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Daily Oral Cabergoline in Lactating Ewes - Efficacy on Prolactin Levels and Reproductive Parameters

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ABSTRACT

***Background*:** Ewes exhibit a seasonal breeding pattern and the management strategy of the *postpartum* period seriously affects the reproductive performance and lambing interval in lactating ewes. Suckling or lactating causes an increase in prolactin levels (hyperprolactinemia) in the early *postpartum* period in ewes. The increase in prolactin level has a suppressive effect on gonadotropins. Dopamine agonists such as cabergoline are ergot-derivated alkaloids that exert an anti-prolactinergic effect. The objective of this study was to investigate the effects of daily oral cabergoline administrations on prolactin suppression and reproductive parameters for 7 days at 60 days *postpartum* in lactating ewes.

***Materials, Methods & Results*:** This study was conducted in 60 mature ewes that received 2 different doses (CABlow, n = 20; or CABhigh, n = 10) of cabergoline at 60 ± 2 days *post partum*. Twenty ewes in the low dose group (CABlow) received daily oral 0.5 mg cabergoline and 10 ewes in the high dose group received daily oral 1 mg cabergoline (CABhigh) for 7 days. Ewes in control groups (CONlow, n = 20; CONhigh, n = 10) received any hormonal application during the study. Blood samples were collected from all ewes to determine prolactin measurement at 60 ± 2 and 67 ± 2 days *postpartum*. Estrous detection was performed at 12 h intervals for 15 days after ram introduction. Pregnancy diagnoses were performed via ultrasonography at 102 ± 2 and 132 ± 2 days *postpartum*. Any adverse effects of cabergoline were not observed in our study. The estrous responses within the 1st 5 and 15 days after introducing rams to flock were 15%, 100%; 10%, 90%; 20% and 100%; 20% and 100% in CABlow, CONlow, CABhigh and CONhigh groups, respectively ($P > 0.05$). Pregnancy rate was 100%, 85%, 90%, and 100% in CABlow, CONlow, CABhigh, and CONhigh groups, respectively. Similar to the estrous response, both doses of cabergoline did not statistically affect the pregnancy rates ($P > 0.05$). Serum prolactin levels were 81.44 ± 11.99, 96.67 ± 9.41, 52.28 ± 3.08, and 94.95 ± 9.92 ng/mL at the onset of study in CABlow, CONlow, CABhigh, and CONhigh groups, respectively. These levels reduced ($P > 0.05$) in all groups (61.01 ± 11.80, 74.66 ± 7.24, 37.07 ± 3.15, and 73.90 ± 8.55 ng/mL, respectively) at the end of the application.

***Discussion*:** Our results showed that administration of oral cabergoline was not effective in improving estrus response and pregnancy rate in ewes. The subsequent increase in estrus response and pregnancy rate in ewes in the CAB groups after introducing rams was unlikely produced by the rebound of PRL because there was a parallel increase in estrus response and pregnancy rate in ewes in the CON groups. Firstly, the failure of cabergoline to improve reproductive parameters and to reduce prolactin levels possibly could have resulted from the administration of oral route. Secondly, higher estrous response and pregnancy rate in control (CON) groups could be masked by the increment of reproductive parameters in treatment groups (CAB). The follicular wave is synchronized for about 3 days with manipulation of a single dose of estradiol-17 beta in anestrous ewes after introduction of rams. Although cabergoline did not contribute to the increment of estrous response and pregnancy rate, improvement of reproductive parameters in both control and treatment groups could be explained by the ram effect.

Keywords: cabergoline, ewes, estrous, pregnancy rate, prolactin.

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INTRODUCTION

Ewes exhibit a seasonal breeding pattern. The managment of *postpartum* or lactating period seriously affects rebreeding [9,23]. It is characterized by uterine involution and return to the ovarian functions needs 4-8 weeks [24]. The 1st *postpartum* estrous varies depending on the timing of lambing in ewes. Therefore, lambing in the non-breeding season acts as the 1st reproductive barrier to shorten the lambing interval due to delayed resumption of *postpartum* ovarian function and first behavioral estrous [1].

Suckling for approximately 60-80 days postpartum (conventional suckling) postpones new the lambing [23]. Suckling or lactating causes an increase in prolactin levels (hyperprolactinemia) *postpartum* period in ewes. The increase in prolactin level has a suppressive effect on gonadotropins. Hence, higher levels of prolactin extend postpartum anestrous and act as the 2nd reproductive barrier for reproduction in ewes [14].

Dopamine agonists such as cabergoline, bromocriptine, or metergoline are ergot-derivated alkaloids that exert an anti-prolactinergic effect. Cabergoline has a highly specific effect on pituitary lactotroph cells by binding to D2 receptors [17]. Injektable cabergoline was banned due to side effects such as recumbency and metabolic disorders resulting in mortality in Europe [4,11,13]. Additionally, there has been no report that investigated the efficacy of cabergoline on estrous response and pregnancy rate in lactating ewes.

The objective of this study was to investigate the effects of daily oral cabergoline administrations on prolactin suppression and reproductive parameters for 7 days at 60 days postpartum in lactating ewes.

MATERIALS AND METHODS

Flock, seasons, and management

The study was conducted at Balıkesir University Livestock Research and Application Center from November to December. Kıvırcık ewes conceived the previous non-breeding season (March-April) through the progestagen-based synchronization, and lambed during autumn in this herd. After the mating period, rams were isolated from ewes in the previous season until the present study. Ewes were housed with their lambs before weaning. Their lambs were weaned at 60 ± 2 days *postpartum* and cabergoline treatment started after weaning. A total of 60 ewes were kept in a single pen (2.5-meter square per ewe) with fresh water and offered *ad libitum* alfalfa hay together with a commercial pellet concentrate (450-500 g/ewe).

Experiments

This study was conducted with 2 different experimental designs and treatment groups received different doses (CABlow, n = 20; or CABhigh, n = 10) of cabergoline [4]. Ewes in different experiment groups were separately housed in the farm. In the 1st experiment (n = 40), 20 ewes in the low dose group received daily oral 0.5 mg cabergoline[1] for 7 days. Twenty ewes in the control groups (CONlow) received any hormonal application during the study. In the 2nd experiment (n = 20), 10 ewes in the high dose group received daily oral 1 mg cabergoline for 7 days. Ten ewes in the control groups (CONhigh) received any hormonal application during the study.

At the end of application, the ram-to-ewe ratio was determined as 1/12 and 5 fertile Kıvırcık rams with mating crayon marks were introduced to the flocks for natural mating at 67 ± 2 days. Ewes were housed together with rams for 15 days and estrous detection was performed at every 12 h. Pregnancy diagnoses were performed via transrectal ultrasound[2] at 102 ± 2 and 132 ± 2 days.

Blood samples and analysis

Blood samples were collected from all ewes to determine prolactin measurement at the onset (60 ± 2 days postpartum) and end (67 ± 2 days postpartum) of hormonal applications. The samples were centrifuged at 3,000 *g* for 15 min after collection and stored at -20°C until analysis. The serum prolactin concentrations were measured by Enzyme-Linked ImmunoSorbent Assay (ELISA)[3] system using commercial sheep kits[4].

Statistical analysis

Data were analyzed by using the SPSS 25.0 package program[5] for statistical analysis. Independent t-test analysis was performed on the data showing homogeneous distribution. Wilcoxon signed-rank test was used to analyze the measurement of prolactin levels between groups. Estrous response (at 5th days and 15th days) and pregnancy rate (at 35 days) were compared using the chi-square test. The significance level was considered as $P < 0.05$ for all analysis.

RESULTS

Estrous response in experiments

Any adverse effects of cabergoline such as metabolic disorders and mortality were not observed in our study. In experiment 1, the estrous response was 15% and 10% within the 1st 5 days after introducing rams to flock in the CABlow and CONlow groups, respectively. Overall, estrous response was 100% and 90% within 15 days after introduced rams to flock in the CABlow and CONlow groups. In experiment 2, the estrous response was 20% within the 1st 5 days and 100% within 15 days after introducing rams to flock in CABhigh and CONhigh groups. Administration of daily oral cabergoline did not increase estrous response compared to control groups (P > 0.05; Table 1).

Pregnancy rate in experiments

Pregnancy rate was 100%, 85%, 90%, and 100% in CABlow, CONlow, CABhigh, and CONhigh groups, respectively. Similar to the estrous response, 2 doses of cabergoline administrations did not statistically affect the pregnancy rates (P > 0.05; Table 1).

Prolactin levels

Serum prolactin level was 81.44 ± 11.99 ng/mL and 96.67 ± 9.41 ng/mL in CABlow and CONlow groups at the onset of the study. Serum prolactin levels was determined as 61.01 ± 11.80 ng/mL and 74.66 ± 7.24 ng/mL in CABlow and CONlow groups at the end of study. Similarly, serum prolactin level reduced from 52.28 ± 3.08 ng/mL to 37.07 ± 3.15 ng/mL in CABhigh group and from 94.95 ± 9.92 ng/mL to 73.90 ± 8.55 ng/mL group in CONhigh group. Although low serum prolactin level was statistically detected at the end of study compared to that at onset of the study, there was no difference in serum prolactin level among groups (P > 0.05, Figure 1).

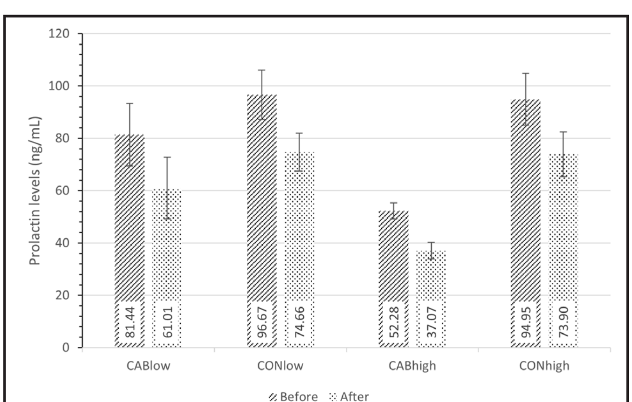

Figure 1. Prolactin values in treatment and control groups of ewes. [CABlow: Cabergoline 0.5 mg; CONlow: Control; CABhigh: Cabergoline 1 mg CONhigh: Control].

Table 1. Estrous response and pregnancy rate in Kıvırcık ewes received different dose of daily cabergolin (CAB) or not (CON).

Reproductive Parameters	Experiment 1		Experiment 2		P
	CABlow (%)	CONlow (%)	CABhigh (%)	CONhigh (%)	
Estrous Response At 5 Days	15	10	20	20	Ns
Estrous Response At 15 Days	100	90	100	100	Ns
Pregnancy Rate At 35th Days	100	90	100	100	Ns
Pregnancy Rate At 60th Days	100	85	90	100	Ns

CABlow: Cabergoline 0.5 mg; CONlow: Control; CABhigh: Cabergoline 1 mg; CONhigh: Control. P > 0.05.

DISCUSSION

Formerly, it was believed that the induction of estrus in bitches by cabergoline was the result of the suppression of prolactin secretion. But, it has been shown that receiving a low dose of bromocriptine has led to a significant shortening of the inter-estrus interval (ovarian stimulation) without a decrease in plasma prolactin concentration in bitches. In the present study, cabergoline did not make a difference in prolactin levels which is supported above mentioned hypothesis. However, It has been reported in the studies carried out on rats that the treatment of single-dose 0.6 µg/kg cabergoline has reduced the concentrations of prolactin [7].

Scientific studies on cabergoline have mostly focused on bitches. It has been reported that the use of cabergoline in the treatment of both primary and secondary anestrus cases in bitches induces estrus and provides a high pregnancy rate [6,25]. In previous studies with cabergoline to stimulate the estrous cycle in bitches [21], reported that cabergoline administration caused an increase in plasma LH level and stimulated follicular development by 70% before proestrus began during the anoestrus period [21]. Cabergoline administration caused an increase in plasma LH level and stimulated follicular development by 70% before proestrus began during the anoestrus period [12]. Oral cabergoline at a dose of 6 mcg/kg to 7 bitches in the early anestrus period and 6 bitches in the late anestrus period until the onset of proestrus symptoms or for a maximum of 14 days to stimulate the oestrus at different stages of anestrus [10]. In their study, estrous stimulation and pregnancy rate was 5/7 in the group in the early anestrus period and 6/6 in the group in the late anestrus period. Researchers stated that cabergoline administration is more effective in the late anestrus period. Cabergoline stimulates the estrus successfully and achieves acceptable pregnancy in bitches [5,19], the studies suggested that cabergoline can be used for estrus induction in bitches. Cabergoline applications are effective to induce estrus without deleterious effects on bitches [26]. The different obtained data can be determined due to animal species (digestive tract difference), dose or/and application route of cabergoline.

This study aimed to focus on the effect of using various doses of cabergoline on serum prolactin levels, estrous response, and pregnancy rate in lactating Kıvırcık ewes. It has been suggested that high prolactin levels may interfere at the early stages of follicular development with the resultant failure of normal luteal function [15]. Dopamine has a direct effect on the lactotrophs of the anterior pituitary by binding to their D2 receptors and reducing prolactin exocytosis and gene expression [8]. Commercial cabergoline as an injectable form was initially authorized by the European Medicines Agency to accelerate udder involution by reducing prolactin levels during dry periods in dairy cows. However, the marketing authorization of cabergoline was finally banned due to side effects. Furthermore, there was suspense for an adequate dose of cabergoline considering the same aim in ewes. A recent study [4] reported that 2 doses of injectable cabergoline (0.56 mg [low] and 1.12 mg [high]) dramatically reduced prolactin levels and milk yield 5 days after administration in dairy ewes. Moreover, adverse effects such as metabolic disorders and mortality were not determined. Similar to the previous study, our study was planned to use similar cabergoline doses (0.5 mg and 1.0 mg) to determine the possible reduction in prolactin levels 7 days later after administration. Administration of daily oral cabergoline for 7 days did not result in any adverse effects in our study.

Our results showed that administration of oral cabergoline was not effective in improving estrus response and pregnancy rate in ewes. The subsequent increase in estrus response and pregnancy rate in ewes in the CAB groups after introducing rams was unlikely to be produced by the rebound of prolactin because there was a parallel increase in estrus response and pregnancy rate in ewes in the CON groups. Few data are available related to the use of dopamine agonists on reproduction in ewes [4]. According to our knowledge, this study is the 1st investigation of cabergoline on estrous induction in ewes. Some scientific studies have been conducted with bromocriptine, which has a similar effect to cabergoline, with induction of estrus in ewes [3,20].

Rodway *et al*. [18] reported that the administration of injectable bromocriptine induced ovulation rate in anestrus lactating ewes. Another study suggested the use of injectable bromocriptine to increase ovulation and luteal function by suppressing prolactin levels in ewes during lactation [16]. The authors also suggested that there was a greater likelihood of an earlier resumption of breeding activity in the ewe and might also depend on the day length period [16]. Some authors showed improvement in estrus induction and pregnancy rates in ewes with different doses of bromocriptine [2]. However, the current study design was different from that study since the use of bromocriptine concomitantly with progestagen-based protocol in estrous induction and fertility in ewes in the previous study [2]. Firstly, the failure of cabergoline to improve reproductive parameters and to reduce prolactin levels could possibly have resulted from the administration of the oral route. Secondly, higher estrous response and pregnancy rate in control (CON) groups could be masked by the increment of reproductive parameters in treatment groups (CAB). The follicular wave is synchronized for about 3 days with manipulation of a single dose of estradiol-17 beta in anestrous ewes after the introduction of rams. Although cabergoline did not contribute to the increment of estrous response and pregnancy rate, improvement of reproductive parameters in both control and treatment groups could be explained by the ram effect [22].

CONCLUSIONS

Administration of daily oral cabergoline for 7 days did not cause any adverse effects in ewes. It can be highlighted that daily oral cabergoline did not statistically reduce prolactin levels and improve estrous response and pregnancy rate in ewes. Further studies are needed about using oral cabergoline on prolactin levels and reproductive parameters in ewes.

MANUFACTURERS

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***Ethical approval*.** Balıkesir University Animal Experiments Local Ethics Committee (HADYEK) proved ethical approval with decision number 2019/2-2. This decision Animal Experiments on the Working Procedures and Principles of Ethics Committees regulation (law no. 28194 dated 14.02.2014) clause k in accordance with the first paragraph, "Clinical for diagnosis and treatment purposes practices" HADYEK it was made subject to the provision that it is not subject to permission.

***Declaration of interest*.** The authors have declared no conflict of interests. The authors alone are responsible for the content and writing of the paper.

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