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Reversible estrous cycle suppression in prepubertal female rabbits treated with slow-release deslorelin implants

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ABSTRACT

The aim of this study was to examine the long-term effect of a 4.7-mg deslorelin GnRH analog implant on ovarian function in the prepubertal female rabbit. Seven female rabbits (group 1) were treated with the implant at the age of 60 days. The implant was inserted subcutaneously in the umbilical region. Two animals (group 2) were not treated and served as a control group. The vulva of all 9 animals was examined for the presence of typical cyclical changes, additionally the occurrence of mounting behavior was recorded. Ovarian function was checked by administration of a short-acting GnRH agonist to induce ovulation and pseudopregnancy (0.8 μg of buserelin per animal intramuscularly). Ten days after each treatment with buserelin, blood was collected for progesterone measurement to confirm pseudopregnancy. After implant insertion, the first blood collection (Day 10) was done without preceding induction of ovulation to screen for implant induced ovulation and pseudopregnancy. The implant was *in situ* for 273 days, and during this time span, 12 attempts of induction of ovulation were carried out in intervals of 21 days, beginning at the age of 81 days. Afterward, it was removed under local anesthesia and 3 further inductions of ovulation by the same scheme were conducted. The insertion of the implant led to the establishment of a pseudopregnancy in 2 of 7 animals; the remaining 5 animals did not show elevated progesterone values. Attempts to induce ovulation by administration of the short-acting GnRH analog while the slow-release GnRH analog implant was in place were not successful in treated animals, and progesterone concentrations were basal. The effect was reversible as ovulation could be induced in 2 subsequent cycles in all animals by the third induction of ovulation after implant removal. Induction of ovulation in control animals at the age of 110 and 131 days resulted in elevated progesterone levels after 10 days. No adverse side effects could be observed in implant-treated animals. The typical red coloration of the vulva could be seen in group 2 and after implant removal in group 1. The results suggest that in 5 of 7 rabbits, puberty was delayed by the treatment with the 4.7-mg deslorelin slow-release analog until the implant had been removed. In the other animals, the treatment induced an initial flare-up phenomenon. Afterward, the treatment could reversibly suppress ovarian function in all 7 treated animals.

1. Introduction

By the continuous long-term administration of GnRH analogs, an initial flare-up phenomenon is followed by desensitization of gonadotrophs in the pituitary gland or downregulation of processes responsible for the release of gonadotropins [1], leading to suppression of sexual function [2]. GnRH implants releasing the GnRH analog deslorelin over a prolonged period are licensed for suppression of sexual function in the adult male dog in several countries. Furthermore, GnRH agonists can be used for suppression of the estrous cycle in the bitch [3–6], the queen [7–10], the ferret [11,12], and the rat [13–15].

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Additionally, a delay in the onset of puberty in female and male dogs [5,6,16,17] and in cats [10] could be achieved.

To our knowledge, no studies about the use of GnRH slow-release analogs in the female rabbit exist. In the buck, a case report describes that the treatment with a 4.7-mg deslorelin implant led to downregulation of testosterone for the duration of 7 months and reduction of testicle size by 50%. The effect on fertility could not be evaluated, as no spermiogram was prepared [18]. Another study treated peripubertal male rabbits with the same implant. Testosterone concentrations were similar to the untreated control animals, and spermatogenesis was not affected. Therefore, the treatment is not judged a suitable alternative to surgical castration [19].

The female rabbit does not have a regular estrous cycle, but periods of increased sexual receptivity for 4 to 10 days have been described [20–23]. During these periods, the vulva is often edematous and has a red color [20]. Ovulations are induced by mating, other similar stimuli, and the use of drugs [20]. If no fertilization of the ovulated oocytes occurs, a pseudopregnancy with elevated progesterone concentrations for 17 [24] to 18 [20,25] days will be established. All progesterone values lower than 2 ng/mL should be considered as basal [26]. The aim of the study was to examine the effect of a GnRH slow-release agonist implant containing 4.7-mg deslorelin on ovarian function in prepubertal rabbits. We hypothesized that in the animals receiving the implant, induction of ovulation and pseudopregnancy by the use of the short-acting GnRH analog buserelin would not be possible and that the onset of puberty could be delayed by the treatment.

2. Material and methods

Animal experimentation was performed in the Clinic of Small Animal Surgery and Reproduction, Center for Clinical Veterinary Medicine, Faculty of Veterinary Medicine, Ludwig Maximilian University, Munich, Germany, and approved by the local authority (Gz. 55.2-1-54-2532-41-11, Kreisverwaltungsreferat Munich, Germany).

2.1. Animals and animal housing

Nine 60-day-old female Zika hybrid rabbits were used. They were housed in groups of 2 to 4 animals. No artificial lightening was provided. Hay and water were available ad libitum. Additionally, each animal received 25 g of pelleted food (Canin Kombo; Asamhof, Kissing, Germany) and a constant amount of vegetables per day. At the age of 2 months, the animals from group 1 weighed on average 1.62 kg (1.35–1.87 kg) and the animals from group 2 on average 1.86 kg (1.82–1.90 kg).

2.2. Experimental design and blood sampling

The study was designed as a monocentric, randomized study. Before the treatment, a complete blood count and a serum analysis were performed. The general condition of all animals was assessed daily. A thorough clinical examination of each animal was performed twice weekly, and the animals were observed for mounting behavior for 1 hour. The color of vulva was recorded, and in addition, the perivulvar region was examined for the presence of vaginal discharge as a possible sign of metropathies.

The animals were randomly divided into the study group (group 1; n = 7) and the control group (group 2; n = 2). All animals of the treatment group received a subcutaneous 4.7-mg deslorelin slow-release implant (Suprelorin; Virbac, Bad Oldesloe, Germany) at the age of 60 days (Day 0). Implant insertion was performed lateral of the umbilicus to facilitate implant removal. Ten days after insertion of the implant, blood was collected to screen for implant-induced ovulation. Twenty-one days after insertion of the implant, at the age of 81 days, the first induction of ovulation was carried out. Each induction of ovulation was performed by subcutaneous administration of 0.8 μg of the GnRH agonist buserelin (Receptal; Intervet Germany GmbH, Unterschleißheim, Germany) per animal in intervals of 21 days. Ten days after each treatment with buserelin, 2 mL of blood was collected from the vena auricularis lateralis for progesterone measurement. After insertion and removal of the implant, the animals were examined for the presence of side effects daily for 2 weeks. At the time of implantation, the animals were weighed by the use of a spring scale (BGS technis 8034).

During the period of treatment, which lasted 273 days, 12 attempts of induction of ovulation were carried out (Fig. 1). Finally, the implant was removed under local anesthesia with lidocaine (Lidocainhydrochlorid 2%; bela pharm GmbH&Co.KG, Vechta, Germany). Twenty-one days after removal of the implant, induction of ovulation was carried out for the first time after cessation of treatment with the GnRH implant. Overall, 3 inductions of ovulation were carried out after the implant had been detached (Fig. 1).

To be sure that the animals from the control group had a physiological ovarian function, the animals had to be pseudopregnant in 2 subsequent cycles after induction of ovulation with 0.8 μg of the short-acting GnRH analog buserelin. The induction of ovulation in the control animals was led out at the age of 110 and 131 days and blood collection took place 10 days after each buserelin administration.

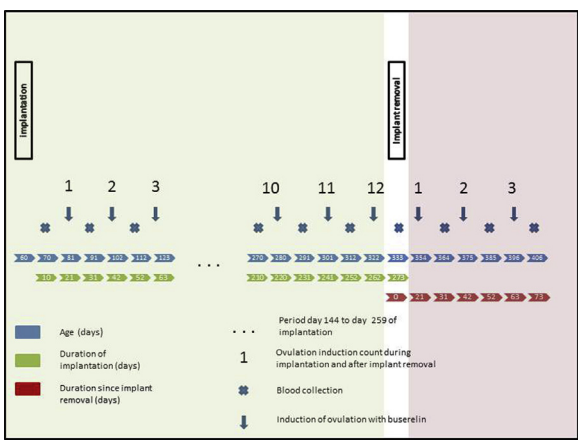

Fig. 1. Overview experimental design animals group 1 during treatment with the GnRH slow-release implant and after implant removal.