EFFECT OF GnRH IMPLANT (DESLORELIN) WITH DIFFERENT FORMULATION ON FERTILITY AND DELAY OF OESTROUS CYCLE IN EWES

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Abstract

The reversibility of anoestrus caused by long-acting GnRH analogue (deslorelin), and the effectiveness of GnRH analogue to induce standing oestrous, and in consequence to the retardation of breeding season, was investigated. During the transition period, 26 fat tailed breed ewes were randomly divided into 3 groups. GnRH analogue Ovuplant and Suprelorin were inserted under the neck skin in group I (n=7) and group II, respectively. No administration was applied in group III (control group, n=10). Suprelorin was removed 60 d after the implant’s insertion. The initiation of sexual activities based on the day of progesterone increase, and the first standing oestrous were 12.9±1.86, 34.7±9.69, 81.9±6.31, and 27.3±1.94, 48.3±9.24, 96.9±5.76 in control, Ovuplant and Suprelorin was administered to groups; respectively (P<0.001).

In conclusion, deslorelin administration resulted in reversible anoestrus in ewes. During the 60 d experimental period, Suprelorin effectively suppressed sexual activity; therefore, Suprelorin could be used to delay the breeding season.

Key words: ewe, deslorelin, oestrous cycle.

Ewes are polyoestrus animals, depending on seasons in terms of features of breeding (6, 13, 18). The breeding or oestrus term in the northern hemisphere is the end of summer and the months of autumn, when daytime begins to shorten and sunlight begins to reduce its effectiveness (2, 3, 28). The length of oestrus season is related to the shortening of the day, management, feeding conditions, breed, and age (5, 8, 29). Ewes become pregnant in early breeding season, and give birth during the coldest month of year (December and January), in which the viability of neonatal lambs is lower (1). Although, reproductive performance of a herd is increased due to different treatments, economical profit from lamb production, decreased because of neonatal lamb mortality. When circumstances of the season are managed, the most suitable time for breeding is the second half of the breeding season lasting 4-5 months (28). Delaying the breeding season for longer period by hormonal applications, is a promising way to achieve this goal.

Applications of exogenous hormones to increase the reproductive performance in domestic ewes are usually focused on oestrous synchronisation (14, 26, 30). Thus, standing oestrus and breeding were synchronised in a short period (11, 12, 17). However; to date, there has been no extensive attempt to delay oestrous cycles for longer periods. Gonadotropin releasing hormone (GnRH) applications as frequent injections and/or long-acting formulations or in the form of implants, are capable to inhibit the activity of GnRH receptor in the adenohypophysis, which compromises FSH and LH secretion, resulting in interruption of follicular development (19, 24, 27). The pituitary gonadotropins, FSH, and LH are key determinants of ovarian follicular maturation, and ovulation in ewes (10, 15, 16). Recently, a long-acting GnRH agonist, deslorelin, has been used for the synchronisation of ovulation, supporting CL function and suppression of oestrus by delaying the formation of a dominant follicle (4, 22). However, the effects of deslorelin have not been investigated, regarding the suppression of oestrus and fertility in ewes so far.

The objectives of this study were: 1) to evaluate the effectiveness of deslorelin for the suppression of oestrus during its application for delaying the breeding season in ewes; 2) to investigate the reversibility of deslorelin-induced anoestrus.
Material and Methods

Animals, treatments, and experimental designs. This experiment was conducted between August and December 2005. The Animal Handling and Ethical Board at the Faculty of Veterinary Medicine approved all experimental design and applications. Twenty-six non-lactating Tushin breed (2-5-year-old) ewes were housed in flock barn, with access to a feeding lot and were fed grass hay ad libitum. The feed was provided two times a day at 09:00 and 15:00.

The ewes were randomly assigned into three groups. The ewes in group I (Ovuplant group, n=7) were inserted with short-acting GnRH analogue, Ovuplant (2.1 mg of deslorelin [6-D-tryptophan-9(N-ethyl-L-prolinamide)-10-deglycinamide]) GnRH, Peptech Animal Health, Australia) under the skin. The ewes in group II (Suprelorin group, n=9) were inserted with long-acting GnRH analogue, Suprelorin (4.7 mg of deslorelin [6-D-tryptophan-9(N-ethyl-L-prolinamide)-10-deglycinamide]) GnRH, Peptech Animal Health, Australia) under the neck skin. The ewes in group III served as the control (n=10) and no administration was applied.

Implant removal and oestrus detection. Because the implants inserted in group I had a short effect, and dissolved in 2-4 d, they were not removed. In group II, all inserted implants were removed with an incision of the skin after 60 d. Afterwards the incisions were sutured surgically and long action antibiotics were applied. The ewes were observed for standing oestrus with teaser ram (1 ram per 10 ewes) twice a day for 30 min each from the onset of the study. The oestrus behaviour was recorded, and ewes in standing oestrus were mated. A pregnancy diagnosis was conducted by transrectal ultrasonography on day 35 following mating. Following the implant’s removal, the day of oestrus expression, rate of oestrus, initiation of the oestrous cycle based on blood progesterone (P4) level, number of breeding, rates of repeats, duration of oestrus, and pregnancy rates in all groups were evaluated.

Blood collection. In order to determine the onset of ovarian activity based on plasma P4 concentrations, blood samples were collected from the jugular vein into anticoagulant tubes three times a week; starting from the day before insertion of the implant, until the ewes became pregnant. The blood samples were centrifuged (Hettich, Universal 3R, 3 000 per/min, 10 min), then plasma was separated and stored at -20°C until analysis. Plasma P4 values were determined by using the method of Prakash et al. (25), and hormone analyses were performed via double antibody enzyme immunoassay technique. The levels of quantification of the assays were 0.25 ng/mL and intra- and interassay coefficients of variations were 7% and 13%, respectively. The day when the P4 concentration was higher than 1 ng/mL at least in 3 consecutive samples, was accepted as the first day of sexual activity.

Data analysis. Mean and standard error of mean (SEM) values were calculated by using the MINITAB statistical package (Version 11.2, MINITAB Inc., State Collage, PA, USA). Parameters in groups were compared with ANOVA and Tukey, as the post-test. The statistical analysis of ewes returning the oestrus chi-square method was used in the same programme.

Results

No important side effects were observed in the ewes, except for local reactions lasting up to 6 d following insertion of the implant.

There were statistical differences among groups regarding the initiation of sexual activities based on the day when P4 rise was higher than 1 ng/mL, and the first standing oestrus approval. Initiation of sexual activities based on the day of P4 rise, and the first standing oestrus were 12.9±1.86, 34.7±9.69, 81.9±6.31, and 27.3±1.94, 48.3±9.24, 96.9±5.76 in control, Ovuplant, and Suprelorin groups, respectively (P<0.001; day 0). The range of days of the P4 elevation and the days of standing oestrus were 1-21, 21-35; 2-60, and 20-74, 58-119, 67-133 in control, Ovuplant, and Suprelorin groups, respectively (Fig. 1).

The time differences between the initial increase of P4, and the day of the first standing oestrus were 14.4±1.00, 13.6±1.43, and 15±1.08 in control, Ovuplant, and Suprelorin groups; respectively, and this result was not statistically significant (P>0.05). The number of oestrous cycles based on standing oestrus, and the number of returning oestrus following breeding did not differ among groups (P>0.05). Analyses of interoestrous interval in ewes returning the oestrus following breeding, indicated that ewes in Ovuplant group (16, 6) had longer interoestrous interval than those in Suprelorin group (11, 8) (P<0.05).

The average P4 concentrations (0.83 ng/mL) following the implant’s removal, were higher than those (0.62 ng/mL) after the implant’s insertion (P<0.001). Like in the transitional period, standing oestrus was weak in ewes administered with Ovuplant and Suprelorin, and they did not become pregnant. At the end of the breeding season only one ewe in the Suprelorin group did not become pregnant among all experimental animals. This problematic ewe had irregular interoestrous intervals with unstable standing oestrus following the implant’s removal.

One week after insertion of the implant, frequencies of P4 were at 3/7 (42%), and 3/9 (33%) in Ovuplant and Suprelorin groups, respectively. Ewes with P4 rise in Ovuplant group got pregnant following the first oestrus (n=2) and the second oestrus (n=1). However, P4 concentrations were at the basal level between two weeks after insertion of the implant, and the day of implant’s removal (day 60) in the Suprelorin group. In one ewe in Suprelorin group, P4 concentrations started to increase at day 58, and this ewe did not get pregnant.
Discussion

As reported previously (9, 24), implants could be used safely because no side effects were observed except for local redness and oedema following the insertion of the implant.

The statistical differences in terms of sexual activity, and the onset of the first oestrus among groups indicated that deslorelin administrations delayed oestrous cycle in ewes. Moreover, no differences in time length between the onset of sexual activity and the first oestrus, and the number of oestrus among groups implied that the effects of deslorelin administration was reversible, and restoring the levels of oestrus was quick. In addition, an increase in the average P4 concentrations following the implant’s removal in the Suprelorin group; indicated that Suprelorin administration reversibly suppressed the oestrous cycle.

The initial GnRH treatment should induce a sufficient release of follicle stimulating hormone (FSH), and luteinizing hormone (LH) (acute phase flare effect) and then cause ovulation or luteinization of the dominant follicle (7). The increase in P4 concentrations in some ewes in either Ovuplant (n=3) or Suprelorin (n=3) groups following implant administration, could be due to the sudden release of LH, leading to ovulation or luteinization of dominant follicles. Compared to Suprelorin; Ovuplant is a shorter acting formulation with less dosage, and it disappears quicker at the inserted area. For this reason, Ovuplant probably induced oestrous cycles in some of the ewes (n=3) during the transitional period. The rest of the ewes in the Ovuplant group, showed oestrus activity later, because of the lack of follicular activity, or individual differences following insertion of the implant, whereas Suprelorin treatment resulted in an increase in P4 concentrations in three ewes following the insertion of the implant due probably to ovulation or luteinization. Afterwards, this increase in P4 concentrations could not be maintained because of the suppression of LH release. However, P4 concentrations did not increase in the rest of the ewes (n=6) following Suprelorin insertion. Regardless of the increase in P4 concentrations following Suprelorin insertion, P4 concentrations were at the basal level during Suprelorin administration. Because GnRH receptors at the adenohypophysis could be downgraded following GnRH implant administration as reported many researchers (9, 20, 23), there is a decline in P4 concentrations in Suprelorin group.

In one of the ewes in the Suprelorin group, the P4 concentrations started to increase two days prior to the implant’s removal, and this ewe was not pregnant at the end of the experiment. This unexpected increase in P4 concentrations could be due to individual differences for the response to deslorelin administration as reported by Herbert and Trigg (9) and/or difficulties in preparation of a standard drug formulation. Padula and MacMillan (21) reported that failure of ovulation and
cystic follicles could exist due to inadequate LH release, despite normal follicular development following removal of deslorelin suppression. Similarly, this inadequate LH release following the implant’s removal, could contribute to irregular interoestrous periods and weak oestrus behaviour in this non-pregnant ewe in Suprelorin group.

In conclusion, deslorelin administration resulted in reversible infertility in ewes. Because Suprelorin insertion; successfully and reversibly, suppressed sexual activity, it could be used to delay breeding season in ewes. But Ovuplat implants unsuccessfully suppressed sexual activity. With this delay in the breeding season, all ewes could be bred at the end of the breeding season, and reproductive as well as neonatal management could be more effective.

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