Pregnancy termination in companion animals

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Abstract

Despite a large body of research and numerous review papers on the subject, there is still a great disparity in treatment protocols for mismated companion animals in the USA and elsewhere. Numerous treatment protocols are available. Ovariohysterectomy has the advantage of permanently removing the risk of an unwanted pregnancy. Medical treatments have varying side effects, depending on the protocol selected, and depend on owner vigilance to prevent future pregnancies. Medical treatment is most often performed in early gestation or mid-gestation. Pregnancy termination after fetal ossification results in abortion of non-viable or poorly viable fetuses.

Early treatment, prior to or shortly after onset of diestrus, results in resorption of fetal fluids and tissues without vulvar discharge, but must be done prior to pregnancy diagnosis. Treatment protocols for pregnancy termination at this stage are associated with more side effects than those for mid-gestation. Pregnancy termination after ultrasonographic confirmation in mid-gestation may result in resorption of all fetal tissues or in expulsion of bloody discharge. Delaying medical treatment until after pregnancy diagnosis minimizes drug risks by avoiding treatment of non-pregnant animals and through the use of lower doses of medication. Several protocols for pregnancy termination at this stage are discussed in detail in this review article.

Keywords: Pregnancy termination, prostaglandin, dopamine agonist, estrogen, glucocorticoid, GnRH

Introduction

Veterinarians in all walks of life—from those that focus on companion animal reproduction to large animal veterinarians with no other small animal experience—are regularly asked “what to do?” with a bitch or queen that escaped at just the wrong time. Furthermore, in a time where thousands of unwanted animals are euthanized daily in the USA, finding the answer to that question carries a real significance and has stimulated a wealth of research and numerous reviews. However, little consensus exists regarding the best approach to pregnancy termination in dogs and cats.

Determining the risk of pregnancy

Treatment choices should be guided by an animal’s actual risk of pregnancy. In dogs, a vaginal swab and cytologic evaluation provide two key pieces of information: 1) detection of sperm heads on cytology can confirm exposure to a male, and 2) determination of estrus stage at the time or presentation. In a study involving 16 females with known breeding histories, Whitacre and coworkers demonstrated that sperm could be seen microscopically in 100% of cases within 24 hours of breeding and in 75% of cases within 48 hours of breeding, using a modified sampling technique. In this study, a moistened swab was placed into the vagina for 60 seconds before removal and then submerged in 0.5 ml of saline for ten minutes. The saline was centrifuged and sediment was examined after staining. Determination of estrus stage is also a key component of determining the risk of pregnancy. Bitches with known or suspected exposure to a male during proestrus are at much lower risk of pregnancy than those exposed during estrus. Cytologic diagnosis of proestrus can be further confirmed with serum progesterone concentrations of <2 ng/mL. In cats, collection of a sample and interpretation of a vaginal cytology is more difficult than dogs and it is not known whether sperm can be easily detected in this species. However, as cats are induced ovulators, serum progesterone will likely be low in unexposed cats (<2 ng/mL) and would rise after coitus in exposed cats.

During the examination, owners should be questioned regarding the intended use of their animal and the relative merits of different treatment options should be explained. Animals that are not intended to be breeding animals should undergo ovariohysterectomy in early diestrus or pregnancy. This will prevent future unwanted pregnancies and may decrease the animals’ risk of several diseases, including pyometra and mammary and ovarian neoplasia.
Early pregnancy termination

Several protocols have been proposed to medically treat bitches as soon as a mismating occurs.\textsuperscript{11-14} This approach has the advantage of rapidly addressing the owners’ concerns and preventing pregnancy, but may pose a greater risk to the animal and have lower success rates than other protocols. As a result, most reviewers have recommended against these treatment regimens.\textsuperscript{3,6,7,9,15}

Estrogens have been widely used for this purpose in the past, but potentially severe side-effects should raise concerns. In a study by Bowen and coworkers, which demonstrated a high efficacy of this drug, two of eight dogs receiving estradiol cypionate developed pyometra.\textsuperscript{11} More recently, Whitehead reported that the risk of pyometra in animals treated with low doses of estradiol benzoate was more than six times greater than the risk in untreated animals.\textsuperscript{16} Further, several reports indicate significant other health risks associated with estrogen treatment in dogs and cats, including infertility and severe myelotoxicity.\textsuperscript{11,17,18}

Prostaglandins are effective at inducing luteolysis early in diestrus.\textsuperscript{4,13,19,20} However, the high doses of prostaglandin required in early pregnancy are associated with substantial clinical side effects, including emesis, diarrhea and cramping. Further, pregnancy may be maintained even after documented luteolysis at this stage.\textsuperscript{4,20,21}

In contrast, work in recent years shows good success for other treatment regimens in early pregnancy. These are currently not available in the USA, but may pose viable treatment options in the future. The progesterone antagonist aglepristone is licensed for veterinary use in Europe, but is restricted in the USA. Antiprogestins have been shown to effectively induce fetal resorption with minimal side effects in early and mid-gestation and fetal abortion in late gestation.\textsuperscript{1,6,14,22-25} Recently, a series of studies by Gobello and coworkers have investigated the effects of the gonadotropin releasing hormone (GnRH) antagonist acyline in dogs and cats. Although this drug is currently not commercially available, several studies suggest that it may be useful to prevent pregnancy if given to either a bitch or queen during proestrus with few side effects.\textsuperscript{26,27}

Pregnancy termination in mid-gestation

Due to a lack of (known) early pregnancy factors in companion animals, which would aid pregnancy diagnosis, any treatment protocol at this stage must be done based on the suspicion of pregnancy. However, in one retrospective study, fewer than 40% of animals that presented because of mismating were pregnant.\textsuperscript{21} Thus, it is likely that even within the pool of high risk animals (based on cytologic and hormonal diagnosis of sperm and estrus), a proportion of animals would be treated needlessly. This can be avoided by delaying treatment until pregnancy diagnosis can be achieved.\textsuperscript{7} In the dog, pregnancy can be readily diagnosed by palpation approximately 30 days after mating, whereas ultrasonographic examination can confirm pregnancy as early as 15-18 days after the luteinizing hormone (LH) surge (~10-20 days after mating). Embryos are easily detectable between day 22 and 25 after LH surge.\textsuperscript{26,29} In the queen, ultrasonographic pregnancy diagnosis can be achieved as soon as 11 days after mating and the embryo becomes visible by 14 or 15 days after mating.

Five major drug classifications have been described for pregnancy termination in mid-pregnancy: prostaglandins (natural and synthetic), dopamine agonists, antiprogestins, glucocorticoids and GnRH antagonists. At this stage, embryonic fluids and tissues are resorbed by the uterus and few clinical signs are expected in response to medical intervention. A bloody discharge may be seen in bitches and queens after approximately 30 days. Abortion (fetal expulsion) occurs after 40-45 days, when fetal ossification is underway.\textsuperscript{8,28}

Prostaglandins

In domestic carnivores, pregnancy maintenance is dependent on luteal progesterone production. Although small amounts of progesterone are also produced by the feline placenta, this does not appear to be sufficient for pregnancy maintenance.\textsuperscript{30}

Natural prostaglandin can be used to terminate pregnancy beginning five days after ovulation, however prior to 25 days, higher doses are required than later in gestation. Common side effects include hyper-salivation, bradycardia, emesis and reflex voiding and are more severe in dogs than in cats.\textsuperscript{4}
Hospitalization and careful monitoring of animals are recommended to control side effects, which tend to be more severe early and diminish during the course of treatment. Side effects may be minimized by using low doses (30-50 µg/kg, 3-4x daily for 4-11 days)\(^4,13,31\) or by starting with a lower dose and gradually increasing it (30-50 µg/kg, increased to 100-200 µg/kg).\(^7\) It should be noted that low doses may not induce permanent luteolysis, resulting in loss of only some pups or fetal death followed by mummification.\(^4\) The synthetic prostaglandin cloprostenol has also resulted in effective pregnancy termination, with few side effects.\(^6,9,31\) In the USA, most practitioners are familiar with protocols using 100-250 µg/kg of prostaglandin 2-3x daily for 4-6 days.\(^4,20,21\)

**Dopamine agonists**

In both the bitch and queen, prolactin plays a necessary luteotrophic role in pregnancy maintenance.\(^6,15,32\) Progesterone can be reduced or eliminated during late pregnancy by administering a dopamine agonist, which inhibits endogenous prolactin secretion.\(^32\) However, treatment success for pregnancy termination has been inconsistent in both dogs and cats and dopamine agonists alone are rarely used in companion animals.\(^9\)

**Progesterone antagonists**

Progesterone antagonists including RU 486 (mifepristone) and aglepristone have been studied extensively and result in pregnancy termination prior to 45 days with minimal side effects in dogs.\(^2,14,22,23,25\) Aglepristone also was effective for pregnancy termination in the cat, with higher success rates early in pregnancy than late in pregnancy.\(^1\) Aglepristone is licensed for veterinary use in Europe, however progesterone antagonists are currently not available for veterinary use in the USA.

**Glucocorticoids**

Administration of oral and injectable formulations of dexamethasone for ten days to pregnant bitches between 28 and 51 days of gestation resulted in resorption or abortion in all treated animals.\(^33,34\) Subsequent studies involving twice daily administration of dexamethasone (200 µg/kg, tapering over the last 3 days) for 7.5 or 9.5 days resulted in pregnancy termination in up to 100% of cases.\(^35\) Premature and term delivery of live or dead fetuses resulted in some cases of animals treated after 45 days, while vaginal discharge was the primary clinical sign in most dogs treated in mid-gestation. Polyuria and polydipsia were the primary side effects noted in these studies and attributed to adrenal suppression. Side effects were transient and disappeared after conclusion of the treatment. Glucocorticoids have the advantage of being inexpensive and are often available in oral formulation. Thus they are easily administered to animals on an outpatient basis and can be administered in food to feral animals. The mechanism of action has not been fully elucidated at this time. The use of glucocorticoids for pregnancy termination has not been investigated in cats.

**GnRH antagonists**

The concept of using GnRH agonists or antagonists for the purpose of pregnancy termination was first described by Vickery three decades ago.\(^36\) At that time, hypersensitivity reactions in dogs prevented their use. Recently, however Gobello and coworkers have shown that a third-generation GnRH antagonist, acyline can terminate pregnancy in dogs.\(^37,38\) Twenty-one animals were administered 110 µg/kg or 330 µg/kg of acyline, or saline via a single subcutaneous injection between 25 and 35 days of gestation. All animals that received acyline, but no animals injected with saline experienced an abortion between two and 12 days after treatment. This approach would potentially be highly valuable for feral populations of dogs, where repeated administration of medication is difficult, but is currently not commercially available. It is not known at this time, whether earlier administration of a GnRH antagonist during pregnancy such as acyline would result in resorption rather than abortion. Acyline was not effective at inducing luteolysis or pregnancy termination in queens.\(^27\)
Combined prostaglandin/dopamine agonist regimen

Extensive work by Verstegen and coworkers, demonstrated that a dual approach to pregnancy termination results in reliable efficacy in mid-gestation. Low doses of either natural or synthetic prostaglandin results in luteolysis, while dopamine agonists inhibit prolactin release. In a series of studies, administration of cabergoline (1.7-5µg/kg once daily for 10 days) and cloprostenol (1-2.5 μg/kg once or twice 5 days apart) resulted in fetal resorption with minimal discharge or unwanted side effects. In cats, pregnancy was terminated in five of five animals administered cabergoline (5 µg/kg once daily) and cloprostenol (5 µg.kg every other day) to effect. In both dogs and cats, treatment was continued until ultrasonographic confirmation of fetal demise. The above protocol has several distinct advantages over other protocols described. Both prostaglandin and dopamine agonists are readily available in the USA. The combined luteolytic and antiluteotropic mechanisms decrease dosages of each drug, substantially reducing side effects. The protocols can be instituted around day 25 days and result in resorption prior to fetal ossification, when most animals would abort formed fetuses. The use of orally administered dopamine agonists and long-acting, synthetic prostaglandin eliminates the need for frequent examination and hospitalization.

Conclusions

In conclusion, risk for pregnancy should be determined at the time of mismating and ideally pregnancy should be confirmed prior to treatment in order to avoid unnecessary and potentially harmful medical side effects. Treatment choices should be based on the animal’s stage of gestation and drug availability and should be tailored to minimize side effects as much as possible. A treatment onset between 25 and 30 days and combination of two drugs, including a prostaglandin and dopamine agonist minimize drug dosage and side effects while inducing fetal resorption rather than abortion. Alternate treatment protocols, including the use of progesterone antagonists of GnRH antagonists may become available in the USA in the future.

References