Clinical usage of GnRH agonists in small animal reproduction: a review
Stefano Romagnoli
Department of Animal Medicine, Production and Health, University of Padova, Italy

Abstract
Gonadotropin releasing hormone agonists have a variety of effects on the urogenital system as well as on behavior in dogs and cats. Although their official indications are limited to controlling fertility, libido and aggressiveness in male dogs, current available information indicates that their use is effective also in inducing estrus in females, blocking cyclicity in queens, preventing male cats from roaming and urine marking as well eliminating the typical “tomcat odor” from their urine. The blocking action on cyclicity of bitches is accompanied by side effects (prolonged heat, increased risk of pyometra) which make this use not currently advisable in the dog, particularly in older females. There is evidence that GnRH agonists can be at least be partially effective in treating post-spaying urinary incontinence in the bitch. Other clinical applications which await confirmation include prevention of mammary tumor metastatic disease, treatment of androgen dependent diseases (benign prostatic hypertrophy, perianal gland adenomas) or treatment of azoospermia in dogs. Side effects of GnRH agonists have been reported in humans but not in small animals, perhaps due to their recent use and shorter life expectancy of dogs and cats.

Keywords: Gonadotropin releasing hormone, contraception, estrus induction, urinary incontinence, behavior modification, azoospermia

Introduction
Historically, reproduction control in small animals has been achieved by inducing a negative feedback on the hypothalamic-pituitary-gonadal (HPG) axis through administration of exogenous progesterone (P4), testosterone (T) or their synthetic analogues. This approach still remains valid for some indications, as a correct and judicious use or natural or synthetic progestogens or androgens poses no threat to reproductive and general health. However, if used for too long, at excessively high dosages or in the wrong patient progestogens may cause reproductive and metabolic side effects. Therefore, the clinical use of these compounds, although largely safe from all points of view, requires a great deal of care in evaluating the patient, the stage of the reproductive cycle as well as all the potential contraindications for each single case. The possibility to block the HPG axis without introducing steroid hormones into the organism would therefore be very advantageous as it would carry fewer risks for the animal and be cheaper for clients.

Despite their vital role for reproduction, endogenous sex steroids may have negative effects on fertility and general health. Cyclical stimulation of mammary glands or endometrium with endogenous estrogens and progesterone is known to predispose the female to develop conditions such as mammary tumors and endometritis/pyometra. Androgens are known to predispose male dogs to prostatic hypertrophy as well as contribute to the growth of prostatic carcinoma and perianal gland tumors. Therefore, gonadectomy has always been advocated as a means to avoid the risk of developing uterine or mammary diseases in females and prostatic or perianal diseases in males. However, both spaying and castration are irreversible modifications which in some countries are considered not acceptable on cultural or psychological grounds. Also, surgical neutering carries the risk of increased incidence of health problems such as urinary incontinence, obesity, change of temperament and dermatological problems.

A recent development in the field of control of the reproductive cycle in carnivores is the use of gonadotropin-releasing hormone (GnRH) and especially its long acting agonists. Gonadorelin is a synthetic form of GnRH, while compounds such as buserelin, deslorelin, goserelin, triptorelin, leuprorelin and nafarelin are synthetic analogues which are available as human as well as veterinary compounds. For instance, leuprorelin (also known as leuprolide acetate), triptorelin and goserelin are almost exclusively available as human drugs, nafarelin is currently studied for its potential use(s) in controlling reproduction in small animals while deslorelin is already marketed for veterinary use in most western countries as a 2.1 mg, 4.7 mg and 9.4 mg implant; the 2.1 mg implant is marketed for use in horses (Ovuplant™), but its extra-label use in dogs is rather common, while the 4.7 (Suprelorin™) and 9.4 (Suprelorin 12™) mg implants are currently marketed in Europe and Oceania.
for the control of fertility and aggressiveness in male dogs but their extra-label use in cats is currently being evaluated. This paper will review current and potential clinical applications of GnRH agonists in small animal reproduction.

Potential clinical applications of GnRH agonists

Gonadotropin releasing hormone agonists act by initially over-stimulating and subsequently downregulating GnRH receptors at the gonadotropes in the pituitary, thereby suppressing the function of the HPG axis. Such a suppressing action on the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) leads to an arrest of secretion of gonadal steroids as well as their by-products. Such blockade of steroidogenesis can be used in dogs and cats for a variety of indications in prepuberal and adult animals. Some clinical applications have already been tested and demonstrated useful and effective, while others are just the result of work in progress or have not been put into practice yet but are theoretically feasible based on the results of experimental studies.

Indications for prepuberal animals

Postponement of puberty

Subcutaneous administration of an early GnRH agonist to prepubertal male and female dogs daily for 23 months partially or completely suppressed dehydroepiandrosterone (DHEA), androstenedione, testosterone, 5-α androstanes and estrogens in males, and DHEA and estrogens in females. Treatment caused a reduction in testicular and prostatic volume, absence of secondary follicles in the ovary and atrophy of pituitary LH-secreting cells in both sexes. After a recovery period of 14 months both male and female dogs showed puberty and their fertility was normal thereafter. Azagly-nafarelin at the dose of 18 mg in a single depot device was administered subcutaneously to 10 prepuberal beagle bitches and left in situ for one year. None of the bitches came into heat or ovulated while the 10 control bitches came into heat regularly during the study period. There was no difference in body weight and growth rate between treated and control animals, and puberty in treated bitches resumed randomly and in a non-synchronized manner after the device was removed.

Gonadotropin releasing hormone agonists can be used to postpone puberty in cats. We administered a 4.7 mg deslorelin implant to 12 domestic shorthair European cats, nine females and three males of 1.4-3.1 kg body weight and 3-9 months of age. None of the cats had shown signs of puberty prior to the start of the study, and penile spikes were not present in any of the three male cats. Cats were given a GnRH stimulation test (two blood samplings before and one hr after IV of 50 μg gonadorelin) prior to study onset, and blood samples for steroid hormone assay were collected monthly for 24 months. Three of nine queens showed signs of estrus one week following implantation, but estrus signs gradually subdued and did not appear again until the end of the study. Serum T increased in the three tomcats on the post-GnRH sample to adult levels, but penile spikes never appeared and none of the three toms ever showed postpuberal behavior until the end of the study. Similar results in prepuberal queens were obtained when comparing the effect of the 4.7 mg deslorelin implant in 15 treated and 15 control 4-month old queens followed for a maximum of 18 months with physical examinations and vaginal cytology. Average age at puberty was 281±21 and 178±11 days in treated and control queens, respectively, while there was no difference in weight at the end of the study. One treated queen showed clinical and ultrasonographical signs of pyometra 92 days after implantation and was immediately spayed.

Gonadotropin releasing hormone agonists are evidently capable of suppressing the hypothalamic-pituitary-gonadal axis of prepuberal dogs and cats leading to postponement of puberty for a prolonged period of time. In dogs, use of deslorelin in young animals shows an age-dependent response, with pups of four months showing no estrus following implantation while all pups implanted after seven months of age will show puberty within a short time. Only prepubertal administration is capable of avoiding implantation-induced estrus response. However, detailed information on onset of susceptibility to exogenous GnRH around the time of puberty is not available for dogs and cats. We have observed vaginal charatinization and a rise in testosterone in prepubertal queens and tomcats, respectively, following administration of a 4.7 mg deslorelin implant; however, these signs were not followed by puberty, which was instead delayed by the implant. Use of GnRH
agonists can be considered as a safe method to postpone puberty in dogs and queens, while more data are necessary in tomcats to draw the same conclusion (although a similar effect is likely to occur).

**Indications for adult females**

**Contraception**

The gonadal block consequent to the suppression of the HPG axis achieved with a GnRH agonist causes onset of anestrus in the bitch. An implant of goserelin acetate (Goserelin acetate, Zeneca, Milan, Italy), administered SC at the dose of 60 μg/kg every 21 days for 12 months suppressed cyclicity in nine adult bitches reducing circulating levels of estradiol and P4.8 Treatment of adult bitches with 3, 6 or 12 mg deslorelin (Suprelorin™, Peptech Animal Health, Australia) suppressed heat for periods varying between 10 (3.0 mg dose) and 20 (6 or 12 mg doses) months.9 Administration of deslorelin during anestrus or in the early stages of proestrus will inevitably be followed by induction of estrus within 4-8 days after implantation,9,10 while administration in diestrus is not generally followed by heat induction.10 However, although a serum P4 concentration of 5 ng/ml is reported as a potential threshold above which estrus is not induced,9 Fontaine et al. have observed estrus induction in four of 28 bitches treated in diestrus.11 When a GnRH agonist is administered to an anestrous bitch the initial response of the HPG axis is a strong secretion of FSH and LH, followed by estrus, ovulation and development of corpora lutea. Therefore, if breeding occurs during such an induced phase conception will follow, but the ensuing pregnancy will only progress until shortly after day 30 because of the downregulation of gonadotropins leading to luteal failure.10,12 Normal pregnancy followed by parturition may occur if a bitch is administered a GnRH implant during the second half of gestation, as it may take up to four weeks to cause downregulation, thereby leaving enough time for normal whelping of live fetuses to occur. The 9.4 mg deslorelin implant has been used in a few bitches, with interval treatment-return to heat of 11 months.10

In order to avoid inducing estrus following treatment with deslorelin, Wright et al. treated anestrous bitches with daily injections of megestrol acetate at 1.0 or 2.0 mg/kg for 2-3 weeks prior to placement of the implant;12 four of five bitches treated with 1.0 mg/kg megestrol showed heat, while none of 10 bitches treated with 2.0 mg/kg showed heat with duration of suppression varying among individuals.12 When the same 2.0 mg/kg dosage of megestrol was administered orally for eight days starting four days prior to placement of a 10 mg deslorelin implant, only one of 10 bitches showed a post-estrus heat response while four of 10 bitches presented a mild vulvar enlargement.13

In wild carnivores, deslorelin has been used effectively as a contraceptive at doses ranging from 3 mg (foxes) up to 12 mg (lionesses) indicating that dosing in larger individuals should probably be related to body surface area rather than body weight.14 Treatment blocked estrus behaviour in the majority of animals leading to lack of conception even when females were housed continuously with males. Simultaneous administration of norgestomet or proligestone in one lioness and three female wild dogs did not suppress deslorelin-induced estrus. Return to estrus in some wild dogs and lionesses was observed to occur 12-18 months after administration. No adverse effects were observed on social behavior, general health and body weight.14 As secondary sex characteristics tend to disappear following prolonged androgen deprivation, GnRH agonists should be used with caution in male lions as their mane (a feature considered as very important for male lions in most commercial zoos) might disappear.

When administered to adult queens at the dose of 4.7 or 6.0 mg, an implant of deslorelin initially stimulates in most queens follicular growth and estradiol secretion, after which no further evidence of estrus is observed for periods of 4-14 or up to 18-26 months.15,16 In Munson’s study five of 10 treated queens had small estrogen increases after 7.5-14 months at which time they were administered a second deslorelin implant,15 while in our study we did not show any such increase.16 It is not known whether deslorelin-treated queens may ovulate if bred, what is their incidence of spontaneous ovulation and what, if any, is their incidence of premature luteal failure as reported for the bitch (see over). General health and social behavior remained unchanged throughout the study period, and introduction of a male did not reverse the deslorelin-induced cycle suppression.16

235
Estrus induction

Administration of deslorelin in anestrous bitches at the dose of 1.05 mg, 2.1 mg or 4.7 mg will induce resumption of cyclicity within 2-9 days. Administration of 150 IU human chorionic gonadotropin (hCG) at day 42 after the LH peak does not solve this problem as after an initial stimulatory effect on serum P4 a drastic decline is observed over the next few days. When using a 1.05 mg implant (half of an Ovuplant™) premature luteal failure is less likely to occur but some suppression of luteal function is still observed. Incidence of suppression of luteal function can be diminished (or its effects attenuated) by early removal of the deslorelin implant, provided that it is placed in easily accessible places such as the vestibular mucosa, the medial side of the leg or the post-umbilical region. Implant removal can be performed either as soon as a vulvar discharge is observed, at the time of the LH peak or at ovulation. Although comparative evaluations of different removal times have not been performed, if one considers reproductive parameters of various studies no clear advantage has been identified in this respect. In bitches induced to cycle with deslorelin ovulation rate, conception rate, pregnancy rate and rate of premature luteal regression were studied by:

a) comparing treated and control bitches using a 1.05 mg (half of an Ovuplant™) or the entire 2.1 mg implant administered into the vestibular mucosa (VM). Ovulation rate was not calculated, all other parameters did not differ.
b) comparing the VM vs the SC (between the shoulder blades) administration using the 2.1 mg implant. Conception rate was either equal or significantly better and a clear trend for a better pregnancy rate and a lower rate of premature luteal regression were evident for VM (66.7% and 16.7%, respectively) vs SC bitches (37.5% and 37.5%, respectively). A control, non-treated group was not used for this study.
c) comparing treated and control bitches using the 4.7 mg implant. Ovulation and pregnancy rates were similar to controls; conception rate was not investigated; all bitches underwent ovariohysterectomy at day 9-19 post-ovulation, therefore it was not possible to assess occurrence and rate of premature luteal failure.
d) comparing bitches treated in early vs late anestrus using the 4.7 mg implant. Ovulation and pregnancy rates were significantly better for bitches treated in late anestrus. Luteal failure was diagnosed in three bitches, and the only bitch whose owner did not agree to a supporting P4 treatment aborted on day 58 after ovulation. A control, non-treated group was not used for this study.

Deslorelin is certainly an effective drug for estrus induction in bitches; in the studies of Fontaine et al, bitches treated in late anestrus showed heat within 4.2±1.4 days in 97% of cases, ovulation occurred in 83% of cases and quite constantly 12±3 days after treatment, and pregnancy rate was approximately 70%. However, prolonged pituitary downregulation causing luteal failure despite early removal or using half dosing remains an unresolved issue. Likewise, prolonged heats and anovulatory cycles have been observed. As the interval between implant insertion and ovulation is generally short, it has been suggested to remove the implant no later than 15 days post-treatment (even if the bitch has not ovulated yet) in order to avoid unnecessary ovarian stimulation.

Prevention of mammary tumor metastatic disease

The role of gonadal steroids in the development of mammary tumors is well established. Neoplastic transformation of normal cells is thought to be effected by an “initiator”, after which...

---

* Ovulation rate: n of bitches ovulating divided by the total n of bitches
† Conception rate: n of fetuses divided by the n of corpora lutea
‡ Pregnancy rate: n of pregnant bitches divided by the total n of bitches
§ Rate of premature luteal regression: n of bitches in which serum P4 drops to basal levels during pregnancy divided by the total n of bitches
abnormal growth is stimulated by a “promoter”. The mitogenic action of estrogens on canine mammary epithelium has been described. Estrogens are considered potential initiators of neoplastic growth in different species, often in conjunction with other hormones. For instance, the “initiating” role is played by estrogens and prolactin in the rat and mouse, by estrogen plus a placental factor and perhaps a novel pituitary hormone in monkeys and humans. In the bitch, the action of gonadal steroids, especially P4, can create a highly proliferative environment in which an important initiating role is probably played by growth hormone (GH). Under the influence of endogenous or exogenous P4, GH can be secreted by the canine pituitary, and if the progestational stimulus is prolonged GH can be secreted by the mammary gland as well. Therefore, gonadal steroids can have a direct as well as an indirect stimulatory action on the canine mammary gland through the production of their needed co-factor, GH.

Normal and neoplastic mammary tissue features receptors for estrogen, P4, epidermal growth factors and prolactin. The amount of such hormonal receptors decreases proportionately to the increase in the degree of differentiation of neoplastic mammary tissue, with malignant mammary tumors having less hormonal receptors than benign mammary tumors. The use of GnRH agonists has proven effective both in rats with hormone-dependent dimethylbenzanthracene-induced mammary tumors as well as in pre-menopausal women suffering from advanced breast cancer. A recent study looked at the effect of goserelin in bitches with spontaneous hormone-dependent mammary neoplasia. Following assessment of presence of estrogen/P4 receptors on a biopsy of mammary tissue, 18 bitches with hormone-dependent lobular/invasive mammary carcinoma were selected and assigned to a control (no drug) or treated (goserelin) group. The nine treated bitches received an implant of goserelin acetate (Goserelin acetate, Zeneca, Milan, Italy), administered SC at the dose of 60 μg/kg every 21 days for 12 months. Goserelin treatment reduced circulating levels of estradiol and P4 and reduced the size of mammary tumors after three months in all treated bitches, with 88% of them showing a relapse-free survival time of two years. Although these results await confirmation, the use of GnRH agonists for the treatment of canine mammary tumors looks promising provided that clinical cases can be selected on the basis of tumor type and presence of steroid receptors.

Treatment of post-spaying urinary incontinence
The involuntary loss of urine which may occur following spaying in the bitch has a multifactorial origin, as demonstrated by the fact that no single treatment (whether medical or surgical) achieves 100% efficacy. The chronic gonadotropin elevation which inevitably occurs after neutering (because of absence of gonadal steroid negative feedback) has been considered as a potential cause of urinary incontinence in castrated bitches. The hypothesis that a downregulation of gonadotropins using GnRH agonists may improve or fully cure urinary incontinence was initially considered valid following clinical trials in which ovariectomized bitches refractory to the use of α-agonists were successfully treated with a GnRH agonist (leuprorelin, buserelin, triptorelin or deslorelin). Because of the initial increase in FSH-LH release, some protocols included also administration of α-agonist treatment for the first three weeks. Results have been quite positive with periods of continence varying from one to some months following a single treatment with different GnRH agonists. Although chronic administration of a GnRH analogue decreases plasma LH and FSH to basal values, in incontinent bitches there is little if any correlation between the effect on gonadotropin levels and the response to treatment. Serum concentration of gonadotropins appears to be involved, directly or indirectly with the pathophysiology of canine post-spaying urinary incontinence, with a greater role played by FSH. However, the exact pathophysiology of this condition has not been clarified yet.

Administration of deslorelin has no significant effect on urodynamic parameters, even when bitches respond positively to the treatment, but rather seems to modulate bladder function allowing for a larger bladder filling volume at the same bladder pressure. Current clinical information suggests that when treated with a 4.7 mg deslorelin implant, previously incontinent bitches will show approximately a 50% recovery rate, with another 10-20% of bitches showing incomplete response characterized by a reduction in the frequency of incontinence episodes and/or an improvement in the response to pharmacological treatment with α-agonists or estriol. We have also used the 9.4 mg implant in a few cases, with periods of continence being prolonged up to almost a year (data not shown). In a pilot study that we conducted in Brazil on efficacy of a 4.7 mg deslorelin implant for
treating canine post-spaying urinary incontinence, three of six incontinent bitches were fully continent for six months following treatment, and a considerable improvement (continence of one to three months) was observed in the other three bitches (data not shown).

**Indications for adult males**

**Contraception**

In male dogs, the use of a GnRH agonist will cause a reversible blockade of fertility. Early studies showed that a controlled-release microsphere formulation providing a daily release of 100-200 mg of a LH-RH agonist causes a temporary increase in plasma T concentration during the first few days (from 1.5 to 43.5 ng/ml) followed by a decrease to castration levels for a prolonged time. Similar results were later obtained with implants of 6.6 mg buserelin, 18.5 mg azagly-nafarelin, or 4.7 mg deslorelin. Dogs treated with implants of 6.0 mg deslorelin typically show initially an acute increase in concentration of LH and T, with both hormones becoming undetectable after about two weeks; histologically, disruption of seminiferous tubules and epithelial atrophy are evident as early as day 16 and 41, respectively; clinically, they start becoming infertile within a six week period and resume normal fertility only after several months. A chronic treatment with a 4.7 mg deslorelin implant causes a progressive loss of pituitary responsiveness to GnRH over a period of four weeks with a lack of response to stimulation of the HPG with GnRH or LH already evident at three weeks and being complete at 40 days after implantation. The decrease in testicular size may vary from a 20-30% reduction during the first few months up to 50-60% at 6 months post-treatment. In male dogs treated with a deslorelin implant, complete sterility is thought to occur within a two month period. We recently looked at semen quality in six adult dogs treated with a 4.7 mg deslorelin implant. Complete sterility (based on presence of <10 million of progressively motile sperms (PMS) and semen volume <0.5 cc) was achieved between 23 and 84 days post-treatment, with two dogs being still fertile around 55-60 days post-treatment and beyond. Also, semen motility and total count actually improved during the first month post-treatment, while semen morphology was unaffected throughout the study, although all dogs eventually became aspermic. As libido might increase during the first few weeks post-treatment, clients should be advised about the initial improvement in fertility parameters as well as of the time needed for deslorelin to achieve complete efficacy. Once the implant finishes its action or is removed, testicular size starts to increase after a few weeks, T concentrations return back to normal in about seven to eight weeks and testicular volume is back to normal in about six months. Considering the normal canine spermatogenic cycle of approximately nine weeks duration, male dogs treated with deslorelin will likely prolong their temporary sterile phase for as long as nine weeks on top of whatever is the period of recovery, depending on their testicular conditions at the end of deslorelin treatment.

In adult tomcats the use of a 4.7 mg deslorelin implant stops roaming, eliminates the classical tomcat urine odor, eliminates penile spikes and reversibly blocks fertility; such effects are generally observed in most cats by the end of the second month post-treatment and in the 15 cats of our study lasted 15±3 months. We observed a partial failure of efficacy in one of 15 cats, in which basal testosterone decreased to basal levels but there was still a normal response to periodic GnRH stimulation tests. Another client-owned cat (not included in the above study) treated with a 4.7 mg deslorelin implant became more affectionate with his owner but remained aggressive with other cats and kept breeding queens, one of which gave birth to a normal litter when mated four months after treatment. In tomcats deslorelin acts rapidly and is highly efficacious, but may be characterized by a failure rate of <10% which needs to be investigated further.

**Reduction of aggressiveness and libido**

The decrease in serum T concentration which follows downregulation of the HPG axis will cause individual animals to become less aggressive. We observed a decrease in aggressiveness based on subjective assessment of number and degree of cage fights while studying serum T secretion in shelter dogs treated with a 4.7 mg deslorelin implant. In our clinical experience, the 4.7 mg deslorelin implant is effective in reducing libido and aggressiveness in male dogs, although occasional failures are encountered; these are probably due to the fact both these aspects of a dog’s temperament...
are not fully dependant on serum T concentration, but there is also a role of experience in their development.

Treatment of androgen-dependent diseases

Benign prostatic hyperplasia. Benign prostatic hyperplasia (BPH) is the most common canine prostatic disorder, with more than 50% of intact dogs developing histologic evidence of BPH after five years of age. Hyperplasia is probably due to an altered androgen:estrogen ratio, and requires the presence of the testes to start and continue to develop. Dihydrotestosterone (DHT) within the prostate gland probably serves as the main hormonal mediator for hyperplasia. Castration is commonly considered the best treatment as the drastic decrease in androgen secretion causes a 70% decrease in prostatic size (due to atrophy) within nine weeks. Following administration of a GnRH agonist, prostatic size decreases in parallel with the decrease of T. When five adult dogs were implanted with deslorelin at a dose of 0.5-1.0 mg/kg body weight, their prostatic volume decreased more than 50% from week six through week 44, and serum T concentrations decreased 90% from week eight through 32 of treatment when compared to controls. Similar results on prostatic growth were observed following treatment with a 6.6 mg buserelin implant, with disappearance of prostatic cyst and prostate returning to approximate pre-implantation volume by week 48. We have observed disappearance of conspicuous (>17 mm diameter) prostatic cysts following treatment with a 4.7 mg deslorelin implant as well as of larger (20x25 mm) prostatic cysts in six adult male dogs with clinical signs of BPH with a 4.7 mg deslorelin acetate administered every six months; an improvement of the clinical situation of all treated dogs was observed without any additional pharmacological treatment already at the first follow-up visit (one month after implant administration) and no further sign of prostatic disease has been observed subsequently in all dogs without any other type of pharmacological treatment being administered (unpublished observation).

Perianal gland adenomas. Perianal gland adenomas are observed in adult male dogs, with adenomas developing about 4.5 times more commonly than carcinomas. Perianal gland adenomas are considered a hormone-dependent disease for which castration (without excision of the gland) can be a successful treatment as it promotes regression without recurrence. We have treated two dogs with perianal gland disease, a 7.1 kg, 16-year old Dachshund Teckel and a 21.5 kg, 12-year old mongrel dog. Both had clinical signs of perianal gland disease characterized by presence of a round, irregular 2-4 cm diameter mass which had developed over the past one to two months. In both cases, administration of an implant of 4.7 mg deslorelin acetate was sufficient to cause a long-lasting regression of the perianal mass without any additional treatment (Romagnoli, unpublished observation).

Treatment of azoospermia due to hypersecretion of FSH

In humans and animals, FSH plays an important role in promoting and maintaining spermatogenesis by binding to specific receptors on the Sertoli cells, thereby stimulating the Sertoli cells to closely interact with germ cells allowing a normal spermatogenic process. Secretion of FSH by the pituitary is regulated by testicular androgen production and, at least in humans and rats, by inhibin which is secreted by the Sertoli cells. In men with primary testicular disorders, Sertoli cell dysfunction is suspected based on an increase in FSH levels and confirmed on histology of a testicular fine needle aspirate or biopsy. Although there is little information on the role of FSH on canine azoospermia, FSH plays an important role in spermatogenesis in the canine, and chronically elevated FSH levels are likely to be associated with spermatogenic arrest in the dog like in other species. In men with a) severe oligozoospermia, b) high FSH concentration and c) low Sertoli cell function (evidenced by inhibin B secretion or testicular histology), suppression of the high endogenous FSH levels with the use of a GnRH agonist combined with low exogenous FSH administration causes a rise in inhibin B production reflecting an improvement of Sertoli cell condition with positive effects on spermatogenesis. In the dog, the main source of inhibin is not the Sertoli cell but rather the Leydig cell, therefore it is not clear whether the specific type of azoospermia treated in men by Foresta et al. with a combined GnRH agonist-FSH therapy could benefit from the use of a GnRH agonist. However, as we gain more information on canine azoospermia, canine Sertoli cell function...
and source of inhibin secretion, a similar clinical application may become useful in the future also in the dog.

**Side effects of GnRH agonists**

The use of GnRH agonists in the dog is considered safe. No immediate side effects are generally noticed following implant placement, and no adverse effects have been reported in long-term studies performed in male dogs.\(^7,^9,^55\) As the prolonged use of a GnRH agonist causes a chemical castration, one might think that side effects of both types of castration could be the same. From this point of view, treating a dog with a GnRH agonist implant might be considered as a way of checking on side effects of neutering before actually performing gonadectomy.\(^38\) However, the effects of a chemical castration differ from the effects of a surgical castration in that the latter is characterized by high serum gonadotropin concentrations (because of the lack of negative feedback from gonadal steroids on pituitary release of gonadotropins), while in individuals treated with a GnRH agonist both gonadal steroids as well as pituitary gonadotropins are absent from the general circulation.

Incidence and type of side effects following chronic administration of GnRH agonists have not been studied in dogs. However, the rather common use of leuprorelin and other GnRH agonists as a chronic treatment in men with prostatic cancer has allowed investigation of this problem highlighting a wide range of side effects related to muscle and bone metabolism, glucose homeostasis, endocrine and reproductive function as well as some local skin reactions at the site of implant. Gonadotropin releasing hormone agonists decrease bone mineral density and increase fracture risk, increase weight and fat mass, and decrease lean body mass thereby affecting muscular strength.\(^56\) Insulin resistance has also been reported in men undergoing chronic treatment thus raising the concern that GnRH agonists may also increase the risk of diabetes mellitus and cardiovascular disease.\(^57\) Subclinical pituitary tumors present at the time of treatment may be stimulated to progress: pituitary adenomas in men treated with a GnRH agonist have been reported to grow and cause symptoms of intracranial hypertension.\(^58\) In men with spermatogenic failure undergoing short-term treatment with Leuprorelin (four months) loss of libido and erectile dysfunctions are occasionally observed towards the end of the treatment period.\(^53\) Currently, it is recommended that routine use of GnRH agonists in men with long life expectancy should be carefully evaluated weighing advantages and disadvantage of GnRH agonists (still considered an excellent treatment for prostate cancer) vs other types of treatment such as GnRH antagonists, androgen antagonists or estrogen agonists.\(^57\)

In humans, “**Additional research is needed to characterize better the unintended effects of androgen deprivation therapy and develop optimal strategies to prevent osteoporosis, obesity and obesity related disease.**”\(^59\) Although the same consideration applies to our canine patients, musculoskeletal side effects of GnRH agonists (especially osteoporosis) in dogs are likely to be less relevant than in men because of shorter life expectancy, and occurrence of local skin reaction has not been reported so far in our patients. However, side effects on glucose metabolism should probably be investigated in the dog. Furthermore, although incidence of pituitary tumors in the dog is very rare, pituitary adenomas constitute approximately 80% of the causes of canine Cushing’s disease.\(^60\) Almost all of the dogs with Cushing’s disease are ≥ 6 years of age, and more than 75% of them are ≥ 9 years of age.\(^60\) As this is the same age range in which canine BPH is more common, a thorough collection of history and a complete cell count and serum biochemistry are warranted prior to administration of a GnRH agonist implant for the treatment of BPH in adult to older dogs.

**Conclusions**

Several factors make GnRH agonist compounds unique:

a) the novelty of their pharmacological mechanism, which achieves a downregulation of the HPG axis without “adding” any other hormone, but rather “removing” all hormones from the general circulation;

b) the highly selective inhibitory action at the level of the pituitary gonadotropes

c) the good efficacy in blocking female steroid hormone secretion and the high efficacy in blocking androgen secretion

d) the reversibility of their effects on gonadal secretion which makes their administration a “reversible chemical castration”.

240
In the bitch, the use of GnRH agonists is still characterized by the hardly avoidable side effect of estrus induction. The administration of a progestogen a few days before the placement of an implant appears to work, although it makes the use of such agonists cumbersome and less applicable for contraceptive purposes in the bitch. Furthermore, the prolonged release of GnRH (prior to down regulation) causes prolonged P4 secretion which may worsen a subclinical cystic endometrial hyperplasia causing a clinical uterine condition (which would probably have developed anyway albeit in a longer time). Such sequence of events may be erroneously perceived by the owner as due to the treatment. Therefore, the use of a depot GnRH agonist to inhibit reproductive cyclicity in adult or older bitches should not be decided without making sure that the owner has fully understood advantages and (potential) disadvantages of such treatment.

It should be noted that veterinary GnRH agonist preparations are long-term compounds whose length of action is 6–12 months. This makes these drugs interesting for human doctors as GnRH agonist-based drugs available on the human market only last for a few weeks. The possibility to induce a temporary sterility might be interesting as a way to achieve contraception in men. Therefore, small animal clinicians should be aware that their misuse in humans would carry serious ethical as well as legal implications.

**Bibliography**


