Mefepronic acid, a PPAR agonist, is inefficient on reproductive performance of ewes in both early and late postpartum period

METEHAN KUTLU[1], HALEF DOGAN[2]*, ERAY AKTUG[3]

[1] Necmettin Erbakan University, Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, Eregli, Konya, Türkiye
[2] Tekirdag Namik Kemal University, Faculty of Veterinary Medicine, Department of Obstetrics and Gynaecology, Suleymanpasa, Tekirdag, Türkiye
[3] Tekirdag Namik Kemal University, Faculty of Veterinary Medicine, Department of Animal Nutrition and Nutritional Diseases, Suleymanpasa, Tekirdag, Türkiye

SUMMARY

The liver is a dynamic organ that plays critical roles in many physiological processes. In farm animals, supporting the liver reduces postpartum metabolic diseases and loss of reproductive and milk yield in the transition period. The aim of this study is to investigate the effects of mefepronic acid (2-methyl-2-phenoxy propionic acid) injection on reproductive performance parameters with short-term progesterone administration in early and late postpartum period Hungarian Merino ewes during the non-breeding season. In the study, 89 adult ewes in the early (n=45) and late (n=44) postpartum (pp) period were used in the study. Control and treatment (MA) groups were formed separately for each pp period. Following insertion of a vaginal sponge containing 60 mg medroxyprogesterone acetate for 7 days, PMSG 500 IU was injected intramuscularly (day 7) to all ewes. In treatment groups (Early MA and Late MA), 10 mg/kg mefepronic acid (Hepagen®, Fatro Günesli) was injected (day 7), and remaining ewes consisted of control groups (Early Control and Late Control). The estrus signs of the ewes were followed and they were hand-mated (ewe: ram=5:1). Pregnancies were determined with transabdominal real time B-Mode ultrasonography with convex probe (3.5 MHz) on day 45 post-mating. There were no statistical differences in estrus rate, pregnancy rate, lambing rate and litter size at 1st service, 2nd service and overall services in early and late pp groups. According to results of this study, administration of mefepronic acid to ewes in the early and late pp period had no increasing effect on reproductive parameters. However, further studies investigating the survival of embryos and prostaglandin metabolism are needed to determine the efficacy of mefepronic acid in ewes.

KEY WORDS

Ewes; Mefepronic acid; Progesterone; Postpartum; Reproductive parameters.

INTRODUCTION

The two most popular accelerated lambing programs are the "three lambings in two years"[1] and the Cornell STAR© system (five lambings in three years)[2]. If these programs are implemented, lambing is possible every 8 months or 7.2 months, respectively. For success in breeding, it is essential to keep exposures brief to reduce the time between lambing, and lambs should be weaned at two months old to enable breeding to occur again[3]. The act of boosting the intake of nutrients and improving overall condition prior to and during breeding is known as «flushing. Its aim is to raise the rate of ovulation, resulting in an increased lambing rate. Flushing is especially advantageous for skinny ewes that have not rebounded from the stress of previous lactation[4]. The delay in weaning of the ewes, which in practice takes 60-90 days, and when it is time to mate immediately, a dilemma will arise. On the one hand, it is necessary not to give the feed for weaning, on the other hand, it is necessary to increase the feed before mating to increase the ovulation rate. During this period, there may be a possibility of body fat mobilization[5], and the liver cannot fully metabolize them[6]. At present, there exist alternative approaches aimed at diminishing the incidence of metabolic disorders[7]. The intention behind these alternative options is to minimize the removal of body fat and the buildup of triacylglycerols in liver tissue, in order to preserve its structure, function, and prevent disturbances in the energy metabolism[8]. Several genes that regulate lipid metabolism and adipocyte differentiation are controlled by the activation of the peroxisome proliferator-activated receptors (PPARs), which belong to the superfamily of nuclear receptors[9]. PPARs are categorized into three isotypes: α, β, and γ. PPARs play a role in regulating lipid metabolism[10-13]. PPAR is triggered by fatty acids, prostaglandins, and fibrates, which are drugs utilized in human medicine for their ability to lower lipid levels[14]. Activation of PPAR promotes mitochondrial activation, peroxisomal -oxidation, hepatic gluconeogenesis, metabolism of lipoproteins, choleretic and cholagogic activity[15]. PPAR interferes with different steps of the inflammatory response such as cytokines (ILs, TNF , IFNy), cytokine receptors, adhesion molecules, acut phase proteins (fibrinogen, C-reactive protein)[15]. Many bovine studies have found that they lower levels of NEFA,

Corresponding Author:
Halef Dogan (halefdogan@gmail.com ; halefdogan@nku.edu.tr)

BHB, AST and other biochemical parameters in transition period[16,17]. There is a close relationship between these hepatic metabolism products and reproduction. In addition, metabolomics researches have shown that lack of certain nutrients directly affect metabolic diseases and thus reproduction in cows and ewes[18,19].

Mefepronic acid (2-methyl-2-phenoxy propionic acid) belongs to the fibrate family of substances that are utilized in treating dyslipidemia[20], which is used in veterinary medicine[15]. Mefepronic acid promotes the liver's physiological functions and activates digestive processes[21]. Although the effects of mefepronic acid on the reproduction of ewes are not known, it has been reported to have positive effects in limited studies on cows[6,7]. Rizzo et al.[6] have emphasized the beneficial effects of mefepronic acid on the hepatic metabolism and reproductive parameters of postpartum dairy cows.

It was thought that the use of mefepronic acid could prevent the negative effects of not feeding the ewes for weaning and reduce lipomobilization in skinny ewes in the early postpartum period. In order to increase fertility within the framework of the mentioned above, the present study was aimed to investigate the effects of mefepronic acid on reproductive performance parameters with short-term progesterone administration in early and late postpartum period Hungarian Merino ewes during the non-breeding season.

MATERIAL AND METHODS

The present study was conducted with approval from Çukurova University Animal Experiments Local Ethics Committee, Adana, Türkiye (2022, 5/4).

Animals

This study was conducted in a commercial sheep farm (Lat: 37° 43' 94.80» N, Long: 35° 73' 37.90» E and Alt: 120 m) in Adana province in Türkiye during the non-breeding season (June) in 2022. A total of 89 adult Hungarian Merino ewes, clinically healthy, 2-3 years old, having 55-75 kg body weight were used. Ewes were grazed on artificial pasture 12 h of a day and not given any compound feed. Water was given ad libitum. No nutritional flushing was applied to animals before mating. Lambs were completely weaned 7 days before estrus stimulation.

Study design

The study design is illustrated in Figure 1. Ewes were grouped as Early Control (Day pp 35-60; 50.6 d ± 1.8; n=22), Late Control (Day pp 60-112; 85.2 d ± 3.4; n=22), Early MA (Day pp 37-59; 51.2 d ± 1.7; n=23) and Late MA (Day pp 60-117; 89.2 d ± 3.2; n=22) in the study.

Following insertion of vaginal sponge containing 60 mg medroxyprogesterone acetate (Esponjavet®, Hipra, Spain) for 7 day, PMSG 500 IU (Oviser®, Hipra) was injected intramuscularly (IM) (day 7) to all ewes. In treatment groups (Early MA and Late MA), 10 mg/kg mefepronic acid (100 mg/mL, 2-methyl-2-phenoxy propionic acid, Hepagen®, Fatro Günesli) was injected intramuscularly (Day 7). One teaser ram was used twice a day for 1 h duration for 24 h after removal of sponges for estrus detection. Ewes determined to be in estrus were hand-mated with one of the proven fertile Merino rams (ewe: ram ratio of 5:1). In all ewes, transabdominal ultrasound examination (Hitachi EUB-405, 3.5 MHz convex probe) was performed to diagnose pregnancy on day 45 post-mating. The litter size was determined at parturition.

Estrus detection rate, pregnancy rate, lambing rate and litter size were calculated as reproductive parameters as follows;

Statistical analysis

All statistical analyses were performed by using the SAS Version 8.2 (2001). For analyzing the calculated reproductive parameters, Chi-squared test, Fisher's exact test and GLIMMIX procedure were used. Proportional data was analyzed with Chi-squared test, Fisher's exact test between in early and late postpartum period within the same service period. Estrus rate, pregnancy rate and lambing rate were analyzed with GLIMMIX procedure between 1st, 2nd and overall service periods. The results were given as the percentage or mean ± standard error of the mean (SEM). Calculated P values less than 0.05 were considered significant.

RESULTS

At 1st service, 2nd service and overall service, estrus rate, pregnancy rate, lambing rate, number of lambs and litter size were determined in Early Control, Late Control, Early MA and Late MA groups. There were no statistical differences (p>0.05) in all reproductive parameters among the groups. Reproductive

Table 1 - Reproductive parameters in Control and Mefepronic acid (MA) groups in early and late pp period at the end of the study.

	At 1st service					At 2nd Service					Overall serviced ewes				
	Early Control Group (n=22)	Late Control Group (n=22)	Early MA Group (n=23)	Late MA Group (n=22)	*P*	Early Control Group (n=11)	Late Control Group (n=9)	Early MA Group (n=8)	Late MA Group (n=10)	*P*	Early Control Group (n=22)	Late Control Group (n=22)	Early MA Group (n=23)	Late MA Group (n=22)	*P*
Estrus Rate	86.4% (19/22)	100% (22/22)	82.6% (19/23)	90.9% (20/22)	***0.24***	72.7% (8/11)	88.9% (8/9)	62.5% (5/8)	90.0% (9/10)	***0.41***	86.4% (19/22)	95.5% (21/22)	87.0% (20/23)	95.5% (21/22)	***0.55***
Pregnancy Rate	50.0% (11/22)	59.1% (13/22)	65.2% (15/23)	54.5% (12/22)	***0.76***	72.7% (8/11)	88.9% (8/9)	62.5% (5/8)	90.0% (9/10)	***0.41***	86.4% (19/22)	95.5% (21/22)	87.0% (20/23)	95.5% (21/22)	***0.55***
Lambing Rate	100% (11/11)	100% (13/13)	100% (15/15)	100% (12/12)	***>0.99***	100% (8/8)	100% (8/8)	100% (5/5)	100% (9/9)	***>0.99***	100% (19/19)	100% (21/21)	100% (20/20)	100% (21/21)	***<0.99***
Number of Kids	14	17	21	16		8	10	5	10		22	27	26	26	
Single	8	9	9	8		8	6	5	8		16	15	14	16	
Twin	3 (6)	4 (8)	6 (12)	4 (8)		-	2 (4)	-	1 (2)		3 (6)	6 (12)	6 (12)	5 (10)	
Litter Size	1.27 (14/11)	1.31 (17/13)	1.4 (21/15)	1.33 (16/12)	***0.99***	1.0 (8/8)	1.25 (10/8)	1.0 (5/5)	1.11 (10/9)	***0.98***	1.27 (22/19)	1.29 (27/21)	1.30 (26/20)	1.24 (26/21)	***0.99***

P>0.05 is considered as non significant.

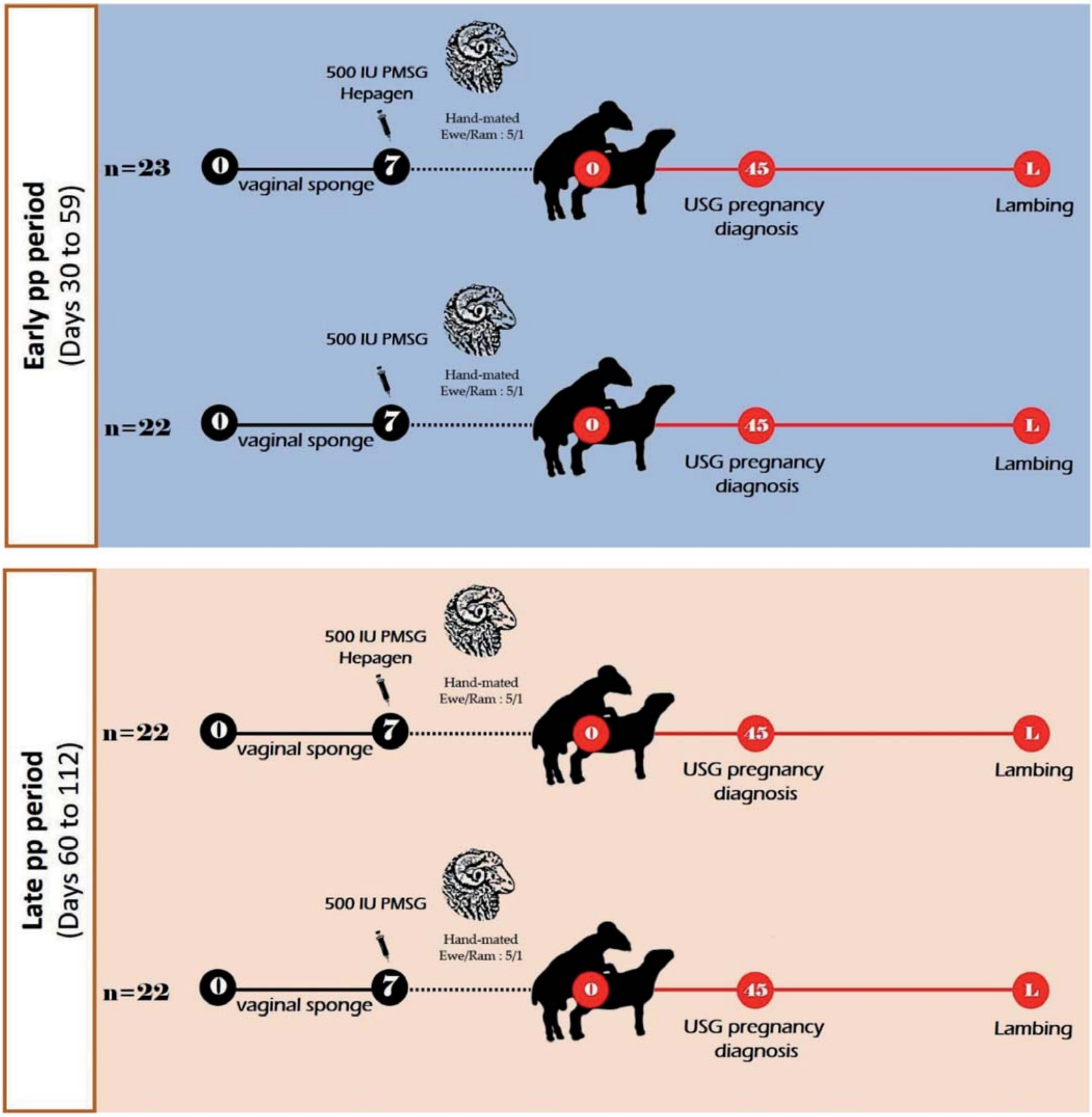

Figure 1 - The schematic illustration of the study. Blue and Pink diagrams represent the Early and Late postpartum period, respectively. Ewes with the same care and feeding conditions in the early and late postpartum periods were used in the study. Mefepronic acid was administered at a dose of 10 mg/kg (100 mg/mL, 2-methyl-2-phenoxy propionic acid, Hepagen®, Fatro Günesli) in the trial groups. Mefepronic acid injections were made on the day of PMSG administration.

parameters are presented in Table 1.

Although a numerical difference in pregnancy rates was determined between the Early Control group (50%) and the Early MA group (65.2%), this difference was not statistically significant.

DISCUSSION

Impairment of reproductive effectiveness is related to hepatic dysfunction (lipidosis and increasing hepatic clearance) through a complicated network of mutual interactions in dairy cows[22]. In this context, supporting hepatic activities may help improve the reproductive performance in ewes. Mefepronic acid (MA), a PPAR agonist, capable of promoting peroxisomal ß-oxidation and hepatic gluconeogenesis, was utilized in this study. In this current study, we have investigated, for the first time, the efficacy of mefepronic acid on reproductive parameters in ewes during early and late postpartum period.

It is well known that intravaginal sponges have been a choice of traditional treatments for estrus induction out of the breeding seasons in ewes[23]. In short term (6-7 days) progestagen applications out of the breeding season, estrus rates were in ewes have been reported by Sareminejad et al.[24] (93.3%), Özyurtlu et al.[25] (91.6%) and Yılmazer[26] (97%). We have previously reported the rate of estrus as 93.4% and 91.1% in Hungarian Merino ewes to which they applied sponges containing medroxyprogesterone acetate for 7 days with 500 IU PMSG[27]. In this study, there were no statistical differences ($p>0.05$) at 1st service between the early control, late control, early MA and late MA groups in terms of estrus rate, 86.4%, 100%, 82.6% and 90.9%, respectively.

Pregnancy rate is one of the most important parameters in the evaluation of reproductive performance and economic profitability in farms. Rizzo et al.[6] have reported that the calving to 1st estrus interval was shorter as it was recorded 74 ± 6.2 days in the control group and 50±3 days in the MA group. Also pregnancy rate increased by 7% in the first and 7% second inseminations of MA applied friesian cows compared to the control group. In this study, in which the efficacy of mefepronic acid in ewes in the postpartum period was evaluated, it was found no statistical differences in pregnancy rate, litter size at 1st service among the groups (Table 1).

However, the pregnancy rate and litter size in the Early MA group was numerically higher at 1st service. These numerical differences could be attributed to two different mechanisms. First, mefepronic acid increases the cholesterol level, which participates in the structure of progesterone. Steroid synthesis commonly begins with cholesterol, which can either be obtained from the diet or produced within the body and transported to the ovaries via lipoproteins (HDL and LDL)[28]. The step that limits the rate of progesterone synthesis is the transportation of cholesterol into the mitochondrion[29]. Progesterone plays a key role in regulation of the implantation of the blastocyst[30], and is necessary at a certain concentration after post-mating, as ewes with lower progesterone concentration suffer greater embryo loss[31]. Rizzo et al.[6] showed that mefepronic acid administration increases cholesterol and HDL levels and thus supports hepatic metabolism and lipogenesis, with an inverse trend to NEFA. The second is with the COX-2 mechanism. Some researchers[32-34] have shown that PPAR can inhibit COX-2 expression. PPARa agonists are able to inhibit the induction of interleukin-6 (IL-6) and cyclooxygenase-2 (COX-2) by interleukin-1 (IL-1)[32]. COX-2 is also involved in the production of prostaglandin F2 alpha. Prostaglandin F2 alpha is the most important factor that controls regression of the corpus luteum[35]. With mefepronic acid injection, it is aimed to prolong the life of the corpus luteum (CL) by suppressing the release of PGF2α during the maternal recognition period. Perhaps, by suppressing the release of PGF2α during the maternal recognition period with mefepronic acid injection, the lifespan of the corpus luteum (CL) can be extended. Rizzo et al.[6] have reported that it increased the progesterone concentration in cows treated with mefepronic acid on the 13th day after insemination compared to the control group (6.47±0.37 vs. 4.24±0.37 ng/mL). In parallel, mefepronic acid has been shown to modulate PPAR expression in bovine liver based on histological results[6].

Although it has been shown that there is an improvement in reproductive parameters with the application of mefepronic acid in the postpartum period in cows[6,7,15], no clinical efficacy of mefepronic acid has been observed in ewes in the early and late postpartum period out of the breeding season. This may be due to the fact that the hepatic metabolism in sheep is not as intense as in cows. For this reason, we suggest that the study should be repeated in sheep herds with high lactation efficiency and intensive feeding conditions.

CONCLUSION

In conclusion, administration of mefepronic acid to ewes in the early and late postpartum period had no increasing effect on reproductive parameters. However, we think that further studies investigating the embryo survival and prostaglandin metabolism are needed to determine the efficacy of mefepronic acid in ewes, especially with high lactation efficiency and intensive feeding conditions.

Author contribution

Conceptualization: Metehan Kutlu; data curation: Metehan Kutlu; formal analysis and investigation: Metehan Kutlu; funding acquisition: Metehan Kutlu; investigation: Metehan Kutlu; methodology: Metehan Kutlu; project administration: Metehan Kutlu; resources: Metehan Kutlu; software: Halef Dogan; supervision: Metehan Kutlu, Halef Dogan; validation: Metehan Kutlu, Halef Dogan; visualization: Halef Dogan; writing-original draft preparation: Metehan Kutlu, Halef Dogan, Eray Aktug; writing-review and editing: Metehan Kutlu, Halef Dogan, Eray Aktug.

Data availability

Not applicable.

Code availability

Not applicable.

Conflict of interest

The authors declare no competing interests.

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