sciendo

Research article

Acta Veterinaria-Beograd 2024, 74 (2), 273-284
UDK: 636.7:612.621.5
DOI: 10.2478/acve-2024-0019

CLINICAL USE OF LONG-TERM GnRH AGONIST IN PREPUBERTAL BITCHES: EFFECT ON P4, E2 AND MELATONIN SERUM CONCENTRATION BEFORE AND DURING FIRST ESTRUS

Vojislav Al DAGHISTANI[1], Ljubodrag STANIŠIĆ[2*], Miloje ĐURIĆ[2], Milan MALETIĆ[2], Slobodanka VAKANJAC[2], Branislav VEJNOVIĆ[3], Vladimir MAGAŠ[2]

[1]LINK A PET, Vajara Đoke Jovanovića 8, Belgrade, Serbia; [2] University of Belgrade, Faculty of Veterinary Medicine, Department of Reproduction, Fertility and Artificial Insemination, Bulevar oslobođenja 18, Belgrade, Serbia; [3] University of Belgrade, Faculty of Veterinary Medicine, Department of Economics and Statistics, Bulevar oslobođenja 18, Belgrade, Serbia

(Received 25 September 2023, Accepted 08 May 2024)

The aim of this study was to determine the length of the contraceptive period after the application of deslorelin implant (4.7 mg) in juvenile, prepubertal bitches and assess the effects on the hormonal status (P4, E2 and melatonin), as well as on the occurrence of normal physiological estrus. Twelve crossbred prepubertal female dogs (4 months of age) were divided into the two groups, the treated group (DESLO) and control (placebo) group (C). Hormone assays, vaginal microbiological and cytological smears and the measurements of electrical resistance of cervical mucus were performed once in 3 weeks until the first signs of proestrus, and every day during estrus. GnRH implant significantly postponed time of onset of estrus (633 ± 30,38 days vs. 143.80 ± 52,30 days, P<0.001). In estrus, DESLO group showed statistically higher E2 (34.58 pg/mL vs. 20.59 pg/mL, P<0.001) and melatonin serum concentration (45.86 pg/mL vs. 18.85 pg/mL, P<0.001) compared to the control group. The average P4 serum concentration had no statistically significant differences between groups. In conclusion, deslorelin implants do not cause "flare up" effect in perpubertal bitches, however, increase of E2 and especially melatonin serum concentrations show the need to explore the consequences and mutual influence of melatonin and deslorelin implants in the future.

Keywords: deslorelin, estrus, hormonal status, melatonin, prepubertal bitches

INTRODUCTION

In modern veterinary practice, many of the problems faced by veterinarians, and of great concern for dog owners, are related to reproduction and reproductive control options. For many years, surgical castration was the only reliable and permanent

*Corresponding author: e-mail: ljstanisic@vet.bg.ac.rs

method of contraception in dogs. Ovariectomy, ovariohysterectomy (OHC) and orchidectomy are the most common surgical procedures routinely performed in small animal practice [1,2]. Prepubertal ovariectomy (or OHC) is defined as the surgical castration of immature female animals between 6 to 14 weeks of age, and it is often associated with some long-term behavior and health effects [3-6]. Therefore, discussions and controversies about surgical spaying are ongoing in many countries, emphasizing the associated benefits and risks in prepubertal animals as undergo physical and physiological changes to become reproductively viable [3,7].

In recent years, numerous contraceptive drugs have come onto the market, many of which have more than one indication and application. They have direct or indirect effect on the sexual cycle of animals. Therefore, their use requires experience, correct and timely dosing and knowledge of side effects and contraindications [8-10]. The chosen method should be acceptable to the owner (single application of injectable medications, uncomplicated oral application, and low cost) [10].

Application of procedures to suppress estrus in female and reduce libido in male dogs are common in small animal practice [11]. Many studies have investigated the use of GnRH agonists as hormonal reversible sterilization in males and its efficacy has been well established [12-15], therefore the commercially available products are registered for use only in male dogs [10]. In the past decades, gonadotropin-releasing hormone (GnRH) agonists had a great perspective in the management and control of estrus in bitches [11,16-18]. Implants are subcutaneous insertions of slow-release GnRH, such as the 4.7 mg and 9.4 mg deslorelin acetate and represent an excellent alternative for reversible control of ovarian activity in diestrus bitches [11]. The first step in the mechanism of action of GnRH agonists is the "flare-up" effect, which is characterized by an increased synthesis of gonadotropins. This stimulating effect is more pronounced in bitches than in males. Estrus induction by this method can be observed in most bitches in anestrus, regardless of the phase of anestrus [16,19]. Most authors have confirmed that all adult bitches respond in the same way regardless of size and age; however, depending on the phase of the cycle, it is possible that the response to the applied implant may be absent [14]. After the "flare-up" effect, the natural pulsatile releases of hypothalamic and pituitary hormones are blocked. This leads to a basal release of gonadotropin, after which synthesis and release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are reduced and consequently prevent follicular development, i.e., it leads to a temporary long-term delay of the estrus cycle [7].

Melatonin (N-acetyl-5-methoxytryptophan) is a neurohormone secreted by the pineal gland and has a circadian rhythm, with low secretion levels during day and high during night. In short-day breed animals, melatonin controls the seasonal biological and reproductive rhythm, onset of estrus and improves sperm quality [5,20]. Melatonin synthesis and secretion play one of the main roles in the complex process of GnRH synthesis, and it is of most importance to determine to what extent deslorelin implant affects the endocrine status in dogs.

There are insufficient data on the length of action of GnRH implants applied to prepubertal bitches and its influence on the appearance of estrus and hormonal status after the discontinuance of action, as well as the possibility of complications. The aims of this study were to determine the length of the contraceptive period after the application of GnRH agonist in juvenile, prepubertal bitches and assess the effects on the hormonal status (progesterone, estrogen and melatonin), as well as on the occurrence of normal physiological estrus.

MATERIALS AND METHODS

Animals

Twelve healthy, crossbred prepubertal female dogs were used in this study, divided into two groups, the treated group (DESLO) and control (placebo) group (C). All dogs were on average 4 months of age, similar constitution, and body weight (range 10-15 kg), and were held in the same housing conditions (indoor/outdoor). They were fed with same commercial granulated food in accordance with age category. Before being introduced into the study, a clinical examination was performed on each animal, blood analyses (hematological and biochemical parameters, hormonal status – progesterone and estrogen), as well as examination of the genital tract (ultrasound, vaginal cytological and bacteriological smear, the electrical resistance of cervical mucus – Draminski DOD2, Poland) with the aim of excluding puberty. This study was reviewed by the Ethics Committee of Ministry of Agriculture, Forestry and Water Management; Veterinary Administration (No. 323-07-07459/2020-05) and has been approved by the owners.

Treatment

Animals in the DESLO group (n=6) were treated with subcutaneous 4.7 mg deslorelin acetate implants (Suprelorin®, Virbac, France) in the umbilical region, and recorded data were submitted in the accompanying health record. The control group (n=6) received a placebo subcutaneous injection (2 ml sodium chloride 0.9%). After insertion, animals were monitored daily for the presence of allergic reactions and estrus by physical examination of the vulva, vaginal smears (Diff-Quick staining) and changes in sexual behavior for the first 5 weeks. Hormone assays, vaginal cytological smears and the measurements of electrical resistance of cervical mucus were performed once in 3 weeks until the first signs of proestrus, and every day during the estrus period. The changes in the cellular profiles obtained by vaginal cytological smears were monitored in order to detect proestrus: from the predominance of parabasal cells in anestrus (accompanied by varying numbers of neutrophils), to the successive alternation of medium-sized squamous cells to large intermediate cells, and then to large keratinocytes until they finally consist entirely (98–100%) of keratinocytes (cornified) cells with an

absence of neutrophils (Concannon, 2011). Gradual increase of electrical resistance of cervical mucus from 120 to 220 ohms was considered as the onset of proestrus (Concannon, 2011). Increase of E2 (during proestrus) and P4 (at the end of proestrus and estrus) serum concentrations indicated follicular growth and ovulation.

Hormone assays

For the hormone analyses blood samples were taken from the v. *cephalica antebrachii* and collected in test tubes without anticoagulants. Blood serum was separated after centrifugation at 3000 rpm during 15 minutes and stored at - 20°C. Progesterone (P4) and 17-beta estradiol (E2) concentrations were determined by the chemoluminescent method, using an automatic hormone analyzer (Access 2 Beckman Coulter, USA) using commercial kits according to the manufacturer's instructions in special laboratory (VetLab, Veterinary laboratory for clinical diagnostics, Serbia).

Statistical analyses

The data were tested for normality using the Shapiro-Wilk's test. If the data were normally distributed (Shapiro-Wilk's test, $P > 0.05$), the unpaired t-test was used for the comparison of two groups. If the data were not normally distributed (Shapiro-Wilk's test, $P < 0.05$), the Mann-Whitney test was used for the comparison of two groups. Significant difference was estimated at $P < 0.05$ level. Statistical analysis of the results obtained in the experiment was carried out using statistical software GraphPad Prism version 7 (GraphPad, San Diego, CA, USA).

RESULTS

Treatment

The implant procedure was done routinely, and no clinically detectable local or systemic side effects associated with the treatment were observed in any of the experimental groups.

Hormone assays

The values of the days to the first signs of estrus showed homogeneity (CV<30%) in DESLO group (CV = 4.8%), while in the control group values showed heterogeneity (CV= 36.36%). The time of onset of estrus between the groups was significantly different ($P<0.001$), whereby the control group had an average 143.80 ± 52,30 days and DESLO group had average 633 ± 30,38 days until first signs of estrus, which was 4.4 times longer in DESLO group (Figure 1).

Application of desloreline implants led to higher average blood serum E2 concentrations ($P<0.01$) in DESLO group one week before the start of estrus

(10.13 pg/mL vs 4.95 pg/mL). It is important to note that serum E2 concentrations were slightly higher, with no statistical significance, in DESLO group between 6-12 days after application of implants, while bitches in the control group showed no increase of E2 concentracion. In estrus, DESLO group showed a statistically higher E2 concentration (P<0.001) compared to control group (Figure 2) with average concentration of 34.58 pg/mL and 20.59 pg/mL, respectively, and E2 concentration in both groups displayed homogeneity (CV<30%). Two of 6 animals in DESLO group showed an increase of E2 serum concentration up to 36 and 40 pg/mL, while maximum E2 concentration in the control group was 23 pg/mL (2/6 animals).

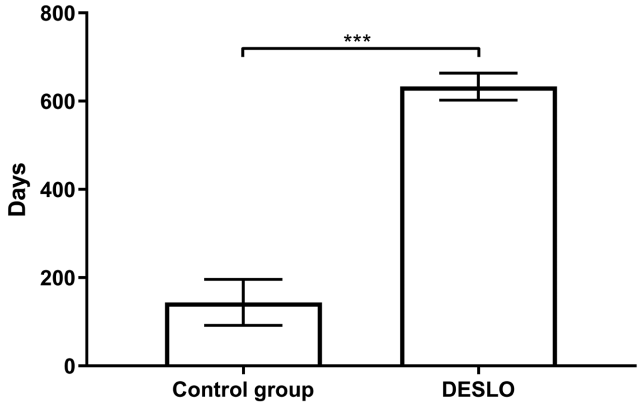

Figure 1. Days to estrus in DESLO (n=6) and C (n=6) group, P<0.001.

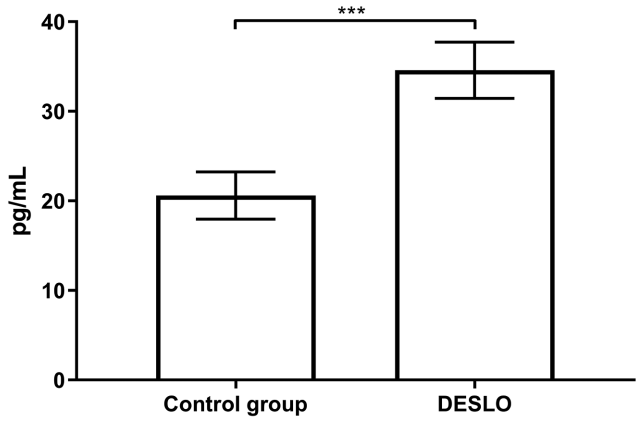

Figure 2. Serum E2 concentration (mean ±SEM) in DESLO (n=6) and C (n=6) group, P<0.001, during first estrus.

During the period of anestrus (monitoring) in the treated DESLO group, P4 serum concentration was under 0.6 ng/mL. The average P4 serum concentrations during estrus were higher in DESLO group (DESLO 13.69 ng/mL and C 10.07 ng/mL), but with no statistical significances between groups, and the P4 concentrations in the control group displayed heterogeneity (CV= 41.99%).

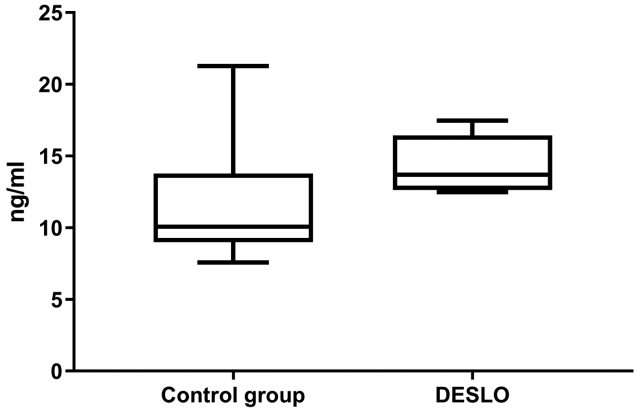

Figure 3. Serum P4 concentration (mean ±SEM) in DESLO (n=6) and C (n=6) group, during first estrus.

Melatonin serum concentrations in DESLO group were statistically significantly higher (P<0.001) during estrus compared to the control group with average concentrations of 45.86 pg/mL and 18.85 pg/mL, respectively. In both experimental groups melatonin concentration displayed homogeneity (CV<30%), and highest values were in DESLO group 3 week after first signs of estrus (52.16 pg/mL).

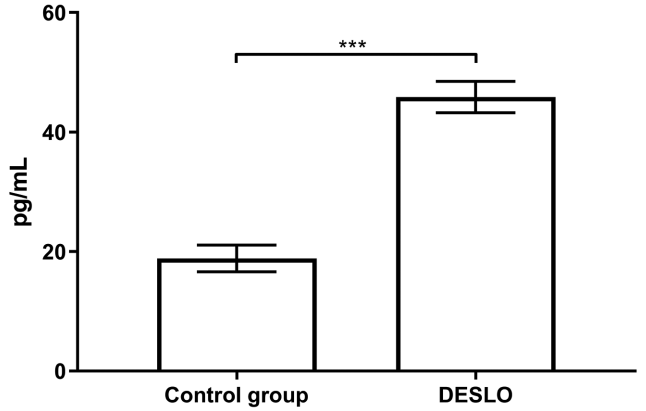

Figure 4. Serum melatonin concentration (mean ±SEM) in DESLO (n=6) and C (n=6) group, P<0.001, during first estrus.

In 2/6 bitches in the DESLO group dorsal vaginal wall hyperplasia (type 1) was noticed after the first signs of estrus which regressed spontaneously and no longer occurred in the following estrus. In addition, 2/6 bitches in the DESLO group and one bitch in the control group developed mild juvenile vaginitis, between the 20th - 30th week and at the 14th week, respectively. These conditions did not require any special treatment and the animals recovered spontaneously.

DISCUSSION

The aim of this study was to evaluate the long-term effects of GnRH deslorelin implants (4.7 mg) on endocrine status, anestrus duration and eventual visible side effects in medium-sized prepubertal bitches. Although the safety and effect of the GnRH agonist application has been proven in dogs [21-25] showing promising results of reversible contraception, these aims in bitches encountered a bit complicated physiological issues. Generally, the definition of puberty in dogs is highly variable since there are many breeds and it is independent on body weight [7,26]. Definition of onset of puberty between male and female dogs is different and has its own timetable, where puberty in females probably starts earlier followed by change in follicular growth, vaginal cytology, and steroid hormones, while in males is marked with mounting and first spermatozoa in the urine [27].

A limited number of previous studies have revealed that a visible response to the administration of deslorelin implants - the "flare-up" effect - occurred in prepubertal bitches at more than 7 months of age, whereas prepubertal bitches at 4 months of age showed no signs of estrus after administration [28-31]. After insertion of the implant, all bitches were monitored for the "flare-up" effect using clinical examination, vaginal cytology, the electrical resistance of cervical mucus and P4 and E2 serum concentration. In DESLO group, like in the previous investigations with bitches at the age of 4 months there was no "flare-up" effect, and the average time of onset of estrus was 633 days (90 weeks). This average period of reversible anestrus was longer than average time to puberty (82.7 weeks) in the investigation of Kaya et al. (2015) using animals of similar size and age. However, 4 animals in the mentioned study showed first signs of estrus on average 101.5 weeks after the application. In favor of deslorelin effectiveness, Faya et al. (2018) treated newborn male and female puppies within 24h after birth and postponed puberty for an average of 76.8 weeks.

During the observation period, the animals from the DESLO group showed small variations in P4 and E2 serum concentrations, as previously explained in the study [31], in which the deslorelin implants showed individually variable P4 and E2 serum concentrations during the observation period of 8 to 19.5 months. The reason for these slight discrepancies in the results could be due to the high variability of factors in each study with similar or different designs and, more likely, individual differences in drug absorption or metabolism between the bitches, as only 1-2 of them showed these variations [7,30,31]. These oscillations of P4 and E2 could be avoided using neonatal

deslorelin administration since there is a lack of sexual hormonal receptors at the early neonatal period [32].

Serum P4 concentrations did not differ among the DESLO and control group as stated in previous studies [31,32] and the status of P4 concentration is in compliance with the conclusion that deslorelin does not have negative effects on ovarian functionality after long-term estrus delay in bitches [34].

Melatonin, as a regulatory neuropeptide, causes many responses to changes in the body, as well as the response of the organism to changes in the environment. For the first time, was brought in connection the suppressive effect of deslorelin on the hypothalamus - pituitary gonadal axis and the status of melatonin serum concentration, since melatonin has one of the most important roles in the synthesis of GnRH. In addition, E2 serum concentration is in discrepancy compared to previous studies [28-31,34], since there are statistically higher E2 concentrations ($P<0.001$) in the DESLO group. Also, melatonin serum concentrations were statistically higher in the DESLO group after onset of estrus. One of the first researches related to the influence of melatonin on endocrine status in castrated and intact male dogs [5,35], showed that increase of melatonin decreased progesterone and estrogen concentrations in the intact and castrated dogs. Since the research was done on male dogs [5,35], it remains questionable how much difference there is in the mechanisms of action and regulation of certain hormones between the sexes, or to be more precise, how estrus effects on melatonin status after deslorelin suppression. It is hypothesized that following deslorelin effect – estrus suppression in prepubertal females - a larger pool of follicles is recruited whose ovulatory capacity is questionable but which are capable of producing a higher concentration of estrogen. During anestrus, deslorelin implant is a source of GnRH, and the hypothalamus - pituitary gonadal axis is suppressed. After long-term reversible contraception effect of deslorelin, activity of melatonin follows the synthesis and release of GnRH, which, in our study, showed high serum concentrations.

In conclusion, deslorelin implants do not cause the "flare up" effect in perpubertal bitches, however, increase of E2 and especially melatonin serum concentrations were observed. Since the positive effects of melatonin on endocrine and immunological development as well as its antioxidant, anticancer and cytotoxic effects have been demonstrated in decades of research [5,35-38], it is of utmost importance to explore the consequences and mutual influence of melatonin and deslorelin implants in the future.

Acknowledgements

The study was supported by the Ministry of Science, Technological Development and Innovation of the Republic of Serbia (Contract number 451-03-66/2024-03/200143).

Authors' contributions

VAD, LjS, and VM designed and conceived the study, selected the animals, carried out examinations and sampling during the experiment, and drafted the manuscript. MM and MĐ participated in material sampling and measurements, coordinated the experiment, and helped draft the manuscript. SV participated in laboratory work and drafted the manuscript. BV participated in the study design and performed the statistical analysis. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Statement of Informed Consent

The owner understood procedure and agrees that results related to investigation or treatment of their companion animals, could be published in Scientific Journal Acta Veterinaria-Beograd.

ORCID iDs

Ljubodrag Stanišić https://orcid.org/0000-0002-5200-2169
Miloje Đurić https://orcid.org/0000-0002-1338-0175
Milan Maletić https://orcid.org/0000-0003-3153-8471
Slobodanka Vakanjac https://orcid.org/0000-0003-2812-7559
Branislav Vejnović https://orcid.org/0000-0002-6328-7446
Vladimir Magaš https://orcid.org/0000-0002-8395-3725

REFERENCES

1. Moxon R, Freeman S, Payne R, Corr S, England GC: A prospective cohort study investigating the behavioral development of bitches in a guide dog training programme neutered prepubertally or post-pubertally. Front Vet Sci 2022, 9: 879.
2. Moxon R, Freeman SL, Payne R, Corr S, England GC: A prospective cohort study investigating the peri-and postoperative outcomes following ovariohysterectomy in bitches neutered prepubertally or post-pubertally. Theriogenology 2023, 197, 283-294.
3. Lucas X: Clinical use of deslorelin (GnRH agonist) in companion animals: a review. Reprod in Dom Anim 2014, 49, 64-71.
4. Romagnoli S: Early-age neutering in dogs and cats: advantages and disadvantages. Rev Bras Reprod Anim 2017, 41, 1:130-132.
5. Salavati S, Mogheiseh A, Nazifi S, Tabrizi AS, Taheri P, Koohi F: Changes in sexual hormones, serotonin, and cortisol concentrations following oral administration of melatonin in castrated and intact dogs. J Vet Behav 2018, 27, 27-34.
6. Yates D, Leedham R: Prepubertal neutering of dogs—some risks and benefits. Companion Animal 2019, 24: 38-42.

7. Schäfer-Somi S, Kaya D, Aslan S: Prepubertal Use of Long-Term GnRH Agonists in Dogs: Current Knowledge and Recommendations. Animals 2022, 12,17, 2267.
8. Kutzler M, Wood A: Non-surgical methods of contraception and sterilization. Theriogenology 2006, 66,3: 514-525.
9. Rhodes L: New approaches to non-surgical sterilization for dogs and cats: Opportunities and challenges. Reprod Domest Anim 2017, 52, 327-331.
10. Asa CS: Contraception in dogs and cats. Vet Clin N Am 2018, 48, 4: 733-742.
11. Borges P, Fontaine E, Maenhoudt C, Payan-Carreira R, Santos N, Leblond E, Fontaine C, Fontbonne A: Fertility in adult bitches previously treated with a 4.7 mg subcutaneous deslorelin implant. Reprod in Dom Anim, 2015, 50, 6, 965-71.
12. Romagnoli S, Nassuato C, Stelletta C, Mollo A, Gelli D: Serum Testosterone Concentrations on Scrotal Diameter in Male Dogs Treated With Deslorelin Implants. In: Proceeding Congress European Veterinary Society for Small Animal Reproduction Amsterdam 2005, The Netherlands, 14th April, pp. 27-28.
13. Romagnoli S, Siminica A, Sontas BH, Milani C, Stelleta C: Semen quality and onset of sterility following administration of a 4.7-mg Deslorelin implant in adult male dogs. Reprod Domest Anim 2012, 47, 6: 389–392.
14. Fontaine E and Fontbonne A: Clinical use of GnRH agonists in canine and feline species. Reprod Domest Anim, 2011, 46, 344–353.
15. Driancourt MA, Briggs JR: Gonadotropin-releasing hormone (GnRH) agonist implants for male dog fertility suppression: a review of mode of action, efficacy, safety, and uses. Front Vet Sci 2020, 7, 483.
16. Volkmann DH, Kutzler MA, Wheeler R, Krekeler N: The use of deslorelin implants for the synchronization of estrous in diestrous bitches. Theriogenology 2006, 66, 1497–1501.
17. Kutzler M, Lamb SV, Volkmann D: Comparison between vestibular and subcutaneous insertion of deslorelin implants for oestrus induction in bitches. Reprod Domest Anim 2009 44, 2: 83–86.
18. Fontaine E, Mir F, Vannier F, Gerardin A, Albouy M, Navarro C, Fontbonne A: Induction of fertile oestrus in the bitch using Deslorelin, a GnRH agonist. Theriogenology 2011, 76, 1561–1566.
19. Fontaine E, Fontbonne A: Use of deslorelin to control fertility in the bitch. In 7th European Veterinary Society Small Animal Reproduction (EVSSAR) Congress 2010, Louvain-la-Neuve, Belgium, May 15–15, pp. 9–10.
20. Haldar C: Experimental endocrinology and reproductive biology. Science Publishers 2007.
21. Paramo RM, Renton JP, Ferguson JM, Concannon PW: Effects of medroxyprogesterone acetate or gonadotrophin releasing hormone agonist on suppression of spermatogenesis in the dog (Canis familiaris). J Reprod Fertil 1993, 47, 387–397
22. Trigg TE, Wright PJ, Armour AF, Williamson PE, Junaidi A, Martin GB, Doyle AG, Walsh J: Use of GnRH analogue implant to produce reversible long-term suppression of reproductive function of male and female domestic dogs. J Reprod Fert Suppl 2001, 57, 255–261.
23. Junaidi A, Williamson PE, Martin GB, Blackberry MA, Cummins JM, Trigg TE: Dose–response studies for pituitary and testicular function in male dogs treated with the GnRH superagonist, deslorelin. Reprod Domest Anim 2009, 44, 5: 725-734.

24. Junaidi A, Williamson PE, Martin GB, Stanton PG, Blackberry MA, Cummins JM, Trigg TE: Pituitary and testicular endocrine responses to exogenous GnRH and LH in male dogs treated with GnRH agonist implants. Reprod Fert Dev 2007, 19, 891–898.
25. Junaidi A, Williamson PE, Trigg TE, Cummins JM, Martin GB: Morphological study of the effects of the GnRH super agonist deslorelin on the canine testis and prostate gland. Reprod Dom Anim 2009, 44, 5: 757-763.
26. Johnston SD, Kustritz MV, Olson PN: Canine and Feline Theriogenology, 1st ed.; Philadelphia, USA: Saunders; 2001.
27. Gobello C: Prepubertal and pubertal canine reproductive studies: Conflicting aspects. Reprod Domest Anim 2014, 49, 70–73.
28. Rubion S, Desmoulins PO, Rivière-Godet E, Kinziger M, Salavert F, Rutten F, A. Flochlay-Sigognault, Driancourt MA: Treatment with a subcutaneous GnRH agonist containing controlled release device reversibly prevents puberty in bitches. Theriogenology 2006, 66, 1651-4.
29. Trigg TE, Doyle AG, Walsh JD, Swangchanuthai T: A review of advances in the use of the GnRH agonist deslorelin in control of reproduction. Theriogenology 2006, 66, 1507–12.
30. Kaya D, Aslan S, Kaya S, Kuru M, Kacar C, Schäfer-Somi S: Clinical and endocrine short-term effects of GnRH analogue deslorelin in prepubertal bitches: does a "flare-up" occur? Kafkas Univ Vet Fak Derg 2013, 19, 2, 299-304.
31. Kaya D, Schäfer-Somi, Kurt B, Kuru M, Kaya S, Kaçar C, Aksoy Ö, Aslan S: Clinical use of deslorelin implants for the long-term contraception in prepubertal bitches: Effects on epiphyseal closure, body development, and time to puberty. Theriogenology 2015, 83,7, 1147-1153.
32. Faya M, Marchetti C, Priotto M, Grisolía M, D'Francisco F, Gobello C: Postponement of canine puberty by neonatal administration of a long-term release GnRH super agonist. Theriogenology 2018, 118, 190-195.
33. Schäfer-Somi S, Kaya D, Sözmen M, Kaya S, Aslan S: Pre-pubertal treatment with a GnRH agonist in bitches-Effect on the uterus and hormone receptor expression. Reprod in Dom Anim 2018, 53, 103-109.
34. Kaya D, Gram A, Kowalewski MP, Schäfer-Somi S, Kuru M, Boos A, Aslan S: Expression of GnRH receptor in the canine corpus luteum, and luteal function following deslorelin acetate-induced puberty delay. Reprod Domest Anim 2017, 52,6: 1104-12.
35. Lakin ML, Miller CH, Stott ML, Winters WD: Involvement of the pineal gland and melatonin in murine analgesia. Life Sci 1981, 29: 2543-2551.
36. Sugden D: Psychopharmacological effects of melatonin in mouse and rat. J Pharm Exp Ther 1983, 227: 587-591.
37. Yu C, Weng S, Chen C: Studies on the analgesic effect and physical dependence of melatonin in mice. Chin J Drug Depend 1999, 8: 58-60.

KLINIČKA UPOTREBA DUGODELUJUĆEG GnRH AGONISTE U PREPUBERTALNOM PERIODAU KOD KUJA: EFEKAT NA SERUMSKE KONCENTRACIJE P4, E2 I MELATONINA PRE I TOKOM PRVOG ESTRUSA

Vojislav Al DAGHISTANI, Ljubodrag STANIŠIĆ, Miloje ĐURIĆ, Milan MALETIĆ, Slobodanka VAKANJAC, Branislav VEJNOVIĆ, Vladimir MAGAŠ

Ciljevi ovog istraživanja bili su određivanje dužine kontraceptivnog perioda nakon primene deslorelin implantata (4,7 mg) kod juvenilnih kuja i procena njegovog uticaja na hormonski status (P4, E2 i melatonin), kao i na pojavu normalnog fiziološkog estrusa. Dvanaest juvenilnih kuja-mešanaca (starosti 4 meseca) podeljeno je u dve grupe, tretiranu grupu (DESLO) i kontrolnu (placebo) grupu (C). Hormonske analize, vaginalni mikrobiološki i citološki brisevi i merenja električne otpornosti cervikalne sluzi vršeni su jednom u 3 nedelje do prvih znakova proestrusa, a tokom estrusa svaki dan. GnRH implantat je značajno odložio vreme početka estrusa (633 ± 30,38 dana naspram 143,80 ± 52,30 dana, P<0,001). U estrusu, DESLO grupa je pokazala statistički vece koncentracije E2 (34,58 pg/mL prema 20,59 pg/mL, P<0,001) i koncentracije melatonina u serumu (45,86 pg/mL naspram 18,85 pg/mL, P<0,001) u poređenju sa kontrolnom grupom. Prosečne koncentracije P4 u serumu nisu imale statističku značajnost između grupa. Ovi podaci su potvrdili da deslorelin implantati ne izazivaju "*flare-up*" efekat kod juvenilnih kuja, ali povećanje koncentracije E2 i posebno melatonina u serumu ukazuje na potrebu da se u budućnosti istraže posledice i međusobni uticaj implantata deslorelina i melatonina.