Non-surgical methods for reproductive management of captive and free-ranging wildlife populations
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Abstract
Fertility control has long been central to reproductive management in captive breeding programs. Species and gender differences in efficacy and safety of contraceptive products have necessitated development and testing of a variety of options, ranging from synthetic progestins to gonadotropin releasing hormone (GnRH) agonists to vaccines against the zona pellucida and GnRH. Specialized centers in the U.S. and Europe provide monitoring, data analyses, and tailored product recommendations to their respective zoo communities. Development and application of contraception or non-surgical sterilization methods for managing wildlife populations has been more challenging. A primary difficulty is gaining access to treat a sufficient number of individuals to achieve population-level impact. Because reversibility is critical in captive populations but often undesirable in free-ranging ones, there is little overlap in contraceptive methods used. Development of better options is needed for both types of programs.

Keywords: Contraception, fertility control, population management, captive breeding

Reproductive management has long been central to successful captive breeding programs. Reversible contraception has been used routinely in zoos since the mid-1970s, but efforts continue to identify and develop new methods appropriate for the wide variety of species in managed programs. Interest in fertility control, either reversible contraception or permanent sterilization, for managing free-ranging populations also spans decades but has proven more difficult, primarily due to challenges with effective delivery of contraceptives or application of treatments.

Contraception has been systematically monitored in the U.S. by the Association of Zoos and Aquariums (AZA) Reproductive Management Center (RMC; formerly the AZA Wildlife Contraception Center) since 1990, hosted by the Saint Louis Zoo (www.stlzoo.org/contraception). Annual surveys are submitted to the RMC and compiled in a database that now contains more than 25,000 records of contraceptive use. About 10 years ago a similar program was started in the EU, the European Association of Zoos and Aquariums (EAZA) Group for Zoo Animal Contraception (EGZAC: www.egzac.org). These two organizations work closely, sharing data and a web-based survey data entry system. Availability of some products varies in the U.S. and Europe, but there is considerable overlap as well as shared challenges.

Development and application of fertility control for wildlife has not been as coordinated and focused as for zoos. However, a regularly occurring symposium (Wildlife Fertility Control) with published proceedings serves to bring together scientists and managers with experience and an interest in the topic. The Botstiber Institute, recently established to promote and support fertility control for wildlife management, will henceforth organize and host this symposium.

Although prevention of reproduction is the objective for both captive and free-ranging wildlife, contraceptive reversal to allow genetically important individuals to reproduce is critical in captive breeding programs. In contrast, permanent sterilization is often preferred in free-ranging populations to avoid the need for repeated treatment, highlighting another major difference, which is that captive animals are easier to access or restrain for treatment.

Contraceptives used in captive breeding programs

Progestins
Synthetic progestins were the basis of the first contraceptive methods used systematically in zoo animal populations, beginning with melengestrol acetate (MGA) silastic implants and
medroxyprogesterone acetate (MPA) injections in lions.\textsuperscript{1} Because cortisol was more affected by MPA, MGA in implants, in feed or as a liquid to be added to the diet, became the preferred option, although MPA (as Depo-Provera, Pfizer) and megestrol acetate (Ovaban or Ovarid, Schering) are used in special cases. Newer generation implants containing etonorgestrel (e.g., Implanon and Nexplanon: Merck) are available for use in wildlife in Europe but not in the U.S.

The MGA implants (first produced by Dr. U.S. Seal and provided to the U.S. zoo community; now sold by Wildlife Pharmaceuticals, Ft. Collins, CO), have been highly effective in females of all mammalian species treated, once an adequate dose is identified, except equids. However, like domestic horse mares\textsuperscript{4} wild equids do respond to altrenogest in the form of Regu-Mate, although the daily oral treatment required is impractical in most cases.

Megestrol acetate implants are effective for at least two years, and if left in place have been observed to be effective for as long as five years, minimizing handling. Reversibility has not been systematically analyzed in many species (golden-lion tamarins 5, tigers 6), but survey reports from program managers (RMC Database) indicate high rates of reversal in most individuals if the implants are removed.

Early in zoo breeding programs, the taxonomic group most in need of reversible contraception was large felids, e.g., lions and tigers. Unfortunately, felids (and by extrapolation, carnivores) respond differently to sex steroid hormones than most other species. Estrogens and progestins, alone or in combination, stimulate endometrial overgrowth in carnivores if ovulatory cycles are not separated by pregnancy. Studies of progestin-treated felids\textsuperscript{7} documented endometrial pathology ranging from hyperplasia to cancer, as well as mammary tumors. Analyses of wild canids revealed similar results.\textsuperscript{8} These outcomes have not been observed in other taxa, such as primates and ungulates which now also have a long history of progestin contraceptive treatment, apparently because of differences in the responses of endometrial and mammary tissue to estrogens and progestins.

Combination birth-control pills

Commercially available oral contraceptives made for women are a good option for apes and some Old World monkeys, because of species similarities in response. They have proven safe and effective and are the preferred method for great apes, in particular (RMC Database).\textsuperscript{9,10} Although they are safe and effective for primates, they are not an alternative for carnivores. In fact, estrogen priming exacerbates the stimulatory effect of progestins on the canid uterus,\textsuperscript{11} an effect that may extend to other carnivores.

GnRH agonists

Due to the risk of pathology from progestin, the GnRH agonist deslorelin (Suprelorin implants, Virbac) has replaced progestins for carnivore contraception (RMC database). In this slow-release form, deslorelin does first stimulate the reproductive axis, but then down-regulation of pituitary GnRH receptors follows. The stimulation phase can be avoided by short-term treatment with oral megestrol acetate around the time of Suprelorin implant insertion, using a protocol developed by Wright and colleagues.\textsuperscript{12} An advantage of GnRH agonists is that they can be effective in males of most species as well as females; a notable exception has been male bovids,\textsuperscript{13} as has also been shown in domestic bulls.\textsuperscript{14} A further advantage is the small size of the implant (grain of rice), which allows insertion by trocar, in contrast to the much larger MGA implants which require a small surgical incision.

Available in two formulations with minimum periods of efficacy of 6 and 12 months, the average period of Suprelorin suppression in the range of species treated in zoos (RMC Database) is more often one and two years, respectively. Lions, however, tend to be suppressed far longer, up to five or even six years (RMC Database).

Anti-GnRH Vaccines

Two products sold by Zoetis in the U.S. (Improvest) and elsewhere (Improvac) have been used in zoos, particularly in ungulates (RMC and EGZAC Databases). As with GnRH agonist, they can be used in both males and females. They appear to be safe and effective, although only a small number of
individuals have been treated. Another GnRH vaccine, GonaCon, produced by the USDA National Wildlife Research Center, can only be licensed for use in free-ranging wildlife and cannot be used in zoo animals.

Porcine zona pellucida vaccine

Porcine zona pellucida vaccine (PZP), produced by the Science and Conservation Center (Billings, MT), has been used successfully for several decades in captive animals, primarily in ungulates.\textsuperscript{15,16} Advantages include being safe for use in pregnant, lactating and juvenile females, plus natural cycles and sexual behavior continue, which is often preferred. Although being injectable is a further advantage, it requires a booster injection at about one month as well as annually. Reversibility decreases with long-term treatment.

Suppression of reproduction and infertility

Captive breeding programs require reproductive management such that each year some individuals receive breeding recommendations and others do not. Options for those not recommended to breed are separation of sexes or contraception, both of which carry some risk to fertility, again, apparently more serious for carnivores than for other taxa. Synthetic progestins as well as natural progesterone in cycling females can cause endometrial hyperplasia (EH) or other abnormal tissue changes.\textsuperscript{17} Even the GnRH agonist implant Suprelorin was associated with increased EH in wild canids unless the stimulation phase, which can induce estrus followed by a prolonged luteal phase.\textsuperscript{18} Lifetime Reproductive Planning is being developed by the RMC to optimize breeding intervals that establish and maintain female fertility.

Fertility control in free-ranging wildlife

Although many fertility control methods have been used in many species, few have advanced to management application. Estrogens and progestins are seldom used in free-ranging wildlife, because of potential side effects (especially in carnivores) and because they pose a danger to humans if they enter the food chain (e.g., white-tailed deer). Instead, PZP (porcine zona pellucida) and GonaCon (anti-GnRH) vaccines have been considered more viable options. Major drawbacks have been application of the vaccine, since capture is required, and the need for boosters to establish and maintain contraceptive effect. However, progestins pose little risk for primates; etonorgestrel implants (Implanon: Merck) are being used successfully to control numbers of Barbary macaques.\textsuperscript{19}

White-tailed deer have been treated successfully with PZP vaccine\textsuperscript{15} in many locations, and more recently GonaCon has been licensed for use in white-tailed deer.\textsuperscript{20} Both products have also been used in African elephants for population management and in American bison to control the spread of brucellosis.\textsuperscript{15,21} GonaCon is being used for wild boar as well.\textsuperscript{22} Although free-ranging domestic horses are not technically wildlife, they have been a popular target species for fertility control.\textsuperscript{23} Horses have been treated most extensively with PZP vaccines, particularly ZonaStat-H\textsuperscript{15} but also with SpayVac.\textsuperscript{24}

Most fertility control products have been used to control mammal populations, and options for other taxa are quite limited. An exception are products containing nicarbazin for pigeons and Canada geese, OvoControl-P and -G, respectively (Innolytics). Nicarbazin, originally developed to control coccidiosis in chickens, has a side effect of preventing fertilization.\textsuperscript{20}

Future directions

Although a considerable number of options are available to the zoo community for captive wildlife, there are no reliably reversible methods for male ungulates. Suprelorin, especially with Ovaban treatment around the time of implant insertion, has been safe and effective in all mammalian females tested, but time to reversal is unpredictable, presenting difficulty for planned breeding. As the importance of reproductive management increases for birds and reptiles, more methods, better suited to these species are needed. The challenges for field application are even more difficult, with targeted delivery and longer duration of efficacy being the most pressing problems. Effective population management and
conservation of many species will depend on reliable methods of fertility control. Development of those methods will require research effort and financial support.

References