

**Finding the Purrfect Solution: An Evaluation of Sterilization Methods in Cats**

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## Introduction

There are around 600 million domestic cats in the world and approximately 80% of them make up the feral population (Vansandt et al.). Stray cats pose a risk to public health in areas with large feline populations. These felines are reservoirs of pathogens, making it possible for them to contribute to the transmission of rabies, *Toxoplasma gondii*, *Sarcocystis neurona*, and more (Crawford et al; Levy). Feral cats also hunt and kill a considerable number of wildlife, contributing to the endangerment and sometimes extinction of a significant amount of wildlife such as small mammals and birds (Crawford et al). In fact, it is estimated that free-roaming domesticated cats kill 1.3 to 4 billion birds, as well as somewhere between 6.3 to 22.3 billion mammals annually in the United States alone (Loss et al).

Not only is feline population control necessary for the environment and for human health, but it is also important for the cats themselves. Cat overpopulation raises ethical concerns due to poor welfare and quality of life. Free-roaming cats are at an elevated risk of injury or death resulting from road trauma, poisoning, predation, and human persecution (Crawford et al). In fact, more than 50% of kittens born outdoors die before reaching maturity (Levy). There are different methods used to control the outdoor cat population such as contraceptives, admittance into shelters, euthanasia, and Trap-Neuter-Return (TNR). The most common method is to admit cats into shelters, but unfortunately, this can put the cats at risk of euthanasia in the shelter. Cats that are ill, aggressive, or never adopted are at a higher risk of being euthanized in the shelter. Furthermore, shelters with limited resources and space may also pose a risk to the cat and lead to euthanasia (Crawford). It is estimated that several million cats are selectively killed in the United States every year (Levy). There are many issues associated with feline overpopulation. Therefore, feline fertility control methods are being used to try to decrease cat populations. This

review analyzes the different fertility control methods in cats to help find the best options available for both owned and feral cat populations.

### **Surgical Methods of Fertility Control**

Surgical sterilization is the most common surgical procedure performed by small animal veterinarians worldwide and the method most often chosen because it is fully effective in preventing fertilization and has been known to prevent reproductive tract diseases such as pyometra and mammary neoplasia (Howe; Romagnoli et al). In fact, it is reported that the risk of developing mammary neoplasia is reduced by 86% in cats that undergo sterilization procedures such as ovariectomies and ovariohysterectomies (Howe). Ovariectomies and ovariohysterectomies are performed for the complete sterilization of the cat without the preservation of the gonadal hormones. An ovariectomy is the removal of the ovaries, a subtotal ovariohysterectomy is the removal of the ovaries and part of the uterus, and an ovariohysterectomy is the removal of the ovaries in addition to the removal of the uterus completely (DeTora & McCarthy).

Ovariectomies can be performed using different surgical techniques. A ventral midline laparotomy, flank laparotomy, and laparoscopic ovariectomy may be used depending on the veterinarian's preference. Ovariohysterectomies can be performed using a ventral midline laparotomy or a laparoscopic sterilization approach, but only the subtotal ovariohysterectomy can be done using flank laparotomy, not the regular ovariohysterectomy. Performing ovariectomies or either type of ovariohysterectomy using laparoscopic sterilization is not recommended for small cats, so it is more commonly performed on larger cat species like lions or tigers (Romagnoli et al). Some believe uterine abnormalities may develop if the uterus is not removed from the patient, therefore some advocate for ovariohysterectomy procedures for

female cat sterilization. On the other hand, some believe that ovariectomies are a better choice for domesticated cats because the incision is smaller, the view of the ovarian pedicle is better, and there is a decreased risk of complications that may be caused from the surgical manipulation of the uterus (DeTora & McCarthy). A hysterectomy is another fully effective surgical procedure that can be used to sterilize female cats, but it is not suitable for every type of cat population. A hysterectomy is the surgical removal of the uterus, and since the ovaries are still present, the gonadal hormones are preserved. The preservation of gonadal hormones increases the risk of mammary gland tumors and undesired behaviors associated with the hormonal cycle which is not suitable to human-owned cat populations (Romagnoli et al). It may be more suitable for research cats and while it is an option for stray cats, it feels unreasonable to choose a hysterectomy over an ovariectomy or ovariohysterectomy because of the lack of research or evidence indicating the importance of the behaviors of the hormonal cycle outdoors.

There are different surgical options available for sterilization of male cats as well. An orchietomy is the removal of the testis, meaning the gonadal hormones are not preserved. Scrotal orchietomies are performed in cats with descended testis and is the current standard procedure for male cat sterilization. However, the procedure cannot be performed normally if the cat has cryptorchidism, a presumably inheritable condition in which the testis do not descend, occurring in approximately 0.4 to 3.8% of cats. In that case, a cryptorchidectomy is done instead of the usual orchietomy (Romagnoli et al). The other options are a vasectomy which removes a section of the spermatic cord or an epididymectomy which is the removal of part of the epididymis. Both methods preserve the cat's gonadal hormones. Just like the hysterectomy used for female cats, vasectomies are recommended more for research cats because it leads to undesirable behaviors, urine marking, and there is not enough evidence that warrants a need for stray cats to maintain gonadal hormones and the associated behaviors. While epididymectomies

also preserve gonadal hormones, its long-term effects on feline behavior and its efficiency for feral fertility control are understudied (Romagnoli et al). For that reason, it might make more sense for epididymectomies to be performed on research cats.

### **High Quality High Volume Spay and Neuter Clinics**

While surgery is effective at stopping feline reproduction, the costs are high. In a survey conducted in the United States, the most common reason reported for not spaying their female cat was the cost of the procedure (Murray et al). The costs of veterinary care, including sterilization, have increased over many years making it difficult for many pet owners to afford the surgery. High quality high volume spay and neuter (HQHVSN) clinics were made to try to combat this problem and make spaying and neutering more affordable for clients by lessening the time it takes to complete the procedure. By minimizing the time needed, costs are also minimized. These clinics choose efficient and safe methods, but also often compete with other veterinary businesses and may pressure them to take up similar methods (Bushby). Overall, there seems to be more benefits reported than downsides.

### **Trap-Neuter-Return**

Trap-Neuter-Return (TNR) is a humane, ethical, and increasingly popular approach to solving feline overpopulation. In this approach, cats are trapped, spayed or neutered, and then released again. This method is used for the sterilization of many free-roaming cats, decreasing the population of stray cats, with the goal of stabilizing the reproductive rates and decreasing the number of feline deaths by euthanasia (Crawford et al; Levy; Romagnoli et al). However, stabilizing the reproductive rates proves challenging as the carrying ability of each specific area must be considered and it can take a long time for the feline population of that area to decrease below the carrying capacity and for effects to be recognized. Additionally, the introduction of

more cats from nearby areas or from relocation can further delay results as the number of new cats may still outweigh the number of adult cats that have died. TNR therefore may work better in areas such as islands and remote communities where it is unlikely for new cats to have travelled to naturally or by relocation (Romagnoli et al). Unfortunately, there is also little evidence that supports TNR improving the welfare of the cats involved. Cats that are released back outside are still at risk of many dangers such as vehicle collisions, poisoning, injury due to fights with other animals and human cruelty. Also, these cats can still pass along pathogens to other animals and people in the community they roam (Crawford et al). TNR does make a difference by lessening the number of fertile cats in the environment, but according to studies, the results are not at once obvious and the quality of life of the cats do not seem to be improved.

### **Non-Surgical Methods of Fertility Control**

Surgery is not the only way to reasonably control fertility of owned and un-owned cat populations. Examples of non-surgical contraceptives include immunocontraception, Deslorelin, anti-müllerian hormone transgene, melatonin, and progestins (Ferré-Dolcet & Romagnoli; Fontaine; Kutzler; Romagnoli et al). Owners who avoid surgical sterilization due to opinions on health effects, possibility of complications, or concerns related to anesthesia, may find non-surgical contraceptive options more desirable (Murray et al). Non-surgical contraceptives can also be desirable to TNR programs that want to save time and money associated with the sterilization process since non-surgical contraceptives can be given without anesthesia and are quicker compared to surgical procedures (Levy).

### **Immunocontraception**

The zona pellucida is a protective glycoprotein layer that surrounds the egg and plays a key role during fertilization, usually starting with the binding of sperm to zona pellucida protein

3 (Levy; Romagnoli et al). After fertilization, this layer is removed. Studies done have shown that porcine zona pellucida proteins can be successful in preventing pregnancy in a few different animal species long-term including, but not limited to horses, deer, elephants, and rabbits. Unfortunately, this method does not suppress the estrus cycle in the animals vaccinated, which would lead to behaviors associated with the feline fertility cycle which are not desirable to owners (Levy). Studies done on this method in cats had inconsistent results and showed no effectiveness in preventing feline pregnancy (Levy; Romagnoli et al). Overall, immunocontraception with zona pellucida proteins is not suitable for feline fertility control.

Another option is to target gonadotropin-releasing hormone (GnRH) through immunocontraception. GnRh is responsible for the release of the hormones LH and FSH which play important roles in spermatogenesis of males and follicular development in females (Levy). GonaCon is a vaccine approved for use in deer, horses and prairie dogs, but has shown to be effective in cats as well (Levy; Romagnoli et al). It consists of GnRH conjugated to a carrier protein known as keyhole limpet haemocyanin, which is surrounded by an oil and water adjuvant that has killed *Mycobacterium avium*. This adjuvant with *Mycobacterium avium* helps to induce inflammatory and immune responses (Levy; Romagnoli et al). A singular intramuscular injection of this vaccine in male cats resulted in 66% developing infertility within three months, with no side effects. Female cats received the vaccine along with the rabies vaccine. This resulted in a reduction of anti-Müllerian hormones and suppression of reproductive cyclicality. This also resulted in 93% of the female cats being infertile for the first year, gradually decreasing to 27% infertile after 5 years (Levy; Romagnoli et al). This would be a practical choice for fertility control of owned cat populations, but whether it is right for stray cat populations may be debated. If the time in which the cats are still infertile were to be longer or more permanent, then it will be more practical for TNR programs.

## **GnRH Agonists and Antagonists**

There are a few other options available for the control of GnRH other than immunocontraceptives. GnRH agonists bind pituitary GnRH receptors to stimulate the effects of GnRH leading to increased production of LH and FSH (Ferré-Dolcet & Romagnoli; Fontaine; Romagnoli et al). Deslorelin is a synthetic GnRH agonist which is released slowly in low doses from an implant which is inserted subcutaneously into either the male or female cat (Romagnoli et al). It is a safe and reversible way to control fertility in cats. For male cats, testosterone levels increase due to the increased release of LH and FSH and rapidly decrease 20 days after the insertion of the implant because the sustained activation of the GnRH receptors later causes suppression of the synthesis and release of these hormones (Ferré-Dolcet & Romagnoli; Romagnoli et al). Effects of this include decreased testicular volume and decreased sexual behaviors because of the lower testosterone levels. Depending on the strength of Deslorelin and the breed of the cat, infertility can last between 6 months and 2 years. Removal of the implant can restore fertility in 2 to 3 months (Romagnoli et al).

Female cats that receive the Deslorelin implant prior to puberty tend to reach puberty 4 months later than usual. When given to post pubertal female cats, Deslorelin tends to be effective for more variable amounts of time, with some cats staying infertile for over three years. Normal reproductive cyclicity is usually restored within three to six months of removal of the implant. Deslorelin has more risks in female cats. Some studies show persistent estrus, weight gain, lactation, and mammary fibroadenomatous hyperplasia occurring within the first couple of weeks, but it is unknown if these risks are associated with pre-existing conditions (Romagnoli et al). This method may be difficult for fertility control in free-roaming cats, because of the difficulty knowing which cats captured need a replacement implant and because it is not permanent or long-acting enough to consider stray cat populations. On the other hand, this

method is beneficial to breeders and other cat owners because fertility can be blocked or restored when needed for behavioral or breeding purposes.

Unlike GnRH agonists, GnRH antagonists block pituitary GnRH receptors and lead to the suppression of LH and FSH secretion. Because the suppression is immediate, there is no initial increase in testosterone of the male cats. There is a lack of research on GnRH antagonist for use as a feline contraceptive. However, one study in which two subcutaneous injections of antide given 15 days apart suppressed ovarian activity in female cats within 17 to 56 days and another study in which one injection of acyline postponed estrus and ovulation for around 18 days. Same treatments in male cats suppresses spermiogenesis but had no other known effects (Romagnoli et al).

### **Anti-Müllerian Hormone Transgene**

Anti-Müllerian hormone (AMH) is essential for fetal sex development. High physiological levels of AMH from gene therapy with an adeno-associated virus vector can suppress or inhibit follicular development and cause permanent infertility in adult female mice. Therefore, a study was conducted to test the effect of AMH transgene in adult female cats and find if it could be a suitable contraceptive choice for community cats. A single dose of a first-generation AAV9-FcMISv1 vector administered in cats resulted in prolonged AMH expression in muscles with a variable amount of anti-transgene antibody response. Histological changes also occurred in the reproductive tract. Administering a single dose of AAV9-FcMISv2, however, resulted in the prolonged secretion of AMH without any adverse effects. The studies showed evidence that the elevated levels of AMH might inhibit luteal phases and lead to impaired induced ovulation of the female cat (Vansandt et al). This method may be beneficial for fertility

control in cats because studies showed it can last over two years, making it a good long-term choice for owned cats.

## **Melatonin**

Melatonin is a neurohormone that can be inserted as an implant to release small doses over time. In one study, estrus was postponed by two to four months in half of the female cats that received the 18mg implant. Implants with 12mg of melatonin effectively suppressed estrus in three of four cats tested for an average of 75 days (Romagnoli et al). In order for the melatonin implant to be the most effective, it should be inserted during interoestrus to avoid interference caused by high estrogen concentrations during pro-oestrus and estrus. If inserted during estrus, postponement of estrus may be delayed between 5 and 30 days. This method has proven to be a safe option for female cats, but there have been reports of cystic endometrial hyperplasia (CEH) in some female cats that received the 12mg implant. Administration of the melatonin implant in males has no effect on their fertility (Kutzler; Romagnoli et al). Melatonin could be a great contraceptive option to choose for breeding purposes because of the reversibility and the control that the owner has on the cats reproductive cycle. Since the implant must be administered in a certain time frame and is effective for only 75 days on average, it may not be suitable for community cats or desired for use by TNR programs.

## **Progestins**

Progestins are synthetic molecules used to mimic the effects of progesterone. Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are two progestins that have been used extensively to control feline reproduction. The effects and efficacy of progestins depends a lot on the type administered, dose, timing, age, and the reproductive health of the feline. MA is short acting and its affinity for the progesterone receptor is between 15 to 25 times higher than that of

endogenous progesterone. It is highly effective in postponing the estrus cycle in cats and is given orally in doses of only 2.5mg per week. Some side effects could include weight gain, temperament changes, and mammary enlargement, but it is relatively safe for use for up to 30 weeks. MPA is longer acting compared to MA, but its affinity for progesterone receptors is only 5 times higher than that of endogenous progesterone. Just like with MA, doses of MPA should be relatively low. A dosage of 0.5mg/kg per day is recommended for safety and efficacy. At this dosage, estrus can be postponed for up to twelve months. Increasing the dosage leads to more adverse side effects and possible overdose from progestins. Therefore, careful consideration is needed when prescribing it to female cats (Romagnoli; Romagnoli et al). This should not be used for fertility control of male cats because of lack of efficacy, risk of mammary hypertrophy, and the risk of developing a diabetic condition (Romagnoli). Since progestin dosages are administered once per week and careful consideration must be made prior to prescribing, this option would not be suitable for feral cats. However, this option may be desirable to breeders because of the reversibility.

## **Conclusion**

The vast majority of cats are strays. Stray cats may transmit pathogens, as well as hunt and kill a considerable amount of wildlife, contributing to the endangerment and sometimes extinction of a considerable number of species. Therefore, it is important to find an efficient way to control the fertility of stray cats. Owners also seek the best method to control their own cat's fertility to prevent undesirable behaviors or for breeding purposes. After reviewing many articles, it seems most reference only a couple of studies that test efficacy and safety in pets. More studies could be beneficial to help clarify existing questions and gaps in knowledge that exists in some contraceptive methods. For example, it might be beneficial to dive deeper into the long-term effects of each of the non-surgical contraceptive methods to better compare that

information to surgical methods. It would also be interesting to explore the reason some cats do not respond to specific contraceptive methods in different studies. Based off the information that is available, progestins, melatonin, and Deslorelin may be better options for cats meant for breeding purposes because these are easily reversible and maintain behaviors associated with the hormonal cycle. For cats that will not be used for breeding purposes, more long-term options that do not preserve gonadal hormones may be best. For that reason, the anti-Müllerian hormone transgene and surgical procedures such as ovariectomies, ovari hysterectomies, orchidectomies, and cryptorchidectomies may be better suited for this population. For stray cat populations, the best fertility control options are permanent or as long-term as possible. Therefore, surgical procedures such as ovariectomies, ovari hysterectomies, orchidectomies, and cryptorchidectomies may be the best suited until other options such as immunocontraceptives or anti-Müllerian hormone transgene proves to work for much longer periods of time.

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