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# Applications of GnRH in the control and management of fertility in female animals☆

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**Abstract**

Gonadotropin releasing hormone (GnRH) has long been recognized as a potential target for the control and management of fertility in female animals. Attempts to apply GnRH-based technology to manage fertility have focussed on the development of GnRH agonists, antagonists and vaccines. All of these methods have potential, but the widespread application of these technologies has been limited to date.

The greatest advance in the use of GnRH-based technology for long-term fertility control in recent years has been the development and commercialization of depot formulations that release GnRH agonists for periods of up to 1 year. These products have a broad range of potential applications in production and domestic animal management.

The further development and commercialization of GnRH vaccines has been hampered by the variability of response between individual animals. The need to use adjuvant and multiple boosters also make this a less attractive option than the current GnRH agonist technology. However, GnRH vaccines have the advantage that they do not induce the initial stimulatory response that follows GnRH agonist administration. GnRH antagonists and GnRH-toxin conjugates show promise but are in an earlier phase of development. To date, no depot or long-acting formulations of antagonists have been developed. GnRH-toxin conjugates have yet to achieve permanent sterilization, but further dose-response trials may advance this approach.


*Keywords:* GnRH; Female contraception; Dosage; Drug delivery

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## 1. Introduction

GnRH is a desirable target for contraception because it acts through specific, high affinity receptors on gonadotropes. Traditionally, there are three different ways that GnRH can be employed to inhibit reproduction by direct suppression of the pituitary-gonadal axis at the level of the gonadotrope: (1) chronic administration of GnRH agonists causing down regulation of GnRH receptors and desensitization of pituitary gonadotropes; (2) immunization against GnRH resulting in the neutralization of GnRH in the hypophyseal portal blood by antibodies; and (3) the use of GnRH antagonists to block pituitary GnRH receptors to occupancy by endogenous GnRH (Fraser, 1982). A more recent phenomenon has been the development of GnRH-toxin conjugates that disrupt pituitary gonadotropes (Sabeur et al., 2003).

Long-term fertility control agents based on GnRH are of interest for the management of reproduction in humans, domestic animals and wildlife. Control of reproductive activity in farm animals is an important management issue from both a behavioral and fertility standpoint, as is the case with domestic dogs and cats. Historically, fertility control has been achieved through surgical sterilization. However, in some species the permanent nature of these procedures is a disadvantage. Other disadvantages include the associated trauma, production setbacks and potential death (D'Occhio, 1993). Fertility control has also become a popular concept for the management of highly valuable but overabundant wildlife species. Here the aim is to decrease population size by reducing the fertility of the population. Since GnRH is highly conserved in mammals, fertility control technology founded on this hormone has a wide range of applications in different species.

## 2. GnRH agonists

### *2.1. GnRH agonists and pituitary down regulation*

GnRH agonists are peptides that are similar to GnRH but are modified at sites of enzymatic degradation of GnRH. This increases resistance to peptidases and enhances receptor-binding affinity, with GnRH agonists having a longer half-life in circulation. Substitution of a D-amino acid instead of the glycine at position 6 and replacement of the C-terminal glycinamide residue with an ethylamide group produces agonists that are up to 200 times more potent than native GnRH (for review see Padula, this volume; Karten and Rivier, 1986). GnRH agonists were originally developed to treat infertility but paradoxically inhibited reproduction because the importance of pulsatile administration had not been realized (Schriock, 1989). This discovery led to numerous indications for the use of GnRH agonists today, including contraception and the treatment of hormone-dependent diseases.

GnRH agonist treatment initially induces a large increase in LH and FSH concentrations (the acute phase), which can last for several days, followed by a return to basal levels (D'Occhio et al., 2000). Continued exposure abolishes pulsatile secretion of LH as a result of down regulation of GnRH receptors on gonadotrope cells (Hazum and Conn, 1988) and an uncoupling of second messenger systems (Huckle and Conn, 1988). This results in a decrease in the synthesis of LH and FSH, which appears to be effected specifically through

Table 1
Structure, potency, dose and duration of slow release GnRH agonist formulations

| Trade name | Agonist | Structure | Relative potency[a] | Route and formulation | Dose (mg) | Duration (month) | Reference |
|---|---|---|---|---|---|---|---|
| Zoladex® | Goserelin | [D-Ser(But)$^6$, AzaGly$^{10}$]GnRH | | SC depot polymer implant | 3.6 | 1 | Fraser (1988) |
| Zoladex LA | Goserelin | | | | 10.8 | 3 | Fraser (1988) |
| Suprefact® | Buserelin | [D-Ser(But)$^6$, Pro$^9$Net]GnRH | 20 | SC depot polymer implant | 3–6 | 3 | Fraser, (1988) |
| Lupron Depot® | Leuprolide | [D-Leu$^6$, Pro$^9$Net]GnRH | 15 | IM microspheres | 3.75–30 | 1, 3 or 4 | Periti et al. (2002) |
| Viadur® | Leuprolide | | | SC osmotic pump implant | | 12 | Fowler et al. (2000) |
| Decapeptyl C.R. | Tryptorelin | [D-Trp$^6$]GnRH | 100 | Microspheres | 7.5 | 1 | Schneider et al. (1998) |
| Suprelorin® | Deslorelin | [D-Trp$^6$, Pro$^9$Net]GnRH | 114 | IM depot implant | 6 | 6 | Trigg et al. (2001) |
| Not yet named | Histrelin | [D-His(Bzl)$^6$, Pro$^9$Net]GnRH | 210 | SC hydrogel implant | 50–60 | 12 | Schlegel et al. (2001) |

SC, subcutaneous; IM, intramuscular.
[a] In vitro potency relative to GnRH.

suppression of production of β-subunit mRNA (Aspden et al., 1997). These conditions affect normal pituitary function such that the pituitary response to endogenous GnRH is impaired. The end-point of these changes is a decline in the concentration of gonadal steroids. In females this is accompanied by an inhibition of follicular development as FSH secretion is suppressed below the threshold required for follicular development and inhibition of the oestrogen induced positive feedback mechanism and ovulation (reviewed by Fraser, 1993). A lack of pulsatile secretion of LH is maintained as long as the GnRH agonist is present above a threshold in the circulation (D'Occhio and Aspden, 1996). The chronic effects of GnRH are further reviewed (this volume).

### 2.2. Delivery

While the potential fertility control applications of GnRH agonists have been recognized for almost three decades, successful development of a commercial product for animals has been limited by failure to develop a suitable delivery system (Trigg et al., 2001). Recent development of bio-compatible GnRH agonist formulations which are easy to use, cost effective and release sufficient quantities of GnRH agonist over long periods of time are now overcoming the previous impediments to long-term fertility control applications (Table 1). The mode of delivery ranges from smooth microspheres (20–30 μm diameter) suspended in vehicle, which are administered by subcutaneous or intramuscular injection, to depot polymer implants that are injected subcutaneously. The majority of these formulations have been developed for the treatment of GnRH-dependent diseases in humans and have a lifespan of 1–3 months. To date only one product has been developed specifically for long-term (6 month) fertility control of domestic animals. This product, with the trade name Suprelorin, releases the GnRH agonist deslorelin from a matrix consisting predominantly of low-melting point lipids and biological surfactant (Peptech Animal Health Sydney Trigg et al., 2001). It has been approved for sale in male dogs in New Zealand and Australia in a 6 month duration form, and a 12 month product is in advanced development for both sexes.

### 2.3. Long-term fertility control

Administration of GnRH agonist formulations can achieve long-term reversible suppression of the pituitary–ovarian axis in a wide range of species (Table 2). Treatment of cats with implants containing 6 and 12 mg of deslorelin suppressed oestradiol secretion for periods of at least 14 months in 80% of animals (Munson et al., 2001). Comparable levels of response to the same peptide have been observed in bitches (Trigg et al., 2001). Large-scale trials of similarly formulated deslorelin in female cattle have demonstrated that implants containing higher doses (12 mg) can inhibit reproduction for >300 days in 100% of animals and >400 days in 90% of animals ($n = 99$) (D'Occhio et al., 2002). These figures demonstrate the extremely high contraceptive success rate achieved using these products. The long duration of release of agonists like deslorelin (1 year) suits livestock production schedules and domestic pet veterinary regimes.

One of the advantages of GnRH agonists is that contraception is effected after a single injection without the need for use of adjuvants. Treatment with agonists has so far proved to be safe, with no serious side effects. Occasionally animals will develop a local reaction at

Table 2
Contraceptive success and duration following treatment with slow-release GnRH agonist formulations in six mammalian species

| Species | Agonist | Dose (mg) | *N* | Oestrus induction | Infertile (%) | Duration (mean ± S.E.M.) (range) (days)[a] | Reference |
|---|---|---|---|---|---|---|---|
| Cats | Suprelorin | 6 | *C* = 5<br>*T* = 5 | Yes[b] | 100[b] | 333 ± 39 (240–420) | Munson et al. (2001) |
| Cats | Suprelorin | 12 | *C* = 5<br>*T* = 5 | Yes[b] | 100[b] | 330 ± 31 (225–420) | Munson et al. (2001) |
| Dogs | Suprelorin | 3<br>6<br>12 | *T* = 8<br>*T* = 8<br>*T* = 9<br>*C* = 10 | Yes (50%) | 100[c,d] | 321 ± 42[c,d]<br>438 ± 105<br>465 ± 51<br>165 ± 15 | Trigg et al. (2001) |
| Heifers | Suprelorin | 8<br>8<br>12 | *T* = 76<br>*T* = 84<br>*T* = 99<br>*C* = 59 | ? | 97[e,f]<br>100[e,f]<br>100[e,f] | 231 ± 3 (*n* = 9)<br>244 ± 13 (*n* = 8)<br>336 ± 3 (*n* = 20) | (D'Occhio et al., 2002) |
| Heifers | Buserelin | 6<br>12 | *T* = 5<br>*T* = 5 | ? | 100[c] | 48.4 ± 3.8<br>87.4 ± 17.4 | D'Occhio et al. (1996) |
| Heifers | Suprelorin | 5<br>10 | *T* = 8<br>*T* = 9 | ? | 88[c]<br>100[c] | 203 ± 26 (111–280)<br>170 ± 28 (70–280) | D'Occhio et al. (1996) |
| Wapiti | Leuprolide | 32.5 | *T* = 4<br>*C* = 5 | ? | 100[c,f] | 225 | Baker et al. (2002) |
| Cheetahs | Suprelorin | 6<br>12 | *T* = 8<br>*T* = 8 | Yes (31%) | 100<br>100 | >485c[c,d]<br>>640[c,d] | Bertschinger et al. (2001)<br>Bertschinger et al. (2002) |
| Wild dogs | Suprelorin | 6 | *T* = 6 | ? | 83 | 365[c] | Bertschinger et al. (2001) |

*N*, number of treated (*T*) and control (*C*) animals; >, trial ongoing and animals still to breed; *n*, refers to the number of animals the mean was calculated from (i.e. calculated on the first animals to resume cycling).

[a] Single values represent the earliest resumption of reproductive activity in the group.
[b] Determination of fertility/oestrus based on plasma oestradiol.
[c] Determination of fertility/oestrus based on plasma progesterone.
[d] Determination of fertility/oestrus based on vaginal cytology.
[e] Determination of fertility/oestrus based on ovarian histology.
[f] Determination of fertility/oestrus based on pregnancy/birth.

the injection site, e.g. in cats minimal oedema developed at the site of implant insertion for 3–5 days (Munson et al., 2001), but these effects were transient and not widespread. In dogs, there was no evidence of inflammation or oedema following treatment of 55 animals (Trigg et al., 2001), and subsequent treatment of 387 dogs (T. E. Trigg, unpublished observations).

The results of numerous studies suggest that a longer duration of fertility control can be achieved using higher doses of agonist within similar formulations. In male dogs there was a positive relationship between the dose of agonist (mg $kg^{-1}$) and the duration of suppression

(Trigg et al., 2001). Similar relationships have been observed in heifers (D'Occhio et al., 2002). The reason(s) for this dose-dependent increase in duration are not clearly understood. It is possible that a higher starting dose of agonist in a slow release system means that the release rate can be maintained above a theoretical critical threshold for down regulation for a longer period of time. It is also possible that the pituitary takes longer to recover from a higher dose. The exact nature of the dose-response relationship for GnRH agonist-induced pituitary down-regulation requires further investigation, as it does not always hold true for all species (Table 2).

The initial stimulatory gonadotropin response to GnRH agonist treatment can induce oestrus in some species. In cats this was characterised by an initial oestrus-like increase in faecal oestradiol concentrations in all animals (Munson et al., 2001). In dogs, oestrus was generally induced within 4–8 days when plasma progesterone concentrations were $<5\ ng\ ml^{-1}$ (Trigg et al., 2001). This agonist-induced oestrus can be suppressed in bitches by progestin treatment initiated before agonist administration (2 mg progestin $kg^{-1}$ body weight orally for 1 week before and 1 week after) (Wright et al., 2001). This dose needs further titration and other progestin products should be analyzed. Trials should also be conducted on a range of species, as simultaneous progestin and GnRH agonist treatment in wild carnivores did not prevent agonist-induced oestrus (Bertschinger et al., 2001). Although agonist-induced oestrus has been observed in many species, not all animals which display oestrus behaviour will allow mating, e.g. female cheetahs and lionesses (Bertschinger et al., 2001).

There can be a wide range of variation between individuals in the interval to resumption of oestrous cycles during GnRH agonist treatment. This variability may be the result of genetic variations in the sensitivity of individual animals to GnRH-induced down-regulation. As the variability is often greatest at lower doses it may represent a dose-response relationship where a particular dose may be sub-threshold for some individual animals. An alternative hypothesis is that there may be some variability in the implant manufacture process.

There also appears to be a proportion of animals that continue to cycle during GnRH agonist treatment, i.e. 'non-responders'. The proportion of these animals can be difficult to determine in larger scale trials that do not regularly monitor progesterone concentrations or ovarian cycles, e.g. if you get a much shorter duration of action in an individual, is this 'non-response' or is this an earlier return to oestrous cycles for a different reason? There is sufficient data to determine that non-responders are present at a very small percentage in some populations (e.g. heifers, wild dogs). The basis of this variability is probably genetic, as repeated treatment of animals and administration of higher doses does not seem to elicit a contraceptive response (Herbert, unpublished data from kangaroo trials).

## 3. Immunization against GnRH

Active immunization against GnRH creates an immunological barrier between the hypothalamus and the anterior pituitary gland. Antibodies bind to GnRH in the hypothalamo-hypophyseal portal circulation, which prevents GnRH from binding with receptors on pituitary gonadotropes. This results in suppression of gonadotropin secretion, inhibiting follicular development and ovulation, as well as reproductive behavior. Because

Table 3
Contraceptive success and duration following immunization against GnRH in four mammalian species

| Species | Antigen | Adjuvant | Booster(s) (wppv) | *N* | % immune response | % infertile | Infertility duration | Reference |
|---|---|---|---|---|---|---|---|---|
| Heifers | GnRH-KLH | Freund's | 8 | *C* = 9<br>*T* = 30 | 100[b] | 80[c,d] | >28 weeks | Adams and Adams (1990) |
| Heifers | GnRH-OVA (Vaxstrate®) | DEAE | 16 | *C* = 200<br>*T* = 400 | ? | 82[d] | >207 days | Hoskinson et al. (1990) |
| Chinese pigs | GnRH-OVA | Specol | 8 | *C* = 12<br>*T* = 12 | 100[b] | 83[c,d] | >18 weeks | Zeng et al. (2002) |
| White-tailed deer | GnRH-KLH | Freund's | 4, 52 | *C* = 4<br>*T* = 8 | 100[b] | 88[e] | Insufficient data | Miller et al. (2000) |
| White-tailed deer | GnRH-OVA | DEAE-dextran | 4, 8, 12, 41 | *C* = 4<br>*T* = 4 | 100 | 50[c] | <60 weeks | Becker et al. (1999)) |
| Mares | GnRH-BSA | Equimune® | 3, 6, 10 | *C* = 1<br>*T* = 3 | 100[b] | 66[c,d] | 13–15 months | Dalin et al. (2002) |
| Dogs | GnRH-KLH | Threonyl-MDP | 3, 6 | *T* = 8 (sc)<br>*T* = 8 (im) | 100 | 0[c]<br>50[c] | 14 weeks<br>>10 weeks | Gonzalez et al. (1989) |
| Cats | IPS-21[a](10 μg)<br>IPS-21(100 μg) | | 4, 96<br>4, 96 | *T* = 5<br>*T* = 5 | 100<br>100 | 100[c]<br>100[c] | >2 years<br>>2 years | Robins (2002) |

wppv, weeks post primary vaccination; *N*, number of treated (*T*) and control (*C*) animals.
[a] Recombinant vaccine.
[b] Immune response significantly lower in non-responders.
[c] Determination of fertility based on plasma progesterone.
[d] Determination of fertility based on uterine and ovarian histology.
[e] Determination of fertility based on births.

GnRH is a weak antigen (due to its low molecular weight) and also a 'self' hormone, it needs to be conjugated to a large carrier in order to elicit an immune response. Common carriers include ovalbumin (OVA), keyhole limpet hemocyanin (KLH), tetanus toxoid (TT) and diptheria toxoid (DT) (Talwar, 1997).

Immunization against GnRH was initially used to gain a further understanding of the role of GnRH in mammalian reproduction. However, scientists soon realized the potential therapeutic applications of this approach for both human and domestic animal medicine. Active immunization against GnRH has been investigated in a range of domestic animals and wildlife species (Table 3). Contraceptive success rates typically range from 50 to 90%, with occasional 100% success rate in some small trials. Long-term fertility control (i.e. ~12 months) can be achieved with this approach, but usually requires multiple vaccinations. The duration of contraception is typically quoted from the time of primary vaccination, which can make comparison with other "single-shot" methods misleading.

Immunization against GnRH has the advantage that it does not have the initial stimulatory acute phase that GnRH agonists have, which thereby avoids the problem of treatment-induced oestrus/ovulation. However, this immunocontraception approach introduces a range of other problems.

The primary problem with immunization against GnRH (or indeed all other 'self' antigens) is the highly variable response between individual animals. In almost all trials it is evident that non-responders are present within the population. These are animals that do not have a contraceptive response to the vaccine. In many cases reproductive function is maintained despite an immunological response to the vaccine. When Chinese female pigs (Zeng et al., 2002), feedlot heifers (Adams and Adams, 1990) and mares (Dalin et al., 2002) were immunised against GnRH, the non-responders mounted immune responses that were significantly lower than those successfully immunocontracepted. This suggests there is a critical immunological threshold that must be attained to adequately neutralize GnRH (Adams and Adams, 1990; Zeng et al., 2002). In the case of feedlot heifers the variability was unlikely to be the result of insufficient dose of immunogen as the number of non-responders was evenly spread across three different dosage groups (Adams and Adams, 1990). It is widely thought that the variation in immune response between individual animals is a result of genetic variation (Cooper and Herbert, 2001). If this genetic foundation of non-response is heritable, the number of non-responders will increase with successive generations, particularly if there is high selective pressure (e.g. if non-responders are the only individuals to breed). Under this scenario the lifespan of these products would be severely curtailed.

Another drawback is that most immunization regimes require repeated secondary immunizations to ensure the production and maintenance of high anti-GnRH titres. In some cases it may take up to three immunizations to see a significant antibody response compared with control animals (e.g. mares; Garza et al., 1986). The need for repeated immunizations can be costly, time consuming and impractical, particularly in large-scale farming operations and free-range wildlife situations. Development of single-injection controlled-release vaccines of 1 year duration could overcome this drawback (Turner Jr. et al., 2002), but they are difficult to successfully develop.

Currently there is a need to use an adjuvant to obtain sufficient immunogenicity to inhibit reproduction. In a study of white-tailed deer, the use of diethylaminoethyl (DEAE)-

dextran as the adjuvant caused local reactions ranging from inflammation, minor alopecia and erythema to dry necrosis, sloughing of the skin and purulent lesions (Becker et al., 1999). In heifers, transient injection site reactions to DEAE were noted in 30% of animals (Hoskinson et al., 1990). Mares immunised against GnRH–BSA with Equimune® adjuvant showed a range of reactions to the booster ranging from fever to oedematous swelling and front leg lameness (Dalin et al., 2002). These reactions at the injection site are not uncommon with adjuvants and animal ethics committees and regulatory bodies throughout the world either do not allow their use or are fazing out the use of some adjuvants, in particular Freund's adjuvant, because of animal welfare concerns. These negative effects can be reduced in some species by reducing the amount of adjuvant used (Dalin et al., 2002), altering the route of administration (e.g. subcutaneous instead of intramuscular) and by using alternative adjuvants (Leenaars and Hendriksen, 1998; Leenaars et al., 1998). Some of these alternative adjuvants (e.g. Specol) cause fewer pathological changes than Freund's adjuvant.

Other concerns about immunization against GnRH and other types of immunocontraception relate to the potential for unknown side-effects. The unforseen consequences of provoking an autoimmune reaction are a concern that may limit the development of a contraceptive vaccine for women (Baird, 2000). In addition, there is concern that as animals with a poor immune response are less likely to be affected than other animals, immunocontraception may artificially select for immunocompromised animals which are more susceptible to diseases (Oogjes, 1997).

The concerns outlined above are likely to affect the successful commercialization of GnRH vaccines. Other impediments include the high cost of antigen, which results from a low efficiency of conjugation. In addition, the fact that these vaccines will be active in humans means that there is also a risk of self-inoculation. This risk is greater with a vaccine than with a GnRH agonist implant. The first GnRH vaccine that was released commercially for prevention of pregnancy in animals (Vaxstrate®, Peptech Animal Health Pty Limited, North Ryde) is no longer on the market due to the need for two injections.

Recent advances in GnRH vaccine technology have included the development of a recombinant vaccine. The antigen consists of eight copies of GnRH linked to each end of a proprietary carrier protein, making it greater than 50 kDa, which is large enough to elicit an immune response (reviewed by Rhodes and Moldave, 2002). This vaccine has successfully inhibited reproduction in 100% ($n = 10$) of prepubertal female cats for periods in excess of 2 years. The vaccine was also effective in 75% ($n = 4$) of male cats following two immunizations (Robins, 2002).

## 4. GnRH antagonists

GnRH antagonists act on the same receptors as native GnRH. When administered, they bind to GnRH receptors in the pituitary but are devoid of stimulatory activity. Receptor occupancy by GnRH antagonists blocks the receptor to occupancy by endogenous GnRH causing an immediate suppression of gonadotropin release (Conn and Crowley, 1994; Schalley, 1999). From the early 1970s an increasing number of GnRH antagonists have been developed. The development process involves a stepwise introduction of hydrophobic residues

that block proteolysis, increase GnRH receptor affinity and increase the pharmacokinetics of the molecule (Fraser, 1988). Initially GnRH antagonists exhibited significant histamine-releasing ability which almost halted their further development (Conn and Crowley, 1994).

GnRH antagonists have successfully been employed to inhibit the LH surge and ovulation in gilts (Brussow et al., 2001) and they have been used to help determine the endocrine control of follicular development in a range of species (e.g. mares; Watson et al., 2000). While GnRH antagonists have the advantage that they do not provoke the initial stimulatory effect of agonists and their effects are immediate, the high dose required to prevent oestrous cycles and the failure to develop an efficient controlled-release system has reduced their practicality. Until an efficient delivery system can be developed, the use of these products is likely to be limited to short-term treatment, e.g. down-regulation of the pituitary during IVF treatment regimes.

## 5. GnRH-toxin conjugates

The approach of coupling a protein synthesis inhibitor (usually cytotoxic) to GnRH is a more recent approach to long-term fertility control. Because GnRH receptors are highly specific a variety of cytotoxic agents could be used in an attempt to disrupt pituitary gonadotropes by conjugating them to GnRH or GnRH analogues. Death of the gonadotrope will occur when the gonadotropes internalise the GnRH conjugate as part of the normal process of receptor deactivation. Following a sufficient reduction in the number of gonadotrope cells, there will be inadequate production of LH and FSH to maintain reproductive function (Nett and Jarosz, 2002). A recent study has attempted to inhibit reproductive function in male dogs with the use of GnRH conjugated to pokeweed antiviral protein (PAP) (Sabeur et al., 2003). GnRH–PAP caused a reduction in basal LH and testosterone concentrations and testes size. By week 20 post-treatment basal LH and testosterone concentrations showed evidence of recovery (Sabeur et al., 2003). The resumption of reproductive activity may be the result of insufficient dose, or it may be the result of undifferentiated stem cells in the pituitary.

## 6. Conclusions

GnRH agonists and vaccines are the only two GnRH-based fertility control methods that have successfully been used in a wide range of domestic animal species and are approaching the commercialization stage. There are now many commercially available GnRH agonist formulations, but most are designed for human use and may therefore be hard to access for animals and/or be prohibitively expensive. There is now one GnRH agonist formulation that has been specifically developed for domestic animals (Suprelorin®) and this is approved in two countries and commercialisation worldwide is proceeding.

The impetus for the development of GnRH-based fertility control has been founded on the potential applications in domestic animals and humans, but a new and emerging field has been the use of these products to control overabundant wildlife. The fact that research and development of this technology has been funded from the more lucrative fields of

human medicine and production animal health has made the transfer of this technology to wildlife relatively cheap (i.e. compared to the development of species specific zona pellucida vaccines for example). The highly conserved nature of the role of GnRH in reproduction has allowed easy transfer of this technology to other species.

GnRH agonists have a much higher contraceptive success rate and less negative side effects than immunization against GnRH in both domestic animals and wildlife. The high variability of response to GnRH vaccines is a problem that may eventually see the pursuit of such 'self' vaccines abandoned. Attempts to further develop GnRH antagonist and GnRH-toxin technology may provide useful products with a range of potential applications.

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