

# Nonsurgical methods of contraception in dogs and cats: Where are we now?

A viable alternative to spaying and neutering for canine and feline population control is being intensively investigated. Here's a look at some possible future options.

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The population of unowned, free-roaming cats and dogs in the world is unknown, but we know an overpopulation of these animals exists. They present a health threat to people and pets. Rabid dogs are the main source of rabies deaths in people worldwide.<sup>1</sup> Free-roaming dogs and cats may also have a negative impact on wild species and the environment.

Furthermore, the welfare of free-roaming animals is debatable and likely varies with location, climate, and people's attitudes. Some evidence indicates that free-roaming cats have shorter life spans than owned cats. One study showed that 87 of 169 (51%) free-roaming kittens died before 6 months of age, and the most common cause of death was trauma from dog attacks or motor vehicle accidents.<sup>2</sup>

## METHODS OF POPULATION CONTROL

The mainstay of population control for dogs and cats is surgical sterilization via ovariectomy and orchiectomy. However, many reasons why surgical sterilization may not be effective as the sole method for population control exist. It requires anesthesia, medical equipment,



a suitable surgical facility, adequate recovery time, and the advanced training of a veterinarian. It carries the risks inherent in any surgical procedure. Many people are unwilling to subject their pets to what they perceive to be a painful and invasive procedure. The cost of surgery is prohibitive for many owners, particularly in developing countries.

In addition, many dogs and cats are not owned; thus, shelters and other animal organizations are responsible for financing the surgeries. Neutering these animals involves some method of capturing or trapping the animals, which can be labor-intensive. Trap-neuter-return programs for feral cats and dogs are one such method.<sup>3</sup>

Nonsurgical forms of contraception are a promising additional method of population control (Table 1). According to the Alliance for Contraception in Cats and Dogs, an ideal nonsurgical product would be safe, effective, affordable, permanent, delivered in a single injection or treatment, available for males and females and for

dogs and cats, and have documented effects on behavior and health.<sup>4</sup> In this article, we will examine some of the nonsurgical methods currently being researched or developed that have the best chances of fulfilling these criteria.

## PHYSIOLOGY REVIEW

A brief review of basic reproductive physiology is necessary to understand the mechanisms of action of these nonsurgical methods. Gonadotropin-releasing hormone (Gn-RH) is a decapeptide hormone produced in the hypothalamus. It is responsible for regulating the release of the glycoproteins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior lobe of the pituitary gland. In females, LH causes ovulation, corpora lutea formation, and progesterone secretion in the ovary. FSH is responsible for follicular development and estradiol synthesis. In males, LH stimulates testosterone production in the Leydig cells of the testes. FSH is necessary for Sertoli cell function.

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## CONTRACEPTIVE DRUGS AND CHEMICALS

These agents include implants that contain a Gn-RH agonist, injections that contain a Gn-RH antagonist, and the chemicals vincyclohexene diepoxide or zinc gluconate.

### Gn-RH agonists

Initially, Gn-RH agonists stimulate the release of FSH and LH, thus causing estrus and ovulation, which is a disadvantage of this method. Contraception can be achieved by sustained exposure to Gn-RH agonists, which causes Gn-RH receptor downregulation of pituitary cells and decreased FSH and LH release. Thus, Gn-RH agonists can be used in males and females. These agonists have low bioavailability orally since they can be broken down by peptidases; therefore, they must be administered parenterally.<sup>5</sup> Current formulations involve the use of slow-release devices.<sup>5</sup>

**Gonazon.** Gonazon (Intervet/Schering-Plough Animal Health) contains azagly-nafarelin in a controlled-release device.<sup>6,7</sup> It received regulatory approval in the European Union in 2006. The implant is inserted subcutaneously in the umbilical area in dogs and in the neck in cats. Gonazon shows promise as a safe, long-term contraceptive in female dogs and cats, and, possibly, male dogs.

In a placebo-controlled clinical trial of 124 female dogs, Gonazon safely prevented estrus for about one year.<sup>6</sup> In a follow-up trial, some of the bitches had the first implant removed and a second one placed. The second implant was left in place for 18 months and was 92% effective at preventing estrus.<sup>6</sup> Gonazon reduces testosterone concentration in male dogs.<sup>6</sup>

In another placebo-controlled clinical trial, Gonazon was implanted in 10 4-month-old beagle bitches for one year, and none of them displayed estrus until after the implant was removed, whereas all of the control bitches displayed estrus during this period.<sup>7</sup> The implantation was safe, as it was nonpainful and no inflammatory reactions occurred.

In a trial with queens, Gonazon was effective for about two years. The implantations were painless, and no side effects were noted.<sup>6</sup>

**Suprelorin.** Suprelorin (Peptech Animal Health) is a controlled-release implant containing the Gn-RH agonist deslorelin.<sup>8,9</sup> It is administered subcutaneously in the interscapular region.<sup>9</sup> It was approved for use in dogs for testosterone suppression in Australia in December 2004 and in New Zealand in September 2005.<sup>8</sup> It was originally approved at a six-month dose but is now also available at a 12-month dose.<sup>8,9</sup> Suprelorin is available in some European countries.<sup>4</sup> Although Suprelorin is not

TABLE 1

## Comparison of Selected Nonsurgical Contraceptives in Dogs and Cats

Nonsurgical Contraceptive	Effective	Permanent	Single Treatment	Male and Female	Dog and Cat	Effect on Behavior
Gonazon	X			X	X	X
Suprelorin	X			X	X	X
Acyline	X			X	Dog	X
VCD*	X	X		Female	Dog	X
Chemical castration	X	X	X	Male	Dog	X
Gn-RH vaccine*	X			X	Cat	X
LH-R vaccine*	X			Female	X	X
Zona pellucida vaccine	X			Female	Dog	

\*Abbreviations: Gn-RH, gonadotropin-releasing hormone; LH-R, luteinizing-hormone receptor; VCD, 4-vinylcyclohexene diepoxide.

labeled for use in female dogs, in one study estrus was delayed for up to 27 months.<sup>10</sup> A similar response was found in female cats for 14 months, and there were no negative side effects.<sup>11</sup>

### Gn-RH antagonists

Gonadotropin-releasing hormone antagonists function in contraception by binding to the Gn-RH receptors in the pituitary and preventing Gn-RH from binding. The advantages of antagonists are their immediate effect, and they do not cause post-treatment stimulation and estrus in females.<sup>12</sup> The disadvantages are that antagonists require higher doses than agonists do, controlled-release systems have not been developed, and antagonists are more expensive.<sup>13</sup>

**Acyline.** Acyline, a third-generation Gn-RH antagonist made up of 10 amino acids, is administered subcutaneously. In male dogs, it causes a slight decrease in scrotal diameter, decreased volumes of the second and third fractions of ejaculate, decreased sperm count and motility, increased sperm abnormalities, and decreased libido and erection without local or systemic side effects.<sup>12</sup> In female dogs, acyline prevents normal estrus and ovulation when it is admin-

istered in proestrus and terminates pregnancy in bitches about one week after it is administered at 30 to 35 days of gestation.<sup>14</sup> Unfortunately, the duration of action in male dogs is only about two weeks.<sup>12</sup> More research must be done before acyline is considered a viable option for long-term contraception.

### 4-Vinylcyclohexene diepoxide

The industrial chemical 4-vinylcyclohexene diepoxide (VCD) destroys the primordial and primary follicles in the ovaries of rats and mice via apoptosis.<sup>15</sup> SenesTech is developing a VCD product called ChemSpay that would have the same effect in cats and dogs.<sup>15</sup>

In a study on the Navajo Reservation, 16 dogs were injected subcutaneously with VCD once daily for six days. VCD-treated bitches had significantly decreased heat behavior in the medium and high concentration dose groups vs. control. The dogs were not mated to determine whether pregnancy was prevented. At day 30 after the treatment, the bitches underwent ovariectomy. Ovarian histology showed a statistically significant reduction in primordial follicles in the high-dose group for the total population and in all dose groups for puppies compared with control dogs.

Blood chemistry analyses did not show any abnormalities, and the dogs were healthy 2.5 years later.<sup>15</sup> This product shows promise as a safe and irreversible method of contraception.

### Chemical castration

Neutersol, an intratesticular injection that contains zinc gluconate neutralized by arginine, causes testicular sclerosis and permanent sterility. It was the first drug approved by the Food and Drug Administration for sterilization of companion animals.<sup>16</sup> It was approved for use in the United States in 2003 for puppies 3 to 10 months of age with testicles measuring 10 to 27 mm in width. The injection volume is based on testicular width. It has been used in larger adult dogs in an extralabel manner. Since 2005 it has not been available in the United States after the patent holder and marketing company discontinued their relationship.<sup>16</sup>

EsterilSol is an identical product available through Ark Sciences in Mexico.<sup>4</sup> Infertile (RhoBifarma Indústria Farmacêutica), which contains zinc gluconate and DMSO (dimethylsulfoxide) for intratesticular injection, was launched in Brazil in March 2009.<sup>4</sup>

Neutersol has the advantages of being

permanent after one administration and does not require general anesthesia.<sup>16</sup> Outpatient clinics in the United States using Neutersol have been very successful.<sup>17</sup> The product is appealing to owners who do not want their dogs to have surgery or who want their dogs to retain the “masculine” look and presence of testicles. Since there is no noticeable difference in testicular size in adult dogs treated with Neutersol, permanent identification such as microchipping or tattooing is necessary to indicate that the animal has been sterilized.<sup>17</sup>

A large field trial to evaluate Neutersol in 10,000 dogs was conducted in three states in Mexico.<sup>18</sup> Some dogs experienced

induce antibody formation, and the immunity would then suppress normal reproductive function. The current vaccine targets are the zona pellucida (ZP), Gn-RH, and the LH receptor. Extensive research has been conducted in the field of immunocontraception for humane control of wildlife overpopulation.<sup>20,21</sup> Consequently, these strategies have been applied to population control of dogs and cats.

### ZP vaccines

The ZP, a mucoprotein layer surrounding the oocyte, consists of three glycoproteins: ZP1, ZP2, and ZP3. Spermatozoa must bind to the ZP before fertilization

in insect cells as well as a DNA vaccine expressing the same fusion protein.<sup>26</sup>

### Gn-RH vaccines

The principle of Gn-RH vaccines is that antibodies to Gn-RH prevent its binding to Gn-RH receptors, shutting down the release of LH and FSH. Gn-RH must be coupled with a large carrier in order to be immunogenic.<sup>13</sup> Some disadvantages of Gn-RH vaccines are variations in individual responses, the need for repeated immunization to keep titers high, and the need for an adjuvant.<sup>13</sup> The Gn-RH vaccines have the advantages of inhibiting hormonal cycling and associated behaviors, and being effective in both females and males.<sup>27</sup>

GonaCon, a vaccine containing Gn-RH coupled to keyhole limpet hemocyanin and the mycobacterial adjuvant AdjuVac, was originally developed for the control of white-tailed deer populations by scientists at the USDA Wildlife Service's National Wildlife Research Center.<sup>21</sup> GonaCon has been tested in male and female cats.<sup>27,28</sup> There was a wide variation in response and duration of action. It was about 75% effective in female cats, and some cats had estrus prevention for up to 3.5 years after a single dose.<sup>28</sup> However, some of the females developed a granuloma at the injection site after 24 months, likely caused by the mycobacterial adjuvant.<sup>28</sup>

GonaCon is not effective for inducing long-term infertility in dogs, and it resulted in severe injection site reactions that persisted for a year until surgical removal.<sup>29</sup> New formulations are being developed to prevent this problem in dogs.

Another Gn-RH vaccine consisting of the antigen IPS-21, a commercially available adjuvant, and the immunostimulant dimethyl dioctadecyl ammonium bromide was tested in four male and 10 female cats.<sup>30</sup> IPS-21 is a recombinant protein made up of eight tandem repeats of Gn-RH fused to a fragment of leukotoxin A from *Mannheimia haemolytica*. It was shown to be effective as evidenced by immunoneutralizing

## A field trial to evaluate Neutersol in 10,000 dogs was conducted in Mexico.

moderate pain in the first 12 hours after injection.<sup>18</sup> In 2.6% of the dogs, severe ulcers developed at the injection site. The ulcers were related to poor injection technique, and the incidence decreased after veterinarians began using separate needles to draw up and administer the solution as well as separate sterile needles for each intratesticular injection in each dog.

In another study on Isabella Island of the Galapagos, 3.9% of 103 dogs given zinc gluconate developed necrotizing injection site reactions.<sup>19</sup> By comparison, 3.4% of 58 dogs experienced wound dehiscence after surgical castration. The zinc gluconate reactions were more severe and required more extensive surgical repair than the traditional surgical complications. The dogs that experienced zinc gluconate reactions were large, mature dogs that received near maximum-volume doses.<sup>19</sup>

### IMMUNOCONTRACEPTION

The goal of immunocontraception is to develop a vaccine against a target in the reproductive system. The vaccine would

can occur. Vaccines against ZP are, therefore, only effective in preventing pregnancy in females. Hormonal cycling is not affected. Continued reproductive behaviors may not be acceptable for free-roaming cats and dogs.

A porcine zona pellucida (pZP) vaccine has been effectively used in many wildlife species, including horses, deer, and elephants.<sup>20</sup> However, single-dose pZP vaccines have not been effective in cats.<sup>22,23</sup> A recent study in which cats were vaccinated with feline ZP subunits showed antibody production specific to feline ZP and lower conception rates compared with the control group.<sup>24</sup>

In dogs, recombinant dog ZP3 was conjugated to a diphtheria toxoid carrier to create a vaccine.<sup>25</sup> It was effective at preventing pregnancy in three out of four bitches, but they required multiple immunizations intramuscularly to keep titers high. Further research is being performed in this area, including the development of a fusion protein of ZP3 and rabies virus glycoprotein expressed



titers to GnRH for almost two years, but required several immunizations. None of the females exhibited estrous behavior or became pregnant. All the cats, including the cat injected with a placebo, showed nonpainful, palpable tissue reactions that resolved by day 28. There were no serum chemistry profile abnormalities.<sup>30</sup>

### LH receptor vaccines

Female dogs and cats have been vaccinated with bovine LH receptor (LH-R) encapsulated in a silastic subdermal implant, followed by four booster injections of LH-R intramuscularly.<sup>31,32</sup> This resulted in the formation of LH-R antibodies with subsequent suppression of serum progesterone concentrations and lack of estrus for about one year. None of the females in these studies was mated to determine whether pregnancy was prevented. Further studies are needed to determine the sufficient LH-R antibody titer to cause infertility.

### CONCLUSION

With the worldwide overpopulation of dogs and cats, a variety of options are needed for population control. Nonsurgical methods of contraception are one such option. Gonazon, Suprelorin, Neutersol, Esterilsol, and Infertile are the only approved products for dogs or cats, but they are limited to certain countries. Extensive research and development are under way on Gn-RH agonists and antagonists, VCD, immunocontraception, and chemical castration. None of the products meets all of the criteria set forth by the Alliance for Contraception in Cats and Dogs. However, it is likely that new products will be available in the future that offer hope for controlling the free-roaming dog and cat populations. ❖

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