) in the MEL group compared to the CON group just after parturition; however, there was no statistical difference between the groups in terms of TAS values at different times ($p>0.05$). IgG and IgM levels before mating and after parturition did not differ statistically significantly between the experimental groups when melatonin was administered. However, a statistically significant increase in the levels of both IgG and IgM was observed in the MEL group on day 15 of gestation. Exogenous melatonin administration did not alter reproductive parameters in New Zealand rabbits; however, it exhibited immunomodulatory effects on the 15th day of gestation and reduced oxidative stress after parturition.

Keywords: blood parameters, gestation, litter size, melatonin, rabbit

Introduction

The breeding of rabbits is an emerging sector in meeting the meat needs of the world's population (Lebas et al. 1997). Rabbit is preferred in meat production due to its features such as short gestation period, ability to get pregnant in the early postpartum period, high number of offspring in one litter, rapid development of the newborn offspring and entering puberty in a short time (Lebas et al. 1997, Cullere and Dalle Zotte 2018). Various studies have been conducted to improve reproductive performance in rabbits. These investigations cover hormone therapies (Boiti et al. 2007), eating (El-Desoky et al. 2021), and light (Gerencsér et al. 2011). Estrus induction and synchronization have been the main uses of hormone applications in recent years (Mousa-Balabel and Mohamed 2011). Biostimulation methods including short-term doe-litter separation, lighting programs, and flushing (Theau-Clément 2000) emerge as the most promising and viable strategies to enhance reproductive performance with respect to animal welfare, serving as an alternative to eCG administration for estrus synchronization (Arias-Álvarez et al. 2010). Although melatonin is frequently used to enhance reproductive function, particularly in small ruminants (Akbulut et al. 2025, Zhang et al. 2025), there aren't many studies on its sustained-release application in rabbits. While melatonin has generally been administered orally in studies (Mousa-Balabel and Mohamed 2011, Hashem et al. 2023) investigating its effects on reproduction in rabbits, sustained-release melatonin implant was used in the present study.

Melatonin is an indoleamine produced mainly by the pineal gland in mammals (Ferlazzo et al. 2020). In recent years, studies have focused on the biological activities of melatonin, such as regulating cellular activity and intercellular and intersystemic relationships (Kvetnoy et al. 2022). Melatonin also regulates other general functions such as lipid metabolism, sugar metabolism, carcinogenesis, immune regulation and reproduction (Korkmaz et al. 2009, Tamura et al. 2014). Melatonin directly neutralizes the harmful radicals that initiate and propagate lipid peroxidation, while simultaneously stimulating the cell's endogenous defense mechanisms (Volpe et al. 2025).

Oocyte quality and early embryo development can be negatively affected by oxidative stress (Tamura et al. 2008), so ways to reduce oxidative stress have become an important strategy in reproductive health (Olcese 2020). Increased oxidative stress in the follicular fluid, accompanied by elevated inflammation, directly impairs fertilization capacity, embryo quality, and implantation success by damaging the oocyte's DNA, cytoskeleton, and cell membrane structure (Artini et al. 2022). Exogenous melatonin has positive effects on embryo viability due to its luteotropic effect (Vazquez et al. 2013). A study conducted reported that exogenous melatonin increased the number of embryo implantations in mice (Zhang et al. 2017). In recent years, studies on the effects of melatonin on colostrum quality and the viability of offspring have increased (Canto et al. 2022, Tekin and Akkuş 2023, Canto and Abecia 2024). A study conducted in sheep reported that maternal melatonin administered throughout pregnancy plays an important role in brown adipose tissue development and thermoregulation of newborns (Seron-Ferre et al. 2015). In the study conducted by Canto et al. it was reported that melatonin applied approximately 40 days before lambing caused colostrum with higher Ig G and milk with lower somatic cell count in sheep (Canto et al. 2022). Additionally, melatonin stimulates the release of prolactin (PRL) (Okatani and Sagara 1993).

Melatonin has been demonstrated to exert stimulatory effects on both humoral and cellular immunity in mammals and poultry. These effects are achieved through the utilization of specific binding sites on immune cells (Fraschini et al. 1998, Tutuncu and Delice 2021). Melatonin has been demonstrated to modulate the activity of various immune cells, including dendritic cells, natural killer cells, neutrophils, and T cells. Additionally, its influence extends to the function of macrophages (Černyšiov et al. 2010). Melatonin administration has been demonstrated to enhance the primary antibody response (IgM and IgG) in vivo, in accordance with a dose-response behavior (Maestroni et al. 1987).

Melatonin may reduce oxidative stress, thereby improving oocyte quality and embryo implantation, resulting in a greater number of offspring. Melatonin's effects on the immune system may lead to healthier offspring. Sustained-release application of melatonin may lead to a more pronounced manifestation of the beneficial effects on reproduction. In this study, the effects of exogenous melatonin administration on blood total antioxidant status (TAS), total oxidant status (TOS), Immunoglobulin G (IgG), Immunoglobulin (IgM) and prolactin (PRL) concentrations as well as pregnancy rates and litter size were investigated in rabbits.

Materials and Methods

Animals

The study was conducted on 26 New Zealand does with live weights of approximately 3-3,5 kg, which were nulliparous and were raised at Necmettin Erbakan

University Application and Research Center of Experimental Medicine (KONUDAM, 37°52′31″N 32°25′58″E). Animals were included in the study after a health screening. Rabbits were housed in cages measuring 70 cm * 50 cm * 75 cm. According to NRC (1977), feed (containing 2500 kcal/kg metabolic energy and 18% crude protein) and water were provided ad libitum.

Ethics approval

Ethics committee approval for this study was obtained from the Local Animal Experiments Ethics Committee of the Necmettin Erbakan University Application and Research Center of Experimental Medicine (27.02.2024, 2024-15).

Study design

26 New Zealand does were divided into two equal groups for the study. In Group 1 (MEL), melatonin implants (18 mg melatonin/implant, Regulin®, CEVA Animal Health Limited, Chesham, Buckinghamshire, United Kingdom) were administered subcutaneously (SC) to 13 does. 13 does in Group 2 (CON) received subcutaneous injections of 0.2 cc of saline. Implants containing 18 mg of melatonin are designed to maintain high plasma melatonin concentrations for at least 60 days. Does were placed in the bucks› cage and observed for mating. Bucks used in the study were selected from a population at KONÜDAM. Does were mated with fertile bucks, and each buck was used in only one mating. After mating was observed, the does were moved to their individual cages.

Blood samples

Samples were collected from the marginal ear vein of all rabbits before mating, on day 15 of gestation, and up to approximately 8 hours after parturition. Blood was collected into tubes containing K3-EDTA for hematological parameters from whole blood, and into tubes with gel clot activator for TAS, TOS, IgG, IgM, and PRL concentrations. Tubes were centrifuged using Nüve NF 800R (Ankara-Turkiye) 2500 rpm for 10 minutes for serum and stored at -20°C for later analysis. TAS, TOS, IgG, IgM, and PRL measurements were performed using rabbit-specific ELISA kits (Sunred, Shanghai, China) and an ELISA reader (BioTek ELx 800, USA). The Mindray BC-5000 Vet (Guangdong, China) was used to analyze hematological parameters, and blood samples were analyzed immediately after collection.

Reproductive parameters

Pregnancy rate and litter size were measured as reproductive parameters. The pregnancy rate was calculated as the percentage of mated does found to be pregnant. Litter size refers to the number of kits per kindling doe.The following formulas were used to calculate pregnancy rate and litter size.

Statically analysis

Statistical analyses were performed using the GLIMMIX procedure in SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Data from the transition period were analyzed using mixed models for repeated measures, with time defined as the repeated factor and animals specified as the random effect. Fixed effects in the model consisted of treatment, time, and the treatment × time interaction. The heterogeneous first-order autoregressive [ARH(1)] covariance structure was chosen based on the lowest Akaike Information Criterion (AIC) (Çetin and Bek 2019). The normality of the residuals was assessed using the Shapiro-Wilk test, and statistical significance was set at $p<0.05$.

Results

The pregnancy rate and litter size obtained in the study are presented in Table 1.

The present study provides a comprehensive overview of blood concentrations of IgG, IgM, TAS, TOS, and PRL before mating, on day 15 of gestation, and after parturition, as detailed in Table 2.

As shown in Table 2, significant temporal variations were observed in IgG and IgM levels within the MEL group, with an elevation detected on day 15 of pregnancy. Conversely, no significant differences in oxidative stress parameters (TAS and TOS) were found with respect to group or time factors. Prolactin levels, however, exhibited a physiological rise in both groups approaching parturition, regardless of the treatment.

The hemogram data obtained in our study are given in Table 3.

According to Table 3, WBC and EOS levels demonstrated significant temporal fluctuations ($p<0.01$) regardless of treatment. Although RBC counts remained statistically unchanged, erythrocyte indices, specifically HGB, MCV, and MCH, showed variations attributed to time or group-by-time interactions. Notably, MCHC was the only parameter to exhibit a significant group effect ($p=0.004$); the MEL group exhibited consistently lower values than the CON group.

Table 1. Pregnancy rate and litter size in rabbits.

Groups	Pregnancy rate %	Litter size
CON	77[a] (10/13)	5.2[a] (52/10)
MEL	92.3[a] (12/13)	6.0[a] (72/12)

There was no a significant difference between the groups in terms of pregnancy rate and litter size (p>0.05).

Table 2. Immunoglobulin G (IgG), Immunoglobulin (IgM), Total antioxidant status (TAS), Total oxidant status (TOS), and Prolactin (PRL) levels in rabbits.

Parameters	Groups	Days			p values		
		0	P15	Part.	Group	Days	Group x Days
IgG (mg/ml)	KON	1.37±0.54	1.49 ± 0.37	1.42 ± 0.31	p=0.31	p=0.02	p=0.17
	MEL	1.30 ± 0.48	1.88 ± 0.52	1.47 ± 0.36			
IgM (mg/ml)	KON	0.68 ± 0.18	0.61 ± 0.15	0.77±0.13	p=0.22	p=0.78	p=0.01
	MEL	0.70 ± 0.24	0.86 ± 0.17	0.66 ± 0.21			
TAS (U/ml)	KON	33.17 ± 9.11	34.62 ± 7.75	38.55 ± 7.80	p=0.58	p=0.23	P=0.68
	MEL	32.76 ± 7.80	35.26 ± 7.15	35.44 ± 5.13			
TOS (pg/ml)	KON	187.98 ± 78.47	185.38 ± 34.11	200.84 ± 24.56	p=0.29	p=0.59	p=0.12
	MEL	169.94 ± 58.35	203.41 ± 51.13	163.36 ± 39.67			
PRL (ng/ml)	KON	26.61 ± 8.29	28.78 ± 7.63	31.02 ± 7.80	p=0.81	p=0.05	p=0.66
	MEL	23.89 ± 8.64	29.74 ± 5.41	31.43 ± 6.73			

0 – Before Mating, 15 – 15th day of gestation Part: After Parturition.

Table 3. Hemogram values obtained in rabbits.

Parameters	Groups	Days			p values		
		0	15	Part.	Group	Days	Group x Days
WBC 10^9/L	CON	7.41 ± 1.65	8.76 ± 0.74	10.26 ± 2.46	p=0.21	p=0.001	p=0.19
	MEL	7.74 ± 1.05	10.36 ± 3.68	9.4 ± 3.74			
NEU 10^9/L	CON	2.44 ± 0.65	2.77 ± 0.09	4.3 ± 2.11	p=0.21	p=0.12	p=0.11
	MEL	2.79 ± 0.26	2.88 ± 0.61	3.04 ± 1.46			
LYM 10^9/L	CON	4.48 ± 1.48	5.33 ± 0.97	5.29 ± 0.93	p=0.42	p=0.20	p=0.30
	MEL	4.4 ± 0.88	4.83 ± 1.36	5.62 ± 2.57			
MON 10^9/L	CON	0.42 ± 0.13	0.55 ± 0.18	0.71 ± 0.39	p=0.88	p=0.07	p=0.91
	MEL	0.49 ± 0.12	0.56 ± 0.26	0.69 ± 0.42			
EOS 10^9/L	CON	0.06 ± 0.02	0.1 ± 0.02	0.07 ± 0.05	p=0.50	p=0.001	p=0.05
	MEL	0.06 ± 0.03	0.11 ± 0.05	0.04 ± 0.02			
RBC 10^{12}/L	CON	5.51 ± 0.76	5.36 ± 0.18	5.66 ± 1.14	p=0.79	p=0.12	p=0.67
	MEL	6.14 ± 0.79	5.18 ± 0.34	5.20 ± 0.63			
HGB g/dL	CON	12.27 ± 1.12	12.4 ± 0.76	12.52 ± 2.62	p=0.26	p=0.05	p=0.58
	MEL	13.01 ± 0.82	11.2 ± 0.32	11.34 ± 1.14			
MCV fL	CON	78.03 ± 4.15	78.40 ± 1.62	77.50 ± 2.79	p=0.46	p=0.05	p=0.01
	MEL	76.04 ± 6.53	73.79 ± 2.61	77.19 ± 3.46			
MCH pg	CON	22.37 ± 1.50	23.13 ± 0.72	22.12 ± 0.87	p=0.21	p=0.38	p=0.04
	MEL	21.37 ± 1.96	21.66 ± 0.93	21.60 ± 0.97			
MCHC g/L	CON	286.86 ± 5.08	295.17 ± 3.66	285.5 ± 10.2	p=0.004	p=0.001	p=0.89
	MEL	281.14 ± 3.89	293.57 ± 3.26	280.09 ± 6.1			

Abbreviations: WBC – White Blood Cells, NEU – Neutrophils, LYM – Lymphocytes, MON – Monocytes, EOS – Eosinophils, RBC – Red Blood Cells, HGB – Haemoglobin, MCV – Mean Corpuscular Volume, MCH – Mean Corpuscular Haemoglobin, MCHC – Mean Corpuscular Haemoglobin Concentration.

Discussion

Pregnancy rate and litter size

In this study, pregnancy rates were 77% and 92.3% in the CON and MEL groups, respectively; mean litter sizes were 5.2 and 6, respectively. There was no significant difference between the groups in terms of pregnancy rate and litter size. In a study conducted on New Zealand rabbits, melatonin was compared with different light regimes, and the conception rate (100%) and litter size (8.5) of the melatonin group were found to be higher than all other groups (Mousa-Balabel and Mohamed 2011). A study in mice indicated that melatonin increases the number of implantation sites during early pregnancy. The mechanism through which melatonin exerts this effect involves the induction of 17β-estradiol levels during gestation and the upregulation of p53 expression in the uterus, which serves as a mediator for MT1/2 activation. (Zhang et al. 2017). A substantial body of research has been conducted on the effects of melatonin on reproductive parameters in small ruminants. The results of some studies have indicated that melatonin has a positive effect on these reproductive parameters. (Haresign et al. 1990, DeNicolo et al. 2008). In this study, the lack of statistically significant differences in pregnancy rate and litter size between groups may be due to the rabbits being nulliparous.

Blood parameters

IgG and IgM

In this study, melatonin administration did not lead to statistically significant changes in IgG and IgM levels between the study groups before mating and after parturition. However, a statistically significant increase in both IgG and IgM levels was observed in the MEL group on the 15th day of gestation (Table 2). A study conducted on rats found that exogenous melatonin administration caused an increase in both IgG and IgM concentrations in aged rats (Akbulut et al. 2001). In a study conducted on sheep, sheep that received one or two melatonin implants for 40 days prior to lambing were found to produce colostrum with higher IgG concentrations than sheep that did not receive implants (Canto et al. 2022). Regodon et al. reported that slow-release melatonin administration significantly increased antibody titers and IgG levels in sheep and can be used as an adjuvant in vaccines (Regodón et al. 2009). It was reported that the administration of melatonin has been shown to increase IgG and IgM levels in murine models vaccinated with sheep red blood cells on days 4 and 5, respectively (Maestroni et al. 1987). Melatonin has been demonstrated to regulate a variety of processes related to T cell activation, differentiation, and proliferation. T cells possess the enzymes and receptors necessary for melatonin synthesis. Melatonin has been shown to increase the production of IL-4, the cytokine produced by Th2 cells, and promote the differentiation of B cells. In summary, melatonin's effects on T cells suggest a potential for interaction with Th2 cells, which may result in the induction of IgG1 production. (Ma et al. 2020). In the present study, the elevated levels of IgG and IgM observed in the MEL group on the 15th day of pregnancy indicate that the immunomodulatory effect of the melatonin implant is more pronounced on the 15th day of pregnancy in rabbits.

TAS and TOS

No statistically significant differences were observed between groups or across repeated measures for TAS and TOS values at various time points ($p>0.05$) (Table 2). Regarding TOS values, an antioxidant effect was observed in the MEL group compared to the CON group only during the postpartum period. Melatonin's antioxidant properties have been demonstrated to regulate physiological processes related to human reproduction (Carlomagno et al. 2018). In a study of 40 athletes, it was reported that melatonin significantly increased TAS levels (Ortiz-Franco et al. 2017). In a study conducted on sheep, melatonin implants were administered in the 4th month of pregnancy, and, TAS levels were found to be statistically higher, while TOS levels were found to be statistically lower immediately after parturition (Tekin and Akkuş 2023). In their study, Mistraletti et al. reported that melatonin increased total antioxidant capacity in patients with various diseases. Furthermore, it was hypothesized that pregnancy and childbirth may exert an influence on antioxidant capacity (Mistraletti et al. 2017). Rios et al. found that TAS decreased in the second month of gestation and on postpartum day 5 in ewes (Rios et al. 2017). A human study has indicated that TAS values reach their peak during the third trimester of gestation. These results suggest that placental antioxidant mechanisms become more effective in counteracting oxidative challenges during this period (Basu et al. 2015). The observed variation in postnatal TOS values in the MEL group may be attributable to the antioxidant capacity of melatonin.

Prolactin

In the present study, melatonin administration did not result in a statistically significant difference in PRL levels compared to the CON group (Table 2). However, in repeated measurements, PRL levels increased as gestation progressed. In the anterior pituitary gland,

melatonin affects lactotrophs that secrete PRL and gonadotrophs (luteinizing hormone (LH) and follicle stimulating hormone (FSH) (Balik et al. 2004). It is widely recognized that PRL, a hormone secreted by the anterior pituitary, functions as both a lactogenic and mammogenic agent (Kutlu and Akbulut 2025). In a study conducted on nulliparous rabbits, the effects of oral administration of 0.7 mg/kg melatonin during the first, second, and both first and second weeks of pregnancy on blood PRL concentrations were investigated, and it was found that PRL levels were higher in all groups administered melatonin on days 21 and 25 of pregnancy compared to the control group (Hashem et al. 2023). The administration of exogenous melatonin during the spring and summer months has been documented to result in a decrease in PRL concentrations in sheep (Molik et al. 2013). A prolonged MEL signal, characteristic of short days, has been demonstrated to inhibit PRL secretion from the pituitary gland. Research findings have demonstrated that prolonged MEL administration to both rams and ewes during the extended-day phase inhibits PRL secretion. (Ciechanowska et al. 2013, Molik et al. 2013). In the present study, the prolonged-release melatonin implant was used, but no significant differences were observed compared with the control group.

Hemogram parameters

According to the table presented, no statistically significant main effect of group was observed between the control (CON) and melatonin (MEL) groups for WBC, NEU, LYM, MON, and RBC parameters ($p>0.05$). However, when the effect of time (day 0, day 15, and parturition) was evaluated, statistically significant changes were detected in WBC, EOS, HGB, MCV, and MCHC levels as gestation progressed ($p\leq0.05$). Furthermore, considering the group-by-time interaction (Group x Days), significant differences between the two groups were found across the measurement days for EOS ($p=0.05$), MCV ($p=0.01$), and MCH ($p=0.04$). In a human study, the difference in hemoglobin values between the melatonin-treated and placebo groups was not statistically significant (Edalat-Nejad et al. 2013). Karaboduk et al. (2025) reported that, contrary to our findings, exogenous melatonin administered to rats caused an increase in hemoglobin and platelet counts, and a decrease in WBC levels. There are studies in which melatonin increased hemoglobin levels in mice (Michurina et al. 2019) and did not affect MCH and MCHC levels (Kurhaluk et al. 2017). It has been documented that the number of offspring can influence hemoglobin levels in pregnant animals. In the study conducted in sheep, it was found that the hemogram values of single-lambing ewes were higher than those of twin-lambing ewes (Zaragoza-Vera et al. 2022). A similar outcome was observed in a study conducted on goats. The study revealed that MCH and MCHC values were lower in goats carrying twin fetuses than in goats carrying a single fetus. (Habibu et al. 2014). In the present study, the statistically lower hemoglobin values on the 15th day of gestation in the MEL group may be attributable to the higher litter size in the MEL group.

Conclusion

The present study demonstrates that exogenous melatonin administration does not affect reproductive parameters in New Zealand rabbits. However, a notable observation was the increase in IgG and IgM levels, particularly on the 15th day of gestation. Concurrently, a decrease in TOS levels was observed after parturition. The immunomodulatory effect of the long-acting melatonin implant in rabbits becomes more evident on day 15 of pregnancy, while its antioxidant property may persist postpartum. Further studies with a larger sample of rabbits could clarify the effects of exogenous melatonin.

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Author Declarations

Ethics approval

Ethics committee approval for this study was obtained from the Local Animal Experiments Ethics Committee of the Necmettin Erbakan University Application and Research Center of Experimental Medicine (27.02.2024, 2024-15).

Use of generative artificial intelligenece

No generative artificial intelligence (AI) tools were used in the preparation of this manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

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