Targets and Historical Approaches to Non-surgical Sterilization in Dogs and Cats – *Purswell*

Note: This abstract was submitted as a paper titled "Historical Approaches to Non-surgical Contraception in Dogs and Cats" by Beverly J. Purswell and Wolfgang Jöchle.

For millennia, surgical castration, removal of the testes or ovaries, has been the only reliable and permanent method of contraception in domestic animals. The oldest evidence for surgical castration of domestic male animals can be traced back to the late neolithicum (7-6000 BC). Documentation for surgical castration in male dogs goes back to ancient China, Siberia, and Greek and Roman antiquity.[1, 2, 3] In literature throughout the ages, many authors discuss dog breeding, management, and health care. Contraception is not a part of this body of literature. This is in sharp contrast to the amount of literature on male and female castration of horses and mules. One English book (that dates back to 1575) on the art of hunting mentions castration of male and female dogs, but does not give any technical details.[4]

From the 15th to the 19th century, evidence of European professionals with a special license for castrating male and female farm animals can be found.[3] The professionals were organized into guilds, and had lists of fees which were approved by local authorities or the ruling princes.[3, 4, 5] Modern veterinary medicine in the late 18th century and 19th century slowly took over the castration business, at least in pets and horses, and brought a level of humaneness to the process. In 1975, in a British Small Animal Veterinary Society publication, it was mentioned that anyone older than 18 years of age was legally entitled to perform castration of a cat or a dog at any time until it is 6 months of age, provided that adequate anesthetic was administered.[6] By 2007, the law had changed and castration of dogs and cats could only be provided by veterinarians. The 20th century saw modern legislation in Europe on animal welfare that forbade any surgery in healthy pets. Once data on the health benefits of gonadectomy (e.g., lessening of mammary tumors in bitches[7] and benign prostatic hyperplasia in dogs[8]) was provided, neutering and spaying of pets became legal again.

Contraception and abortive medications in dogs and cats have only had recent attention in the later half of the 20th century. Around 1960, due to the availability of orally active and increasingly more effective progestins ("The Pill"), efforts began on a larger scale to control reproduction in dogs and cats. As oral contraception products became widely available for women, the desire to use these products in pets became more mainstream. The status of dogs and cats also changed during this time to true companions, family members, and even child substitutes. It was at this time that animal stewards began to be concerned about the fate of unwanted and unplanned offspring and the horror of increasing numbers of dogs and cats destroyed each year. Progestin-based "Pills for pets" were developed in Europe, coming to the market in 1963.[9, 10]

Progestins, progesterone-like compounds, have been the most common compounds used to address estrus control in the dog. These progestins, administered orally or by injection, have had varying results and acceptance by veterinarians and pet owners. Medroxyprogesterone acetate (MAP) in tablet form was the "Pill" that was marketed first in Europe in 1963. In the U.S., MAP was marketed as an injectable product with disastrous results.[11] Introduced in 1964, MAP was produced as a long-acting crystalline suspension (4-5 months duration, Promone E or Depo-Provera, Upjohn). This product was very effective in estrus suppression but caused pronounced cystic endometrial hyperplasia in the uterus, resulting in an epidemic of pyometra. This problem resulted in a withdrawal of the product from the market two years later, never to appear again for this use. As a further consequence, veterinarians in the U.S. lost confidence in any hormone-based contraception. The veterinary profession in North America thus went to a strictly surgical means of estrus control.

Because of the veterinary and animal welfare environment in Europe, veterinarians worked with the available pharmaceuticals to develop safe protocols for progestins. During the 1960s and 1970s, other progestins were introduced, such as chlormadinone acetate (CAP), delmadinone acetate (DMA), and proligestone (PRO). Use of the progestins was refined by lowering the dose and timing of administration.[12, 13] Emerging insights into the canine reproductive cycle began to allow for strategies uniquely suited for the species. In the bitch, pregnancy and pseudopregnancy are endocrinologically and morphologically very similar.[14, 15, 16] Treatments for estrus prevention and an interruption of cyclicity was found to be safe when begun 4 months after an estrus, and at least 1 month prior to the next anticipated estrus (i.e., during an estrus). The treatment could be repeated every 4-5 months for years of safe estrus prevention.

Megestrol acetate (MGA) was another early progestin that was marketed in Europe, the U.S., and Canada, beginning in the early 1970s. This product is an oral tablet that has been the only product approved for use in the breeding bitch in the U.S. Marketed as Ovaban®, there were two protocols approved for use in the dog. One was at a higher dose and short duration to stop a cycle once begun. The other protocol was at a lower dose and longer duration to prevent the cycle from occurring. Although the marketing of MGA as a specific veterinary product has been discontinued, MGA is used routinely

in women (Megace®) and is thus readily available to veterinarians in North America. Many generic forms of MGA are now available at a very reduced cost to the client.

In cats, progestins have proven to be problematic. Progestins have never been as popular as they were in the dog. Their use has been restricted to oral MGA or MAP, once or twice weekly for estrus suppression or prevention.[17] Cats have problems with progestins causing an adverse effect to the adrenals, resulting in irreversible diabetes.[18, 19] Because of this significant, life-altering side effect, progestins are not typically used in the cat.

In addition to progestins, androgens have been used for estrus control in the dog. Testosterone, either oral or injectable, is used routinely in racing greyhound bitches while training and competing.[20] The side effects of masculinization, while desirable in the racing athlete, limits the use of testosterone in the wider pet population. Another compound with androgenic activity, mibolerone (MIB), was marketed in North America. Introduced in 1978, MIB (Cheque®, Upjohn) was discontinued in 1990. Veterinarians continue to use MIB for estrus control in the bitch by accessing it from compounding pharmacies. Mibolerone requires daily oral use, begun at least 30 days from the onset of an estrus, to successfully prevent cycling. Widely accepted use of MIB, aside from the show-dog world, has been limited in the pet population due to its androgenic side effects (clitoral enlargement, musky body odor, and behavioral changes).[21]

Contraception, in a wider sense, includes methods that interrupt pregnancies after mating has taken place. Prevention of nidation (embedding of a fertilized ova into the endometrium) or interruption of a pregnancy (induction of abortion) are two areas upon which veterinary attention has been placed. The use of estrogens after "mismating" for the prevention of nidation is still widely used. Safety issues are a concern when using estrogens for this purpose. Long-acting estrogens, such as estradiol cypionate (ECP, Upjohn), can cause cystic endometrial hyperplasia resulting in pyometras.[13, 22] Protocols using diethylstilbestrol (DES) are described for the same purpose.[22] Estrogen is known to be toxic to the canine bone marrow, producing an irreversible and fatal aplastic anemia.[23] Because of these two life-threatening side effects, use of estrogen for mismating is questionable.

Interruption of a pregnancy, elective abortion, has been a tool used to prevent unwanted or unintended litters in dogs and cats. Several categories of drugs and hormones have been shown to induce abortion effectively. Prostaglandin F2alpha (PGF) was shown in 1973 to be luteolytic in the bitch.[24] The dog and cat, being luteal-dependent species, require the corpora lutea (CL, the ovarian structure responsible for producing progesterone) for the duration of the pregnancy. Any lysis of the CL will result in the termination of pregnancy. The use of PGF for elective abortions was quickly confirmed.[25, 26] Acceptance of elective abortion using PGF has been limited due to the side effects and variable time to effect.

In 1973, it was shown that prolactin, essential for lactation in the bitch and queen, can be blocked by ergot derivatives.[27] Starting in 1984, it was shown that prolactin was an essential luteotropic hormone during the second half of pregnancy in the bitch and from day 28 to day 42 of gestation in the queen.[28, 29, 30] The abortive effects of treatments using prolactin inhibitors, bromocriptine, metergoline, and cabergoline, alone or in combination with PGF, in bitches or queens have been confirmed and are widely used.[31, 32] The suitability of protocols using cabergoline in feral cats has been shown but does not appear to be economically feasible.[33]

The next hormonal approach to contraception in small animals to be developed was gonadotropin Releasing Hormone (GnRH) analogs. The advantage to using GnRH or its analogs is that it is high enough in the hormonal cascade to be effective in males or females.[34, 35] Also, GnRH has complete homology within mammals, making any product potentially useful in a variety of species. The development of a long-acting preparation has long been sought. Compounds began to emerge as promising candidates. Long-acting powerful analogs have been shown to occupy GnRH receptors at the pituitary and after a short period of stimulation render them reversibly insensitive to endogenous GnRH in a process called "receptor down-regulation." As down-regulation occurs, production of gonadotrophins ceases, thus effectively shutting down spermatogenesis and androgen production in the male and cyclic ovarian function in the female. This effect is well known and as early as 1989 had been suggested as a potential estrus suppression hormone for the bitch.[36]

Three factors have prevented rapid development of a GnRH product for use in estrus suppression in small animals: (1) high cost of these analogs, (2) initial induction of a (sometimes) fertile estrus prior to down regulation, and (3) strong individual variations in the duration of contraception. Leuprolide (Lupron®) came onto the market for human use in the 1990s, but its substantial cost prevented its veterinary use. Peptech Animal Health in Australia developed a much less expensive implant for a 6- or 12-month release using the analog deslorelin. Treatments with these implants, containing down-regulating doses of deslorelin, resulted in cycle control in the bitch and queen,[37, 38] and in suppression of spermatogenesis, libido and aggressiveness in male dogs.[37] Approval for its sale under the trade name Suprelorin® was obtained in New Zealand and Australia in 2003, and in the European Union in 2007. Another GnRH analog, a azagyl-nafarelin implant, has been approved for sale in Europe in 2006 under the tradename Gonazon® for use in dogs and possibly in

cats. Both of these preparations are examples of a novel approach to defining duration of drug effects: it is based not, as usual, on the medium duration of relevant drug effects, but on the minimal duration of such effects in a large population with widely varying duration of effectiveness. The usual low toxicity of these analogs allows for repeated treatments even if the effect of a prior treatment has not expired. Induction of estrus and ovulation as an initial treatment response can be avoided with either implanting bitches during their luteal (progesterone) phase, 60 days post-estrus, or after a short-term pretreatment with exogenous progestins, such as MGA.[39]

Male dogs have been subject to contraceptive treatments only in the last decade. Surgical castration of male dogs continues to hold a wide taboo among many cultures. Efforts have been made to find a safe single intratesticular treatment causing the testes to atrophy. A variety of compounds have been tested. The first product (Neutersol®, zinc gluconate/arginine) to fulfill both the safety and effectiveness criteria became commercially available in 2003.[40] Distribution was halted in 2005 when the patent-holder and marketing company severed ties. Neutersol® is no longer available in the U.S., but a Latin American version of the drug, Esterilsol, is available in Mexico. Contrary to the reversible GnRH treatment, these intratesticular treatments result in irreversible destruction of germ cells and hormone-producing tissues.

Another avenue for contraception is immunocontraceptive vaccines. Anti-zona-pellucida vaccines derived from porcine oocytes have been used in a variety of species. These vaccines have been shown to cause reversible infertility in ruminants, horses, seals, and elephants. In bitches, an irreversible infertility was induced by destroying the entire ovarian follicle pool[41] but was totally ineffective in the queen.[42] These results have led to efforts to identify canine-specific and feline-specific antigens in canine and feline zonae pellucidae and to use suitable candidates for crafting immunocontraceptive vaccines for bitches and queens.[42, 43]

Another avenue to immunocontraceptive vaccines are hormonal antigens, preferably peptide hormones. The antigenicity of GnRH complexes has been confirmed since the 1970s. Because small peptides make weak antigens, potent but safe adjuvants are needed. Adjuvants must render the vaccine effective with a minimum number of injections needed, but must also cause minimal site reactions. These vaccines would be effective in multiple species and in both males and females.

Pfizer recently received provisional approvable of a GnRF vaccine for use in male dogs for the treatment of benign prostatic hyperplasia. This vaccine is currently no longer available. This vaccine required two injections, 4-6 weeks apart, to be repeated every 6 months. Similar vaccines are currently available in swine (Improves™) and in horses (Equity™). The availability and success of these GnRH(F) vaccines hold promise for its use in cats and dogs.

Other avenues to non-surgical pet contraception are being explored. They include GnRH antagonists, and non-peptide GnRH antagonists.[44] Depot preparations will need to be developed. Cost, again, will need to be addressed to gain widespread acceptance for use in companion animals. The advantages of these approaches may be quick action, reversibility of effects, and safety.

The future will belong to products that are economically feasible, safe, and effective, and will return the pet in regular intervals to the veterinarian's office. This can potentially allow the creation of an entire pet wellness program around these visits for the benefit of all parties concerned.

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