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RESEARCH ARTICLE

The Effects of Prepartum Vitamin E, Selenium and Melatonin Treatment on Uterine Involution of Awassi Sheep in Hatay

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ABSTRACT

The aim of this study was to investigate the effects of prepartum Vitamin E, Selenium and Melatonin treatments on uterine involution in Awassi sheep. The study included a total of 24 ewes with singleton pregnancies. Fifteen days before their expected delivery, ewes were randomly divided into three groups. Group VE (n=8) received Vitamin E and Selenium intramuscularly. Group M (n=8) received a subcutaneous ear implant containing 18 mg of melatonin. Group C (n=8) served as the control group and received no treatment. The mean time for completion of uterine involution in Group VE, Group M, and Group C were 20.57±1.21; 19.13±1.13; 18.67±1.09 days, respectively (p>0.05). Uterine diameters were 9.66±0.59; 9.54±0.35; 7,95±0.22 in Group VE, Group M, and Group C, respectively. Uterine diameters in Group VE and Group M were significantly greater than Group C on Day 3 of postpartum (p<0.05). Mean outer caruncular diameters were 1.93±0.10; 1.60±0.10; 1.65±0.07 in Group VE, Group M, and Group C. respectively. Mean outer caruncular in Group VE were significantly greater than Group M and Group C (p<0.05). Mean outer caruncular diameters were greater on Day 3 compared to Day 6 regardless of groups (p<0.05). Mean inner caruncular diameters were greater on Day 3 compared to Day 6 regardless of groups (p<0.05). There was no differences in terms of mean inner caruncular diameters between groups (p>0.05). In conclusion, it was found that prepartum administration of Vitamin E, Selenium and Melatonin had no significant effects on the completion time of postpartum uterine involution on Awassi ewes.

Keywords: Melatonin, Selenium, Sheep, Uterine Involution, Vitamin E

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İvesi Irkı Koyunlarda Prepartum Vitamin E, Selenyum ve Melatonin Tedavisinin Uterus İnvolüsyonu Üzerine Olan Etkileri

ÖZ

Bu çalışmanın amacı, prepartum dönemde Vitamin E, Selenyum ve Melatonin uygulamalarının İvesi ırkı koyunlarında uterus involüsyonu üzerine etkilerini araştırmaktı. Çalışmaya tekil gebeliğe sahip toplam 24 koyun dahil edildi. Beklenen doğum zamanlarından 15 gün önce koyunlar rastgele üç gruba ayrıldı. Grup VE'deki koyunlara (n=8) intramüsküler yoldan Vitamin E ve selenyum uygulandı. Grup M'deki koyunlara (n=8) 18 mg melatonin içeren subkutan kulak implantı uygulandı. Grup C'deki koyunlar (n=8) ise kontrol grubu olarak kullanıldı ve bu gruba herhangi bir tedavi uygulanmadı. Uterus involüsyonlarının tamamlanma süresi Grup VE, Grup M ve Grup C için sırasıyla 20,57±1,21; 19,13±1,13; 18,67±1,09 gün olarak tespit edildi (p>0,05). Uterus çapları Grup VE, Grup M ve Grup C için sırasıyla 9,66±0,59; 9,54±0,35; 7,95±0,22 olarak belirlendi. Doğum sonrası 3. günde Grup VE ve Grup M'deki uterus çapları, Grup C'den anlamlı derecede büyük tespit edildi. (p<0,05). Ortalama dış karunkular çapları Grup VE, Grup M ve Grup C için sırasıyla 1,93±0,10; 1,60±0,10; 1,65±0,07 olarak ölçüldü. Grup VE'deki ortalama dış karunkular çapları, Grup M ve Grup C'den anlamlı derecede büyük olduğu görüldü (p<0,05). Gruplardan bağımsız olarak; 3. gündeki ortalama dış karunkular çapları, 6. güne kıyasla daha büyük olarak tespit edildi (p<0,05). Aynı şekilde 3. gündeki iç karunkular çapları da 6. güne kıyasla daha büyük olarak tespit edildi (p<0,05). Gruplar arasında ortalama iç karunkular çapları açısından fark tespit edilmedi (p>0,05). Sonuç olarak, prepartum dönemde Vitamin E, Selenyum ve Melatonin uygulamasının, İvesi koyunlarında postpartum uterus involüsyon süresinin tamamlanması üzerinde önemli bir etkisinin olmadığı görüldü.

Anahtar Kelimeler: Koyun, Melatonin, Selenyum, Uterus İnvolüsyonu, Vitamin E

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INTRODUCTION

In sheep, the postpartum period commences immediately following the expulsion of the placenta after parturition and continues until the genital organs return to their pre-gravid state. This period encompasses key physiological processes, including endometrial restoration, elimination of bacterial contamination, resumption of ovarian cyclicity, and uterine involution (Noakes 2001). Uterine involution is generally completed between 17 and 21 days postpartum (Rubianes and Ungerfeld 1993; Fernandes et al. 2013), though it may extend to 28–35 days postpartum depending on factors such as parity and the occurrence of dystocia (Hauser and Bostedt 2002; Zdunczyk et al. 2004; Fernandes et al. 2013). In sheep, the uterine involution is also influenced by a multitude of factors, including suckling intensity, season of lambing, delivery type and frequency, nutritional status, milk production levels, litter size, and postpartum body weight loss (Mbyahaga et al. 1998; Hayder and Ali 2008; Hauser and Bostedt 2002; Pollott and Gootwine 2004; Medan and El-Daek 2015; Liu et al. 2022).

In traditional sheep production systems, monitoring postpartum uterine involution and the initiation of ovarian cyclicity is rarely prioritised due to characteristics of the reproductive physiology in ewes. However, with the increasing adoption of extensive production systems, the acceleration of uterine involution and stimulation of ovarian activity in the postpartum period have gained importance. Shortening the postpartum anestrus period and accelerating the postpartum uterine involution is one of the viable strategies for enhancing lambing rates and overall reproductive efficiency (Morris 2017). Therefore, several attempts have been made to accelerate uterine involution and induce ovarian activity in the postpartum period in ewes. Gonadotropin-releasing hormone (GnRH) and nutritional supplementation during the postpartum period effectively stimulate ovarian function (Mitchell et al. 2003). Additionally, specific hormonal treatments, including prostaglandin F2α (PGF2α) (Dal et al. 2020), carazolol (Enginler et al. 2023), and oxytocin (Li et al. 2025) have been shown to expedite uterine involution when administered during the postpartum period. Also, the effects of Melatonin, Vitamin E and Selenium on various post-partum reproductive performance parameters, including uterine involution, in goats and sheep have been studied in many studies (Abdel-Raheem et al. 2019; Afzaal et al. 2023).

Melatonin, a hormone secreted by the pineal gland, plays a pivotal role in regulating various reproductive processes, including the hypothalamic-pituitary-gonadal axis, placental function, fetal development, ovarian follicular dynamics, corpus luteum activity, ovulation, and embryo development (Reiter et al., 2009). The effects of melatonin on the reproductive axis are seasonal, primarily promoting the release of luteinizing hormone-releasing hormone (LHRH). Subcutaneous administration of melatonin has been shown to increase the frequency of LHRH release and luteinizing hormone (LH) pulses, achieving approximately 10 pulses per 6 hours after a delay of 40–50 days (Malpaux et al. 1996). In small ruminants, melatonin treatment is widely employed for estrus synchronization, enhancing twin survival rates (Flinn et al. 2020), and regulating ovarian activity (Kusakari and Ohara 1997; Afzaal et al. 2023). For instance, in a study conducted on Payoya goats, subcutaneous melatonin administration significantly increased estrus response, ovulation rates, fertility, and conception rates (Zarazaga et al. 2013). Similarly, melatonin supplementation in postpartum Suffolk sheep reduced the interval to estrus and ovulation (Kusakari and Ohara 1997). Furthermore, melatonin administration during the prepartum period has been reported to enhance postpartum reproductive performance by shortening the time to first postpartum ovulation and expediting placental expulsion (Afzaal et al. 2023).

Vitamin E and Selenium are important units of antioxidant system, which prevents peroxide radical formation within cell membranes by neutralizing peroxides and hydroperoxides. Vitamin E plays pivotal roles in oocyte maturation, oocyte quality, fertilization, and early embryonic development (Kott et al., 1998). Deficiency of Vitamin E results in several reproductive disorders, such as early embryonic death, fetal resorption, stillbirths, and fetal muscular dystrophy (Kott et al. 1998; Kaçar et al. 2008). Selenium, a vital component of the endogenous antioxidant defense system, exerts its effects through its role in the activity of glutathione peroxidase (GSH-Px), an enzyme essential for mitigating oxidative stress (Köse et al. 2013). Selenium deficiency is related with infertility, anestrous, retained placenta, abortion and stillbirth in dairy cows (Kamada 2016; Uematsu et al. 2016). Selenium supplementation increased progesterone concentrations and decreased incidence of metritis, ovarian cyst, and retained placenta (Spears and Weiss 2008; Wei et al. 2022). In ewes, Vitamin E and selenium supplementation improves the estrus, fertility, and prolificacy rates (Efe et al. 2023; Samimi et al. 2023; Semra et al. 2023). Vitamin E and selenium supplementation during late pregnancy is also associated with improvement in the lamb survivals (Zanghishe et al. 2023). Similarly, in goats, Vitamin E and selenium supplementation has been reported to improve uterine health, suggesting its potential as a novel tool for enhancing fertility and pregnancy outcomes (Alalaf and Alnuaimy 2024).

Although the effects of Vitamin E, selenium, and melatonin on pregnancy rates, lamb survival, and certain reproductive parameters are well-documented, research on their impact on uterine involution remains limited. This study examines the effects of prepartum supplementation with Vitamin E, selenium, and melatonin on postpartum uterine involution in Awassi sheep in Hatay

MATERIALS and METHODS

Ethics Approval and Location of The Study

This study was approved by the Hatay Mustafa Kemal University Animal Experiments Local Ethics Committee for Animal Experiments with the decision numbered 2024/01-06 on 26/01/2024. The present study was conducted on a sheep farm located in Reyhanlı District of Hatay province of Türkiye (latitude 36°25' N and longitude 36°53'E) between June 2024 and January 2025.

Estrus Synchronization, Experimental Design and Vitamin E, Selenium and Melatonin Treatment

Vaginal sponges containing 60 mg medroxyprogesterone acetate (Esponjavet®, HIPRA, Spain) were inserted into the vagina of 50 sheep in their reproductive season, aged 1 year and weighing 45-60 kg, using a special speculum for estrus synchronization. The sponges were kept in the vagina for 12 days and 500 IU PMSG (Chronogest/PMSG, 6000 IU, Intervet, Istanbul, Turkiye) and 0.075 mg d-cloprostenol (Senkrodin®, Vetaş, Turkiye) were administered intramuscularly at sponge withdrawal. The rams were introduced to the flock 24 hours after the sponge removal, with sessions lasting one hour each, twice a day, in the morning and evening. The ear tag numbers of sheep detected in estrus and successfully mated were recorded, and these sheep were separated into different pen. Pregnancy examinations were performed 50 days post-mating using a real-time ultrasound device (Falco, Pie Medical, Netherlands) with a 5-8 MHz transabdominal probe. Twenty-four pregnant sheep with single fetus were randomly selected. These selected sheep were divided into three groups using a random sampling method 15 days before their expected delivery dates. Group VE (Vitamin E and Selenium) (n=8) received 2 ml of selenium and vitamin E (1 mg/ml sodium selenite and 60 mg/ml vitamin E, Yelvit®, Teknovet, Türkiye) intramuscularly. Group M (Melatonin) (n=8) received an ear implant containing melatonin (18 mg melatonin, Regulin®, Ceva, Türkiye). Group C (Control) (n=8) received no treatment and left as a control group. All deliveries occurred in November and December among the 24 pregnant Awassi sheep. The number of offspring born was recorded, and only sheep giving birth to a single lamb were enrolled in the study. Estrus synchronization protocol, treatments and groups were illustrated in Figure 1.

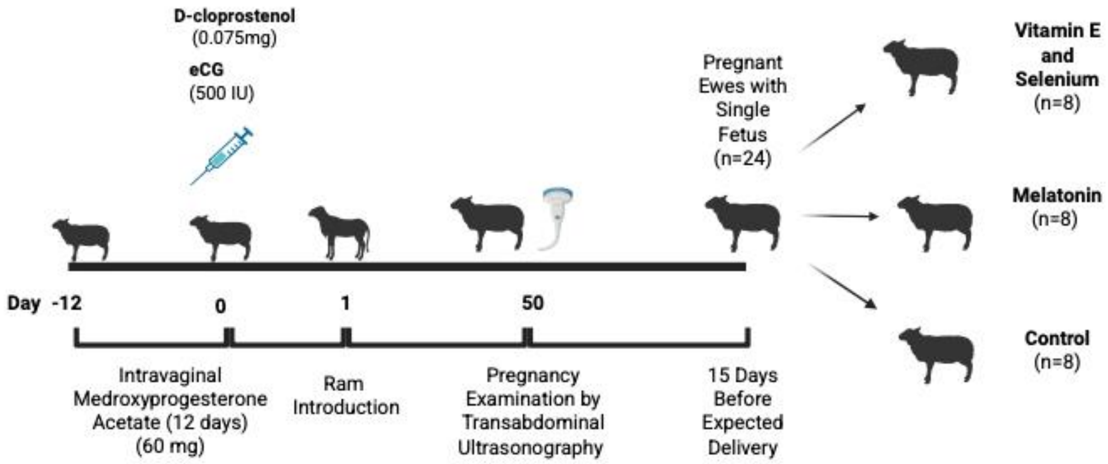

Figure 1. Schematic illustration of the estrus synchronization protocol, treatments and groups in ewes

Ultrasonographic Examination

Starting from the third day postpartum, uterine involution was monitored during the first three weeks postpartum at 3-day intervals using a real-time ultrasound device with a convex 5–8 MHz probe (Falco, Pie Medical, Netherlands). During the first 10 days postpartum, transabdominal ultrasonography was performed using a 5 MHz frequency. After the 10th day postpartum, transrectal ultrasonography was conducted with linear probe (5-8 MHz frequency). For transabdominal ultrasonography, the procedure was carried out while the sheep were standing. Before the examination, ultrasound gel was applied to the examination site. In the transrectal ultrasonography method, feces were removed from the rectum using a lubricated sterile glove before inserting the lubricated ultrasound probe into the rectum. During both transabdominal and transrectal examinations, the maximum diameter of the uterine horns was measured. For the measurement of caruncular diameters, three caruncles were evaluated, and their internal and external dimensions were recorded (Figure 2a). Uterine involution was considered complete when the transverse diameter of the uterus was less than 2 cm and the uterine lumen was empty (Figure 2b). The postpartum uterine ultrasonographic examinations were illustrated in Figure 3.

Statistical Analysis

Descriptive statistics for each variable were calculated and presented as mean ± std. error (SEM). Kaplan Meier survival analysis was used to calculate mean uterine involution time and life curves. To test the difference between the life curves, the Breslow test was used. A linear mixed model for repeated measures was used to test the differences in each caruncle. was used to test the differences in each caruncle. Animals were included as a random factor in all models while group, sampling time and their interaction were included as a fixed factor. Pairwise comparisons were done using a Bonferroni adjustment. $p<0.05$ was considered significant in all analyses. All statistical analyses were performed by using the IBM SPSS 23.0 package programme for Windows.

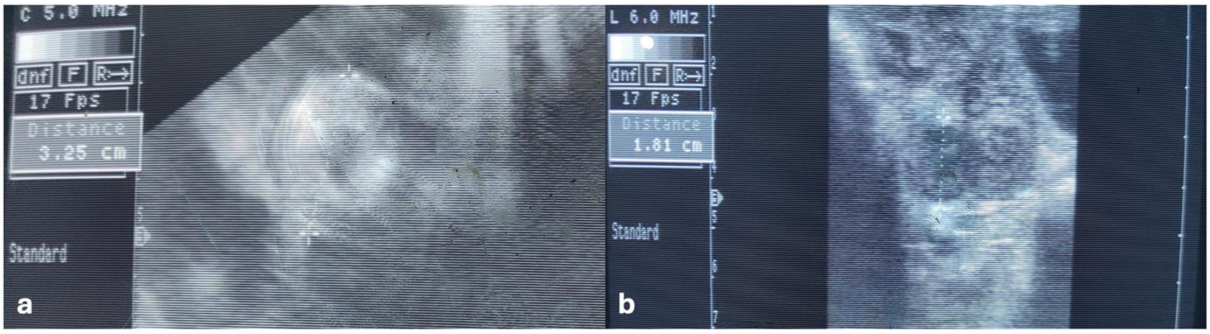

Figure 2. a. outer caruncle diameter b. cornu uterine diameter

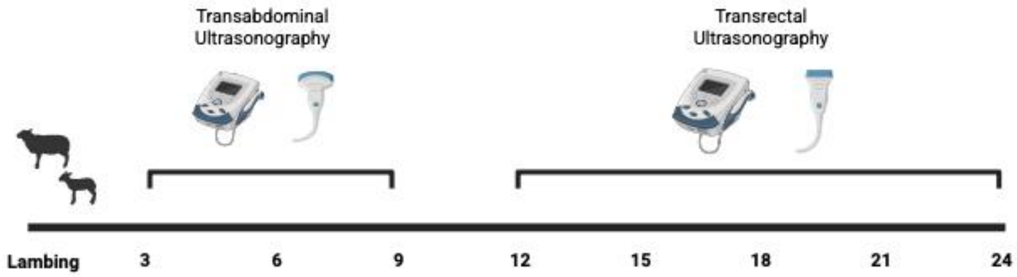

Figure 3. Schematic illustration of the postpartum uterine ultrasonographic examination in ewes

RESULTS

Uterine Horn Diameter Difference

In Group VE, a statistically significant reduction in the uterine horn diameters was observed during the first 3–12 days postpartum (pp) ($p<0.05$). However, after the 12th day postpartum, although a decrease in the uterine horn diameters was noted, no statistical difference was detected ($p>0.05$) (Table 1). The time required for the completion of uterine involution in Group VE was determined to be 20.57±1.21 days (Table 2). In Group M, a statistically significant reduction in the uterine horn diameters was observed during the first 9 days postpartum ($p<0.05$). However, after the 9th day postpartum, although a reduction was observed, no statistical difference was detected ($p>0.05$) (Table 1). The time required for the completion of uterine involution in Group M was determined to be 19.13±1.13 days (Table 2). In Group C, although the reduction in the diameter was observed, no statistically significant decrease in the uterine horn diameters was observed during the first 6 days postpartum ($p>0.05$). However, after the 6th day postpartum, a statistically significant reduction was detected ($p<0.05$) (Table 1). The time required for the completion of uterine involution in Group C was determined to be 18.67±1.09 days.

Caruncular Diameter Difference

The outer caruncular diameters were 2.10±0.12; 1.85±0.12; 1.67±0.09 cm and 1.76±0.13; 1.34±0.11; 1.63±0.12 in Group VE, Group M, and Group C, respectively on Day 3 and Day 6 ($p>0.05$). The mean diameters of the outer caruncle were 1.86±0.07 and 1.57±0.08 respectively on Day 3 and Day 6 ($p<0.05$). The inner caruncular diameters were 0.87±0.07; 0.73±0.08; 0.69±0.06 cm and 0.64±0.05; 0.53±0.04; 0.58±0.06 in Group VE, Group M, and Group C, respectively on Day 3 and Day 6 ($p>0.05$). The mean diameters of the inner caruncle were 0.75±0.04 and 0.58±0.03 respectively on Day 3 and Day 6 ($p<0.05$) (Table 3).

Table 1. The mean diameter of the cornu uteri in Group VE, Group M and Group C within 18 days of postpartum.

Parameter	Group	Time						p		
		Day 3	Day 6	Day 9	Day 12	Day 15	Day 18	Group	Time	G*T
Uterine Diameter	Group VE	9.66±0.59 $^{a, A}$	7.27±0.51 ^{b}	4.24±0.34 ^{c}	2.60±0.17 ^{d}	2.34±0.15 ^{d}	2.19±0.17 ^{d}	0.020	<0.001	0.017
	Group M	9.54±0.35 $^{a, A}$	6.69±0.37 ^{b}	3.46±0.42 ^{c}	2.57±0.18 ^{cd}	2.29±0.15 ^{cd}	1,.94±0.12 ^{d}			
	Group C	7.95±0.22 $^{a, B}$	7.41±0.41 ^{a}	3.35±0.30 ^{b}	2.47±0.09 ^{bc}	2.13±0.08 ^{c}	2.03±0.08 ^{c}			

A,B; a-d: Different superscripts indicates the statistical significance among the groups (p<0.05)

Table 2. Means for survival time of uterine involution

Groups	Mean^{a}			
	Day	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Group VE	20.57	1.21	18.20	22.95
Group M	19.13	1.13	16.92	21.33
Group C	18.67	1.09	16.53	20.81

Kaplan-Meier, Breslow Test; p= 0.504

Table 3. Mean caruncular diameter in the postpartum period

Parameter	Group	Time		LS Mean (Group)	p		
		Day 3	Day 6		Group	Time	G*T
Outer caruncular	VE	2.10±0.12	1.76±0.13	1.93±0.10 ^{A}	0.019	0.003	0.108
	M	1.85±0.12	1.34±0.11	1.60±0.10 ^{B}			
	C	1.67±0.09	1.63±0.12	1.65±0.07 ^{AB}			
LS Mean (Time)		1.86±0.07 ^{a}	1.57±0.08 ^{b}				
Inner caruncular	VE	0.87±0.07	0.64±0.05	0.75±0.05	0.109	0.001	0.616
	M	0.73±0.08	0.53±0.04	0.63±0.05			
	C	0.69±0.06	0.58±0.06	0.63±0.04			
LS Mean (Time)		0.75±0.04 ^{a}	0.58±0.03 ^{b}				

A,B; a-d: Different superscripts indicates the statistical significance among the groups (p<0.05)

DISCUSSION

There are several reports indicating that uterine involution in the ewes completed within the 17-28 days of postpartum (Rubianes and Ungerfeld 1993; Hauser and Bostedt 2002, Fernandes et al. 2013). However, uterine involution can extend to by the 35th day postpartum in case of dystocia or assisted delivery (Hauser and Bostedt 2002). Hauser and Bostedt (2002) also observed that 80% of the uterus regresses by the 11th day postpartum, while Ahmet et al. (2016) reported that in Awassi sheep, 50% of uterine regression occurs between the 3rd and 14th postpartum days. In the present study, uterine involution completed within the first 23 days of postpartum regardless of the homonal treatments. Prepartum Vitamin E, Selenium and melatonin treatments have no effects on the completion time of uterine involution in Awassi ewes. Decrease in the postpartum uterine diameter in the first 12 days of postpartum was significant in Group VE, Group M, and Group C whereas changes in the uterine diameters beyond the 12th day postpartum was stable, which is compatible with the previous studies (Hauser and Bostedt 2002; Ahmet et al. 2016).

Prepartum Vitamin E and Selenium treatments are widely implemented in large animals to counteract oxidative stress-related diseases, such as mastitis, ovarian cysts, retained placenta, and postpartum metritis in the periparturient period (Xiao et al. 2021). In the prepartum period, Vitamin E and selenium treatments are also carried out in sheep (Milewski et al. 2021; Zanghishe et al. 2023) and goats (Barcelos et al. 2022; Nurmala et al. 2024) to improve lamb survival, colostrum quality and immune system of the ewes. In addition, Vitamin E and Selenium treatments are also used for enhancing reproductive performances. Abdel-Raheem et al. (2019) stated in Ossimi sheep that prepartum Vitamin E and Selenium treatment results in faster uterine involution but does not affect the duration of the completion of the uterine involution. In the same study, treatments caused the earlier resumption of ovarian function and the ovulation of large-size ovulatory follicles and the increase in the small, medium, and large-sized follicles. In the present study, complete uterine involution in ewes is not affected by the Vitamin E and Selenium treatment, as previously described by Abdel-Raheem et al. (2019).

In the present study, the uterine diameter was greater in Group VE and Group M compared to Group C on day 3 postpartum. However, on Day 6 postpartum, there was no significant differences between groups in terms of uterine diameter. Results of the present study indicated that hormonal treatment of melatonin, Vitamin E and selenium lower the uterine involution on the first 3 postpartum days, whereas uterine diameters were similar on day 6 of postpartum. The greater uterine diameter observed in the melatonin group may be related with effect of melatonin on prostaglandin synthesis (Abecia et al. 1999), steroid hormone receptors (Vazquez et al. 2013), and endometrial hemodynamics (Abdelnaby et al. 2020). Vázquez et al. (2013) reported that melatonin implants increase the expression of progesterone receptors (PR) in the deep glandular epithelium during the postpartum period in sheep, thereby enhancing sensitivity to progesterone. In contrast, they found that melatonin reduces the expression of estrogen receptors (ER) in the deep stroma, thereby weakening the luteolytic effect of the estrogen-ER complex. They suggest that this may contribute positively to the preparation of the uterus for pregnancy. Association of melatonin with inhibition of prostaglandin, which is a uterotonic agent, synthesis is well known effect of melatonin (Abecia et al. 1999; Fierro et al. 2013). Melatonin also causes an increase in blood supply to ovarian and uterine arteria (Abdelnaby et al. 2020) and inhibits the apoptosis in the sheep endometrial epithelial cells by regulating the estrogen function (Duan et al. 2023). Melatonin also improves the angiogenesis in caruncular endometrium in early pregnancy in ewes (Viola et al. 2024). All these abovementioned factors may be related with the greater uterine diameter in the Group ME compared to Group C.

In the present study, the uterine diameter was greater in Group VE compared to Group C on day 3 postpartum. However, on Day 6 postpartum, there was no significant differences between groups in terms of uterine diameter. Also, the outer caruncle diameter was greater in Group VE compared to Group C, which is expected and compatible with the literature (Hauser and Bostedt 2002). Caruncule, cotyledon, and placental weights are affected by several factors, such as nutritional restriction and nutritional supplementation. Several reports indicate the conflicting results of the effect of the Vitamin E and Selenium supplementations. Selenium deficiency caused a decrease in the placental size of sheep (Freer and Dove 2002) whereas prepartum adequate and high levels of selenium supplement did not change placentom number, mass, and caruncular and cotyledonary weight (Lekatz et al. 2010). Vural et al. (2008) also stated in ewes that Vitamin E treatments have no effects on the caruncle count and measurements. Therefore, greater diameters that were observed in the Vitamin E and Selenium group were unexpected. In a study conducted on the women concluded that Vitamin E supplement caused improvement in the uterine vascularity and increase in the endometrial thickness (Tasasaki et al. 2010). In a histological study carried out in goat by Alalaf and Alnuaimy (2024), it was observed that Vitamin E and selenium treatments caused larger caruncles and thicker myometrial musculature by improving the epithelial disintegration, uterine glands integrity, and uterine microvasculature. So, greater outer caruncle diameters might be related with effect of Vitamin E and Selenium on the uterine's epithelial, glandular and vascular system. Further research is needed to elucidate the interaction between Vitamin E, Selenium and uterine physiology.

CONCLUSION

In conclusion, prepartum Vitamin E, Selenium and Melatonin treatment did not cause any statistical differences on the uterine involution completion time. In all groups, uterine involution time was found to be completed within literature's values. Although caruncular diameters were also not affected by the treatments, mean caruncular diameter were greater in ewes treated with selenium, which may be caused by Vitamin E and Selenium effect's of uterine physiology. Further studies are needed to demonstrate effect of Vitamin E, selenium and melatonin on postpartum physiology in ewes.

Author's Contributions: AG, OB, GU, and EA contributed to the project idea, design and execution of the study. AG, OB, GU, EA, RS, BK, GT, MKS, GD contributed to the acquisition of data. AG and UK analysed the data. AG, OB and GU drafted and wrote the manuscript. MKS, GD, OB and GU reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical Approval: This study was approved by the Hatay Mustafa Kemal University Local Ethics Committee for Animal Experiments with the decision numbered 2024/01-06 on 26/01/2024.

Conflict of Interest: The authors have no conflicts of interest to report

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