

Advances in reproductive control technology

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INTRODUCTION

Population control of both domesticated and wild, free-roaming animals is a major problem in remote and indigenous communities. In fact, overpopulation of free-roaming animals is a problem worldwide. This overpopulation has led to social problems, degradation of the ecosystem and increased risks of zoonotic disease.

It is clear that an inexpensive and non-surgical method of permanent contraception would be of enormous benefit in reducing these populations. Reproductive control is considered a more sensible, humane and ethical management approach than allowing young to be born and then later spending valuable resources to capture and euthanase them. However, the ethics of using a particular method of population control will depend on its humanness, its safety and its effectiveness compared to other available methods. These factors have to be weighed against euthanasia or just doing nothing.

The objects of this paper are firstly to review current dog and cat reproductive control methods, and secondly to discuss advances in this field and how these advances might apply to animals in remote and indigenous communities.

REPRODUCTIVE CONTROL AT A POPULATION LEVEL

Most methods of fertility control have examined effects on reproduction only, without looking at the effects any control mechanism might have on population dynamics. Such information is essential for estimating the value of any population control technique. Numbers and composition of populations are forever changing and these changes are the result of many factors, only one of which is reproduction.

With polygamous matings at a population level (eg. free-roaming and feral dogs and cats), the effect of sterilisation of males will have no impact at all on population size. A very high level of female sterilisation is needed in these populations to achieve a decrease in numbers. Modelling suggests that between 80-90% of females need to be sterilised to obtain zero population growth.

The effectiveness of any fertility control program will depend on the balance between survival rates and the productivity of the remaining fertile animals. For example, the reduced production of young caused by sterilisation is compensated for by an increased survival rate of juveniles and the remaining adults.

METHODS OF FERTILITY CONTROL

There are 3 main methods of manipulating fertility in mammals: surgical and the non-surgical methods of chemosterilisation and immun contraception.

Surgical sterilisation is considered the 'gold standard' of fertility control and is still the method of choice for

managing small accessible populations. Its main advantage over the newer developments is that the sterility obtained is permanent. Its main disadvantages are that it is costly, time consuming, there are infection risks and it is impractical for large populations.

Non-surgical methods

The six non-surgical mechanisms suggested for blocking reproduction in the female are:

- suppression of anterior pituitary secretion of gonadotrophins,
- prevention of follicle development and maturation,
- blocking the passage of ova in the oviduct,
- prevention of fertilisation,
- prevention of implantation,
- interference with gestation.

In males there are three suggested mechanisms:

- suppression or interference with secretion of gonadotrophins,
- inhibition of spermatogenesis,
- interference during transport and storage of sperm.

Chemosterilants are chemicals that cause permanent or temporary sterility in either sex, reducing the number of offspring or altering the fertility of offspring produced.

Immun contraception is the technique of raising antibodies against sperm, eggs or reproductive hormones, and so inhibit reproduction.

Immunosterilisation involves the ability to produce an immune response that leads to the animal's sterilisation.

Currently, the following antibodies have been produced against:

- Gonadotropin Releasing Hormone (GnRH),
- gametes (Zona Pellucida antigens and sperm),
- implantation and gestation (HCG).

Currently available methods (mainly producing temporary sterility)

1. Synthetic progestins -
 - MGA (melengestrol acetate) implants
 - MPA (medroxyprogesterone acetate) injections
 - Covinan (proligestone) injections
 - Norplant (levonorgestrel acetate) implants
 - Ovarid (megestrol acetate) tablets
 - Tardak (delmadinone acetate) injections
 - Implanon (etonogestrel) implants
 - Cyproterone acetate injections
2. Progesterone antagonists
 - RU486 (mifepristone) tablets
3. Prolactin inhibitors
 - Bromohexal, Parlodel (bromocriptine) tablets
 - Dostinex (cabergoline) tablets

4. Androgens
 - Cheque (mibolerone) drops
 - Testosterone implants
5. Vaccine
 - Porcine Zona Pellucida vaccine (PZP) injections
6. Gonadotropin Releasing Hormone (GnRH) agonists
 - Lupron (leuprolide acetate) injections
7. Chemical Methods
 - Neutrosol (intra-testicular injection of sclerosing agent)
 - Biotumer (copper IUD)

ADVANCES IN NON-SURGICAL TECHNIQUES FOR FERTILITY CONTROL

Because of a need for newer non-surgical techniques to produce either temporary or permanent sterility, some advances in reproductive control technology have been made in the past few years. (There have been advances in anaesthetic agents that have led to improvements in the surgical approach to fertility control, but these are beyond the scope of this paper). The need for new strategies has arisen as a result of the side-effects from the long-term use of progestins and the unreliability and undesirable reactions from many of the contraceptive vaccines.

It is important to remember that in remote and indigenous communities, the use of any product that prevents pregnancy without preventing oestrous cycles would be a poor alternative to surgically sterilising dogs and cats.

Products being developed but not yet available commercially.

1. Prolactin Inhibitors
 - Melatonin implants
2. Vaccine
 - CSL's Luteinising hormone-releasing hormone (LHRH)
 - GnRH conjugate (gonexPets)
 - Sperm antigens e.g. LDH-C₄
3. Gonadotropin Releasing Hormone (GnRH) Agonists
 - Deslorelin / Suprelorin (PepTech)
4. Chemical
 - Novel peptides targeting primordial follicles producing permanent sterility

REPRODUCTIVE CONTROL TECHNOLOGY RESEARCH - CURRENT SITUATION

A variety of the above methods of reproductive control technology have been explored, but to date, none have shown sufficient efficacy to be widely deployed. In fact, it was summarised at the *2002 International Symposium on Nonsurgical Methods for Pet Population Control*, that a commercial product – an alternative to surgical castration or ovario-hysterectomy for either dogs or cats – might still be 10 years away. Despite scientists investigating methods for the control of reproduction for over 30 years, there are still no commercially successful products being marketed. Ideally, the perfect non-surgical sterilisation method would cause permanent loss of fertility, permanent loss of sexual behaviour and be effective in dogs and cats – both males and females. It

would be given in a single delivery, be inexpensive, and be safe to both targeted animals and to humans inadvertently exposed.

There are still many questions that remain regarding the development of effective, affordable, long lasting and safe immunocontraceptive vaccines in female dogs and cats. This is disappointing, as immunocontraception using porcine zona pellucida as an antigen is already a reality for wildlife population control. SpayVac™, a commercially available porcine derived ZP did not induce contraception in cats. Some studies using PZP have demonstrated significant side-effects such as cystic ovaries in dogs.

The main disadvantage of PZP vaccines is that treated females tend to have recurring and sometimes prolonged oestrous cycles. However, a hybrid antigen consisting of ZP3 and a universal T-cell epitope, creates a substantial enough reaction in canine ovaries to eventually destroy the integrity of the ovary. This results in immunosterilisation, and at the moment, looks to be a promising approach for nonsurgical sterilisation, though several injections 3 to 4 months apart have to be administered.

In Australia, a contraceptive vaccine is being developed by a group from the CRC for Vaccine Technology in Brisbane, the University of Melbourne and CSL. Their contraceptive vaccine is designed to render a dog or bitch infertile for at least six months. It works by generating antibodies to luteinising hormone-releasing hormone (LHRH) and therefore suppresses the production of the sex hormones.

It is worth noting that when a vaccine for reproductive control is used, animals with a poor immune response are affected less than animals with a good immune response, so immunosterilisation could, therefore, select for immunocompromised animals that are more susceptible to disease.

An Australian Biotechnology company Peptech Animal Health has developed a GnRH analogue implant to produce reversible long-term suppression of reproductive function in male and female dogs and cats.

It has been demonstrated that the slow release pellet containing the GnRH analogue deslorelin, which is placed under the skin in the neck of the dog, acts as a reversible anti-fertility agent in dogs for periods exceeding one year. In females, postponement of oestrus for periods up to 27 months has been observed. Deslorelin has recently been registered in New Zealand as Suprelorin®. Its approval for registration in Australia is anticipated within the next six months.

There are two new non-surgical methods that have been developed to permanently sterilise male dogs. Of interest is Neutersol™, which is a zinc and l-arginine based compound injected into each of the testicles of pups, causing permanent sterility. At the moment, its use is approved in USA for male pups between three and ten months.

There is another method being developed in USA in which a hand-held, high intensity focused ultrasound is used on the epididymides of anaesthetised dogs to induce thermal coagulative necrosis and subsequent epididymal occlusion. It is claimed to provide a rapid non-invasive alternative to vasectomy.

CONCLUSION

Although non-surgical methods for permanent sterilisation for dogs and cats have been explored for quite some time, we appear to be only a little closer to achieving that goal. We are battling the biology of reproduction that has enabled dogs and cats to survive for many thousand of years.

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Graeme Brown BVSc, graduated from the University of Sydney and spent five years working for NSW Agriculture and various mixed veterinary practices in Australia and UK. In 1972, he established Merewether Veterinary Hospital and has developed a strong interest in wildlife diseases and population biology.

Graeme is currently enrolled as a post-graduate student at the University of Newcastle studying the 'Population dynamics of free-roaming dogs in Aboriginal communities'.

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