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Pharmacological Approaches to Pregnancy Termination in Dogs and Cats Including the Use of Prostaglandins, Dopamine Agonists, and Dexamethasone (13-Aug-2002)

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Introduction and Overview
Several methods for the termination of unwanted pregnancies in dogs and cats have been described and reviewed in recent years [1-9]. These have been further characterized, supplemented and refined by additional experimental and clinical studies [10-16], as summarized in this review. The current status of clinical methods for the termination of pregnancy in dogs and cats is the basis of the present review. The basic aspects of canine and feline pregnancy have been reviewed elsewhere [17,18].

The use of estrogens as an immediate treatment for an unwanted mating (mismating) in dogs is no longer recommended or considered ethical by some authors and veterinary societies for several reasons [5,8]. Reasons include the facts that (a) many mismated dogs are not actually pregnant; (b) no dose of estrogen (estradiol-cypionate (ECP) or diethylstilbestrol (DES)) has been demonstrated to be routinely both efficacious and safe; (c) prostaglandin-F 2alpha (PGF) administration and several other therapies exist for pregnancy termination at or shortly after implantation and early diagnosis of pregnancy, as well as during mid-gestation; (d) administration of estrogen as a contraceptive has been observed to result in uterine disease; and, (e) in a prospective study, doses of estrogens that appeared to be safe were not routinely effective and doses that appeared to be routinely effective, were observed to cause uterine disease, at least when administered after ovulation [19]. Whether a recently proposed use of very low doses of estrogen formulations to prevent pregnancy following mismating are entirely safe and effective remains to be determined and does not appear to have been subjected to prospective study.

The mechanism of action of estrogen as a mismating treatment regimen appears to involve estrogen-induced persistent closure of the tubal-uterine junction and prevention of embryo transport as well as a potential direct embryotoxic effect, based on studies in cats [20].
Most methods currently proposed for pregnancy termination in dogs and cats act by interrupting or interfering with the supportive action of progesterone on the uterus and placental attachment. Maintenance of pregnancy in all mammalian species requires progesterone throughout gestation. These effects of progesterone include stimulation of the development, differentiation and glandular secretion of the endometrium of the pregnant uterus; endometrial secretion of specific compounds required for preimplantation embryo development, embryo attachment and nidation; support of placenta formation; maintenance of placental attachment; and reduction of myometrial contractility and maintenance of uterine quiescence by multiple mechanisms.

Natural PGF and the more potent PGF-analogs are effective in the termination of pregnancy because (a) PGF is luteolytic in dogs as in most species [1], and (b) corpora lutea are the only source of progesterone in the pregnant bitch [8] . A PGF-induced luteolysis causes a decline in progesterone, withdrawal of progesterone action and, as a result, termination of pregnancy. Prostaglandin is also utero-tonic and the uterine contractions caused by PGF facilitate its abortifacient action. While the use of PGF to terminate pregnancy is an extra-label and experimental use of the drug, it is being used increasingly for this purpose in many veterinary practices. PGF administration is by injection, at intervals typically more frequent than

once a day, and thus can become labor intensive and expensive due to the costs of hospitalization and professional time.

Dopamine agonists are also used clinically to terminate pregnancy in dogs, either alone, or in conjunction with prostaglandin, especially in European countries where they are marketed as veterinary drugs. Dopamine agonists and related compounds, including bromocriptine, metergoline and cabergoline, are effective because they suppress prolactin secretion. Prolactin is a required luteotrophin in the pregnant bitch. Dopamine agonist administration causes a suppression of prolactin secretion and thus results in luteolysis and termination of pregnancy due to progesterone withdrawal. The dopamine agonists bromocriptine and cabergoline are marketed in the USA for human use only and their use in small animals is extra-label and considered experimental. Bromocriptine has significant side effects, cabergoline less so. Cabergoline is available in some European countries as a veterinary drug for treatment of pseudopregnancy, but it is also used for pregnancy termination.

Corticosteroid administered orally is also an option. Several published and unpublished clinical studies have demonstrated the efficacy of oral dexamethasone therapy in terminating pregnancy in dogs, especially in situations where hospitalization or frequent treatment by a veterinarian or other qualified health professional are not options. However, the questions of whether this is an appropriate use of corticosteroid therapy, and of whether the administration of doses that are also immunosuppressive to dogs that are otherwise healthy is appropriate, require further consideration.

For termination of pregnancy in cats, PGF and dopamine agonist treatments are apparently effective, but the number of studies is limited. The efficacy of dexamethasone in cats has not been studied. In both dogs and cats, combination therapies using both prostaglandin and a dopamine agonist have been developed as pregnancy termination protocols.

Finally, anti-progestins (progesterone antagonists) similar to the human abortifacient RU486 can be very effective in terminating unwanted pregnancy in any species, although their availability is currently very limited. If and when such drugs will be available more widely than in the few European countries that currently have access to them, is not known.

It is important to also consider that for most modes of pregnancy termination there may be a distinct advantage to delay treatment until after confirmation of pregnancy. In one study, over 60% of bitches presented for mismating were discovered not to be pregnant [21]. Therefore, when providing an anti-conceptive treatment to bitches, over half of the animals are apparently being treated unnecessarily.

Organization - The sections included in this review are titled as follows. They can be reviewed independently, but are intended to be read sequentially.

Disclaimer - The authors provide this information without any claims as to efficacy or recommendations for use. Many of the treatments described are extra label and experimental, and clinicians should address any legal or ethical concerns before considering their use.

Use of Prostaglandins to Terminate Pregnancy

Prostaglandins (PGs) are naturally occurring prostanoids derived from arachidonic acid and are found in all tissues. PGs are regulatory substances with varied and multiple effects on the biochemical activity of vascular, gastrointestinal, respiratory, and reproductive tissues. The prostaglandin-F2alpha (PGF) has been found to have luteolytic and uterotonic properties in most mammalian species studied. In addition, PGF has potential effects on other body systems. Common side effects of PGF in dogs include hyper-salivation, bradycardia, reflex defecation and urination as well as emesis [3]. Prostaglandin-F2alpha is marketed in the form of the tham-salt of naturally occurring PGF. Prostaglandin-F2alpha can be used to terminate pregnancy in dogs at almost any time beginning about one week after the end of estrus if administered frequently enough and for a sufficiently long duration. However, there are many decisions to be made about the doses, timing and management when this therapy is used. It is also experimental and an extra-label use of the drug. Caution in the use and handling of the drug by

clinicians and technicians is critical, in that side effects can be debilitating, including broncho-constriction. It should not be handled by women who are pregnant.

Prostaglandin-F2alpha in Dogs - The abortifacient efficacy of PGF involves induction of luteolysis, stimulation of uterine contraction and cervical dilation. Of these, the luteolytic effect is the most important. In dogs, the progesterone supporting pregnancy comes entirely from the corpora lutea throughout gestation. Prostaglandin-F2alpha will induce luteolysis and depress progesterone concentrations to nearly non-detectable levels more readily after Day 25 or 30, than earlier in pregnancy. Prostaglandin-F2alpha is rarely capable of inducing luteolysis in very early pregnancy (Day 1 to 15) if treatment is not continued well beyond Day 15 or 20. The later in the cycle PGF is administered, the easier and more rapidly the induction of luteolysis. Use of PGF requires intramuscular or subcutaneous administration 2 or 3 times a day, for 4 to 6 days or longer. Most reviewers consider hospitalization as part of the protocol, to allow for the monitoring of adverse side effects and confirmation of efficacy [3]. Some clinicians allow bitches to be returned home after side effects have been carefully checked by the clinician after the first PGF administration, and the treatment continued at home by the owner where local regulations and liability issues permit. The PGF product most frequently used in dogs in North America is PGF-2alpha tham-salt, commonly referred to as dinoprost (Lutalyse), and is marketed for use in cattle. Use of this product in small animals, as for all prostaglandin products, is an experimental, extra-label use and a release form or statement of understanding should be used to document consent of the pet owner. No PGF products are marketed in North America with an indication for use in dogs or cats. Other veterinary PGF, i.e., dinoprost, produced in other countries include: SincroBovis and Dinolytic.

PGF in Mid-Gestation - A course of PGF therapy starting in mid-gestation (around Day 30) can be successful if injections are given at least twice a day (Table 1). Efficacy can be achieved using:

a) Lower, moderate doses (30 to 50 ug/kg) for 5 - 9 days;
b) Increasing doses, starting with 30 - 50 then increasing to 100 - 200 ug/kg after several days; or,
c) High doses throughout (200 - 250 ug/kg).

The attendant side effects include emesis, salivation, defecation, urination, and respiratory distress. Side effects are typically acute and short-lived, dose dependent and self-limiting, and decreasing in intensity with repeated dosing. Since side effects are often self limiting, and since dogs vary in the extent of sides effects, it may be best to initiate treatment with low doses of 50 ug/kg or less, and to then increase the dose over time in relation to the response of the patient.

The half-life of PGF is only seconds, and it is only in the circulation for a few minutes following an IM injection, or perhaps a little longer when it is administered by subcutaneous injection. Therefore, administration multiple times per day is an absolute requirement for efficacy whether using low, moderate or high doses. Treatment must be continued until verification of efficacy by ultrasound or palpation. Partial abortion of litters can occur if treatment is discontinued prematurely. With any dose, 9 or more days may be required to terminate some pregnancies, although 5 to 7 days is usually sufficient.

PGF in Mismated and Early-Pregnant Dogs - High doses of PGF will terminate pregnancy as early as shortly before implantation at Day 22 post-luteinizing hormone (LH) surge [14,22]. Early pregnancy termination was accomplished with PGF-treatment starting at 5 to 15 days after the onset of metestrus (i.e., at 5 to 15 days after the end of vaginal estrus) when using high doses (150 - 250 ug/kg bid) for 4 to 5 days. In many instances, the pregnancy was confirmed before the start of treatment, thereby demonstrating the efficacy of the early treatment. The time of treatment in relation to the LH surge would have been approximately Day 15 to 25 of pregnancy (Table 1). The advantages of waiting until there is a confirmation of pregnancy should be weighed against the convenience of initiating treatment at the time of first presentation.

Low Dose PGF Therapy in Early or Mid-pregnancy - Low-dose prostaglandin therapy, as with high doses, can fail if not administered frequently and for long enough time. However, doses of 20 to 30 ug/kg produce minimal or no side effects, and were used in the first study to demonstrate abortifacient efficacy of PGF in dogs [1]. The same low doses were reported to be effective in terminating pregnancy in each of 14 pregnant bitches when started at 35 to 49 days of pregnancy, and given 3 or 4 times a day for 4 to 11 days [12]. More recently, others have used doses of 20 ug/kg three times a day for 7 days beginning even earlier in pregnancy [15]. In the latter study, pregnancy was prevented by frequent administration of low doses beginning at the end of estrus, and early pregnancy was terminated by administration beginning at the time of the first diagnosis of pregnancy at about 21 days after ovulation. No side effects were noted other than transient hyperventilation in some instances. However, these low doses administered in early pregnancy did not induce a permanent luteolysis in some bitches, and they may be more appropriate for use after Day 25 of pregnancy, when they will cause complete luteolysis in

most cases. One advantage of treatment with low doses is that it can reduce or prevent side effects. Alternatively, doses can be steadily increased during the course of treatment, from relatively low doses (20 - 30 ug/kg) to begin with, and increasing to moderate doses (50 - 100 ug/kg) after a few days. Most bitches appear to accommodate to the drug over time, and side effects become less severe with each administration. Finally, any dose will be more effective and tend to result in permanent luteolysis when administered after Day 25 than when administered before Day 25.

Table 1. Prostaglandin-F2alpha (PGF) and PGF-analog treatments reported to have high abortifacient efficacy in dogs when given "to effect"

Drug	Dose(s)	Day of Pregnancy	Duration
PGF	20 - 30 ug /kg, BID or TID	After Day 25	4 - 7 days or longer
	100 ug /kg, BID	After Day 25	4 - 7 days, or longer
	150 - 200 ug /kg, BID or TID	After Day 15	4 - 7 days, or longer
Cloprostenol	2.5 ug/kg, every 48 hours	After Day 30	4 days, or longer

Using a "25-50-100" moderate-dose PGF protocol in dogs - In general, it would appear that the following "25-50-100" ug/kg regimen would be appropriate in most instances. PGF can be administered, subcutaneously or intramuscularly, 2 or 3 times per day, for 7 days or longer. It would be preferable to begin as soon as possible after confirmation of a viable pregnancy. The protocol involves starting with doses of 25 ug/kg for 1 or 2 days, increasing to doses of 50 ug/kg, and then either continuing with doses of 50 ug/kg or increasing to doses of 100 ug/kg or higher after the 4th day if the higher doses are well tolerated by the bitch (Table 2). The initial confirmation of a viable pregnancy should include either (1) ultrasonographic detection of fetal heartbeats, or (2) successive palpations of enlarging uterine vesicles 4 to 7 days apart. Ideally, treatment would begin between Day 25 and 35 of pregnancy, to ensure that the result is resorption or discharge of minor amounts of uterine contents.

Table 2. Proposed multi-dose PGF protocol to terminate pregnancy in dogs, beginning between Day 25 and 35 of pregnancy, and using SQ injections of PGF two (or three) times a day until confirmation of pregnancy termination

Days of Treatment	Day 1	Days 2 - 3	Day 4 onward
PGF injection doses	25 ug/kg	50 ug/kg	50 or 100 ug/kg or higher

Confirmation of Abortifacient Efficacy of PGF - Whatever the timing, protocol or dosage used, PGF treatment in the absence of untoward side effects should be continued until the confirmation of efficacy. Ideally, this would involve confirmation by ultrasound examination, although in some bitches palpation of the reproductive tract may be sufficient. Ultrasound examination is the only reliable means to evaluate the viability of fetuses in early and mid gestation. Examination by radiography to confirm efficacy based on the absence of fetal skeletons would not be reliable until after Day 45 of gestation, at which time fetal skeletons would normally be detectable. Monitoring of serum progesterone concentrations is not always reliable. Progesterone concentrations can be depressed to less than 1 or 2 ng/ml for several days, or longer, and nevertheless some or all fetuses may survive to term. The expected decline in serum relaxin concentrations following pregnancy termination is not sufficiently rapid or complete to be a reliable means to confirm efficacy. In mid gestation, the observed expulsion of fetal elements is not confirmatory, since partial abortion of litters has been documented.

Synthetic Prostaglandins in Dogs - Highly potent, synthetic PGF-analogs, such as cloprostenol (Estrumate, Veteglan), have not been extensively promoted for pregnancy termination in dogs in North America, because there are no dose-response studies to demonstrate the minimal effective doses. Furthermore, error an dosing by mistakenly using the doses commonly suggested for natural PGF could be fatal. However, cloprostenol has been routinely and effectively used in Europe for pregnancy termination in dogs, being used at a dose of 2.5 ug/kg, administered three times, at 48 hour intervals [10]. Side effects have been reduced by administration of various drugs, including anti-cholinergic drugs like atropine. A study of 67 pregnant bitches demonstrated a 100% efficacy in termination of pregnancy using cloprostenol at the dose of 2.5 ug/kg, subcutaneously, administered three times, at 48 h intervals, starting at Day 30 of pregnancy [23]. Pre-medication given at 15 minutes before prostaglandin-analog injection included atropine sulfate, prifinium bromide, and metopimazine, and it eliminated side effects in 58% of the bitches, and presumably reduced them in others. Cloprostenol at even lower doses has

been used in combination with dopamine agonist treatment to terminate pregnancy in dogs shortly after implantation, as reviewed below. The PGF agonist alphaprostol (Gabbrostim) has also been used to terminate pregnancy in bitches, at a doses to 20 ug/kg, BID. Another PGF agonist is luprostiol (Prosolvin).

Prostaglandin (PGF) for Pregnancy Termination in Cats - PGF treatments were successful in terminating pregnancy in cats when injected after Day 40 in one study, but not in another, as reviewed previously [5]. More recent studies have shown that PGF alone, at a dose of 2 mg/cat IM once a day, beginning at Day 33 of pregnancy, can induce luteolysis and terminate pregnancy by expulsion of fetuses in pregnant cats [24]. Side effects included prostration, vomiting and diarrhea. More recently, the PGF analogue cloprostenol has been studied in combination with the dopamine agonist cabergoline in cats (see below).

Use of Dopamine Agonists to Terminate Pregnancy

Dopamine Agonists In Dogs - Prolactin secretion by the lactotroph cells of the anterior pituitary gland is under the control of multiple neuro-transmitters and hormones. The major control mechanism is the suppression of prolactin secretion by endogenous dopamine released from dopaminergic neurons in the hypothalamus. Prolactin is a major luteotrophic hormone throughout the luteal phase in pregnant as well in nonpregnant bitches, meaning that the secretion of normal amounts of progesterone by the corpora lutea requires the presence of prolactin [2]. Prolactin appears to be an absolute requirement for progesterone secretion by Day 30 after ovulation. Dopamine agonists like bromocriptine or cabergoline are ergot alkaloids, with strong dopamine D2-receptor agonist activity, and thus they can reduce prolactin secretion and thereby suppress progesterone levels. The serotonin antagonist metergoline stimulates endogenous dopamine secretion and thus can inhibit prolactin secretion as well.

Bromocriptine - The dopamine agonist bromocriptine (Parlodel) at doses of 0.1 mg/kg, PO or IM, daily or BID, for 6 days was shown to terminate pregnancy when initiated after Day 30, but typically fails to do so when administered earlier [2]. As reviewed elsewhere, lower doses of 30 ug/kg, PO, were successful in terminating pregnancy in dogs in one report, whereas doses of 62 ug/kg were not effective in another [5,8]. Anecdotal evidence suggests that treatment should not be discontinued until termination of pregnancy has been confirmed. This can require up to 9 or 10 days of treatment. Bromocriptine is marketed for treatment of hyper-prolactinemia in humans, and is not approved for veterinary application in the USA. Bromocriptine is available in tablets, which can be broken into sections sufficient to dose larger dogs. For other dogs, tablets can also be pulverized, and the powder weighed and placed in gelatin capsules, and adjusting for the drug content vs. binder content of the powder in formulating capsules with specific drug doses. Bromocriptine has potent dopamine receptor agonist activity, and often produces side effects including aphagia, ataxia, and emesis. Emesis is presumably due to interaction with dopaminergic elements in the emesis center of the brain and the ability of the drug to cross the blood brain barrier. The emetic effect may reduce the absorption of the total dose administered, and thus compromise efficacy. Therefore, animals should be hospitalized and monitored for side effects and efficacy.

Cabergoline - Dopamine agonists available for veterinary use in Europe have also been used successfully, particularly cabergoline. Cabergoline is also an ergot alkaloid but, compared to bromocriptine, it is a more potent dopamine agonist, is effective at lower doses and has fewer and milder side effects. Cabergoline is effective in terminating pregnancy in dogs when administered at mid-gestation or later [25]. In pregnant bitches treated after Day 30, pregnancy was terminated in most but not all animals when cabergoline was given at a dose of 1.7 ug/kg, SC, every 2 days for 6 days [13,26]. When bitches were treated after Day 40, doses of 5 ug/kg, PO, for 5 days, or doses of 1.7 ug/kg, SC, every 2 days for 6 days, were effective in all bitches treated [13,26]. When cabergoline is started earlier in pregnancy, at Day 25, treatments that were effective later in pregnancy failed in most bitches and the pregnancy continued until terminated by re-treatment at Day 40. Cabergoline treatment did not produce any side affects at these doses. Cabergoline can be administered orally using a liquid formulation marketed in Europe as Galastop for treatment of pseudopregnancy. The side effects of cabergoline are milder (compared to those of bromocriptine) presumably due to the fact that it appears to be a more specific D-2 dopamine receptor agonist and is less able to cross the blood-brain barrier and have CNS effects. Compared to bromocriptine, cabergoline produces fewer and less pronounced side effects in humans as well.

Dopamine Agonists in Cats - The use of dopamine agonists alone appears not to have been studied extensively in cats. Production of litters by feral cats was prevented by addition of cabergoline to the diet of pregnant individuals at a dose of 5 - 15 ug/kg/day for 4 - 12 days [27. In a controlled laboratory study, cabergoline at doses of 1.7 ug/kg given IM daily for 5 days, starting at Day 30 of pregnancy, induced luteolysis and terminated pregnancy in 4 of 5 cats, with negligible side effects [24]. In another study, an oral cabergoline formulation, Galastop administered per os at a dose of 15 ug/kg for 4 to 7 days terminated pregnancy in 8 cats when started between Day 30 and 42, but failed in 2 cats when started at Day 45 [28]. This failure of abortifacient efficacy in late pregnancy is perhaps not surprising, since there is evidence that the feline placenta produces progesterone during the last 3 weeks of pregnancy [18]. Emesis was a side effect in some animals.

Dopamine Agonist plus Prostaglandin Combination - Therapy to Terminate Pregnancy

Combination Therapy in Dogs - Several such protocols have been reported (Table 3). The goal is to have abortifacient efficacy with minimal side effects, without the need for daily injections or daily clinical visits. They were developed after a combination-treatment involving daily injections of the dopamine agonist cabergoline in addition to daily injections of a prostaglandin analog was shown to terminate pregnancy in dogs with treatment starting as early as Day 25 of gestation. Daily subcutaneous injection of cabergoline doses of 1.7 ug/kg, and cloprostenol doses as low as 1 ug/kg, induced luteolysis and terminated pregnancy when initiated at Day 25 of gestation [13]. Whether pregnancy is terminated by resorption or by abortion appears mostly a matter of when in gestation treatment is initiated (J. Verstegen, unpublished observations). The use of oral administration of a dopamine agonist in combination with less frequent administrations of a PG-F2alpha analog such as cloprostenol has also been effective in dogs (Table 3), as well as in cats (see below). When dogs were treated starting at about Day 28 of confirmed pregnancy, each of the five treatment combinations shown in the table resulted in resorption of fetuses [29-31].

Table 3. Combination treatments of dopamine agonist and prostaglandin analog reported to terminate pregnancy in dogs when administered starting around Day 28 of pregnancy
a. Oral cabergoline at 5 ug/kg per day, and cloprostenol injections of 1 ug/kg SQ every other day, to effect, for up to 9 days
b. Oral cabergoline at 5 ug/kg per day for 10 days, and cloprostenol injections of 1 ug/kg, twice, on days 1 and 5 of treatment
c. Oral cabergoline at 5 ug /kg per day for 10 days, and a single cloprostenol injection of 2.5 ug/kg at the start of treatment
d. Oral bromocriptine at 30 ug /kg TID for 10 days, and a single cloprostenol injection of 2.5 ug/kg at the start of treatment
e. Oral bromocriptine at 30 ug /kg TID for 10 days, and cloprostenol injections of 1 ug/kg, twice, on days 1 and 5 of treatment

Side effects were minor using low 1 ug/kg doses of cloprostenol, and were present but acceptable with the higher 2.5 ug/kg dose of cloprostenol. In many instances treatment also results in shortening of the interestrus interval, from an average of about 200 days to an average of about 120 days.

Combination Therapy in Cats - In cats, pregnancy was terminated by resorption in each of 5 animals receiving cabergoline doses of 5 ug/kg, PO, daily and cloprostenol doses of 5 ug/kg, SC, every 48 hours, continued until confirmation of pregnancy-termination [24]. Treatment lasted 7 to 13 days. The high efficacy is likely dependent on continuation of treatment until confirmation of resorption by ultrasound.

Use of Corticosteroids to Terminate Pregnancy

Use of Dexamethasone in Dogs - Dexamethasone administered beginning at mid-gestation can terminate pregnancy in dogs, presumably by activating endogenous mechanisms similar to those involved in parturition. It has not been studied in cats. Dexamethasone is a synthetic glucocortcosteroid typically used for its anti-inflammatory and immuno-suppressive effects. Concerns about its use in dogs have focused on the limited published information, lack of data on the extent of effect on adrenals, and the use of intramuscular injections in the first report of the method. These concerns have been partially addressed by recent studies at the University of Buenos Aires demonstrating abortifacient efficacy of dexamethasone given orally, two or three times a day for 10 days, beginning at Day 30 to 45 of pregnancy, with individual oral administrations of doses progressively decreased from the initial 200 ug/kg doses given for 7 days, to 10-20 ug/kg doses during the last 3 days [7].

Advantages of such a therapy for pregnancy termination include the fact that it involves only oral administration of a relatively inexpensive drug, and the resulting potential for it to be used on an outpatient basis in instances where hospitalization is not practical. More recently, studies in Buenos Aires on larger numbers of dogs, reported that twice daily administration of similar doses of dexamethasone for 7.5 day terminated pregnancy in 58 of 62 bitches. The abortifacient efficacy appeared to be better (100%) with twice daily administration for 9.5 days (Table 4) in a study of 18 bitches [16]. Studies on additional dogs using the same 9.5 day schedule of dexamethasone suggest that the efficacy of the method is about

97% (Wanke 2001, unpublished observations).

Table 4. Dosing schedule for dexamethasone (ug/kg) used in a 9.5-day protocol of twice daily oral dexamethasone administered for termination of canine pregnancy [16].

Time of Day	1	2	3	4	5	6	7	8	9	10
Morning	200	200	200	200	200	200	200	120	40	10
Evening	200	200	200	200	200	200	160	80	20	

The time of pregnancy termination in these studies was estimated based on the timing of observed episodes of vaginal discharge, reports of abortions observed by owners, and an ultrasound examination conducted following treatment. Results indicated that the time of pregnancy termination was between 7 and 13 days after the start of dexamethasone treatment. The average time to pregnancy termination was 10 days.

With the use of dexamethasone as an abortifacient treatment, some bitches have a brownish vaginal discharge at the time of abortion, whereas no such signs or other discharge is observed in other britches. When the treatment was started late in gestation at or after 45 days of pregnancy in a few bitches, live fetuses were aborted. Side effects observed in all dexamethasone-treated bitches were polydipsia and polyuria, beginning shortly after the start of treatment and persisting until a few days after treatment was ended. Other side effects observed in some bitches were transient weakness and milk secretion during the period of abortion or resorption.

The few failures of dexamethasone to terminate pregnancy have included the delivery of live, normal pups at term; delivery of dead pups near term; and, partial abortions in which bitches resorbed or discharged the contents of some of the 5 to 6 gestational vesicles previously diagnosed by palpation or ultrasound and later delivered 1 or 2 dead pups near term.
More recent studies demonstrate that, as expected, the dexamethasone treatment causes adrenal suppression and inhibits adrenal responses to ACTH challenges during the treatment period (Wanke 2000, unpublished data). However, the adrenal suppression is transient and in preliminary studies serum cortisol concentrations were observed to be normal within about one week after the end of treatment (Wanke, unpublished data). The use of declining doses of the corticosteroid over the last 2 to 3 days of treatment is considered unlikely to significantly alter the outcome or side effects, or affect the time course of recovery from transient adrenal suppression. Therefore, a simplified protocol suggested for further study involves using the 200 ug/kg doses throughout 10 days of treatment (Table 5).

Table 5. A proposed single-dose, twice daily, 10-day protocol of oral dexamethasone administration for termination of canine pregnancy beginning between Day 30 and 35 of gestation.

Regimen: Dexamethasone tablets, twice daily, am and pm.
Dose: 200 ug/kg, BID, PO, for 10 days
Expected resorptions or abortions: 7 to 13 days after start of therapy
Expected side effects: PU/PD as symptoms of hypercorticoidism during therapy
Recommendation: follow-up visit to confirm efficacy 4 to 8 days after end of treatment
Caveat: extra label use requiring consent and signed release statement by owner

Results to date suggest that dexamethasone therapy, despite the side effects encountered, can be a viable method for pregnancy termination when no alternative is available and in situations where hospitalization, administration of drugs by a veterinarian, or clinical monitoring are either not possible or not affordable.

Mechanism of Dexamethasone Abortifacient Efficacy - The mechanism of action of dexamethasone in terminating canine pregnancy is not fully understood. In most instances there is a decline in progesterone in response to treatment. Whether the decline in progesterone is an effect of the corticosteroid, and part of the mechanism involved, or a consequence of abortion, or both, is not known. There is indirect evidence that in dogs, as in some other species, normal parturition involves the secretion of luteolytic amounts of prostaglandin-F in response to an increase in corticosteroid secretion by the fetal adrenal at term [18]. One possibility, then, is that the exogenous corticosteroid has an up-regulating effect on uterine or placental

prostaglandin synthesis. However, some dexamethasone-treated dogs terminated pregnancy before progesterone levels were reduced to basal levels, and possible mechanisms of corticosteroid action beyond induction of luteolysis remain unstudied. It is possible that cells that form the placental attachment are differentiated such that a corticosteroid, including endogenous cortisol, can act as an antiprogestin. Such an action has been suggested in other species.

Corticosteroids in Cats - The authors are not aware of any reports on the use or efficacy of this treatment modality in cats.

Progesterone Antagonists (Antiprogestins)

Antiprogestins (progesterone antagonists) are synthetic steroids that bind to the progesterone receptor, but fail to initiate activities normally initiated by progesterone, and by occupying the receptors they prevent the actions of endogenous progesterone. Progesterone is required for the maintenance of pregnancy, as it provides the hormonal stimulus for endometrial development and placental attachment, and also acts to maintain uterine quiescence by reducing the contractility of uterine musculature. Anti-progestins disrupt reproduction and terminate pregnancy in all species studied to date. All anti-progestins tested to date also have anti-glucocorticoid activity, but are more potent as anti-progestins than as anti-corticoids.

Anti-progestins in Dogs - The anti-progestin mifepristone (RU486) is a drug developed for human application, is available in a few countries and is not marketed for veterinary use. This antiprogestin has been shown to terminate pregnancy in all species studied. In dogs, mifepristone terminates pregnancy by resorption when administered at a dose of 2.5 mg/kg, BID, PO for 4.5 days beginning at Day 32 of pregnancy [4]. Efficacy was without side effects. The study required placing a powdered formulation into gelatin capsules in amounts that provided the appropriate dose for individual animals. Single injections of RU486 can terminate pregnancy including early pregnancy in dogs, but dose vs. day of pregnancy data are very limited.

An injectable formulation of an analog of RU486, i.e., RU 534 or aglepristone, has been made available for veterinary use in France since October 1996. It is currently marketed or scheduled for market in several other European countries. It appears that in some countries, it will only be available if RU486 is also available for use in humans. However, since the original manufacturer of the drug has relinquished its license, the future of the compound for veterinary use remains unclear even in Europe. Aglepristone is currently marketed in Europe with an indication for pregnancy termination in dogs (Alizine). It is also currently under review for approval as a canine abortifacient in New Zealand. The potential for the introduction and veterinary use of this or similar drugs in North America remains unclear.

The protocol reported for the clinical use of aglepristone involved a study of 104 bitches injected subcutaneously with 0.33 ml/kg/day repeated once 24 hours later [10,23,32]. The aglepristone preparation is an oily-alcohol solution containing 30 mg of aglepristone per ml (Alizine). The resulting aglepristone dosage was 10 mg/kg, administered two times. The early administration of aglepristone at 0 to 25 days after mating always resulted in prevention of pregnancy. The later administration of aglepristone, at Day 26 to 45 after mating induced resorption or abortion within seven days in 96 % of cases studied. There were no untoward side effects. Details on the use of aglepristone in clinical trials in dogs is provided elsewhere [33]. The absence of side effects suggests that the use of aglepristone at the recommended dosages is the ideal method for pregnancy prevention or pregnancy termination when administered before Day 35, in situations where the drug is available and affordable.

Antiprogestins in Cats - A recent preliminary report suggests that aglepristone can prevent pregnancy in cats [34].

Other Methods for Pregnancy Termination

Progesterone Synthesis Inhibitors - Epostane is a drug that inhibits the hydroxy-steroid-dehydrogenase delta 4 - 5 isomerase enzyme system, and thus will reduce progesterone levels in dogs. It terminates pregnancy when administered at 50 mg/kg/day, PO, for 7 days beginning at the onset of diestrus/metestrus. It is reasonable to think it would also be effective in cats. The status of commercial development is not known [5,35]. Concerns about possible effects on adrenal steroidogenesis have been a factor in the development of this drug. Use of other inhibitors of steroidogenesis appears not to have been studied in dog or cats.

GnRH Antagonists - GnRH antagonists are capable of inhibiting LH secretion from the pituitary gonadotroph cells, which is normally under the control of GnRH from the hypothalamus. Since LH is a required luteotrophin, and is required for luteal secretion of progesterone throughout pregnancy, its suppression by a GnRH antagonist causes disruption of pregnancy in dogs. A potent antagonist of GnRH was reported to terminate pregnancy in bitches whether administered one week before implantation, near the end of estrus, or administered later in pregnancy [36]. However, there appear to be no plans to market

such compounds as veterinary drugs in the foreseeable future.

Summary

Several protocols exist for the termination of pregnancy in dogs, fewer for cats (Table 6 and Table 7). Evidence exists that the majority of dogs presented for abortifacient therapy following an unwanted mating are in fact not pregnant. This suggests that therapy is more appropriately initiated after confirmation of pregnancy, preferably by ulatrasonography of fetal heartbeats and/or assay of serum relaxin between Day 26 and 30.

Table 6. Protocols for the termination of confirmed pregnancy in dogs at about Day 28 to 32 of gestation.
1. Injections (SC) of the prostaglandin PGF in initially low doses (25 - 30 ug/kg) and then moderate doses (30 - 100 ug/kg) given 2 or 3 times per day for 6 to 9 days, or longer, and until confirmation of efficacy, preferably by ultrasound.
2. Injection (SC) of the prostaglandin-agonist cloprostenol (2.5 ug/kg) every other day for 5 to 9 days or longer, and to effect.
3. Oral administration of the dopamine agonist bromocriptine at moderate to high doses (100 ug/kg) provided 2 to 3 times a day for 7 to 10 days, or longer, and to effect.
4. Oral administration of the dopamine agonist cabergoline at recommended doses (5 ug/kg) daily for 7 to 9 days, or longer, and to effect.
5. Oral administration of bromocriptine at low doses (30 ug/kg) provided 3 times per day for 10 days, following a single injection of cloprostenol (2.5 ug/kg), with a follow-up visit to confirm efficacy, preferably by ultrasound.
6. Oral administration of the dopamine agonist cabergoline for 10 days, following a single injection of cloprostenol (2.5 ug/kg), with follow-up visit as above.
7. Oral administration of cabergoline for 10 days, with injections of low doses of cloprostenol (1 ug/kg) on days 1 and 5 of treatment, with follow-up visit as above.
8. Oral administration of dexamethasone tablets at high doses (200 ug/kg) two times a day for 10 days, with a follow-up visit.
9. Injections of the antiprogestin aglepristone (10 mg/kg), twice, 24 h apart, with a follow-up visit to confirm efficacy.

Table 7. Protocols for the termination of confirmed pregnancy in cats at about Day 20 to 25.
1. Oral administration of the dopamine agonist cabergoline (5 ug/kg) daily and injections of the PGF agonist cloprostenol (5 ug/kg, SC) every 48 hours, for 1 to 2 weeks, and until confirmation of pregnancy termination.
2. Injections of the antiprogestin aglepristone (10 mg/kg) every other day, to effect (yet to be confirmed).

The clinical management of dogs and cats presented for mismating treatment requires an understanding of these protocols, potential modifications that can be made, expected side effects, the sources of the drugs involved, and possibilities for diluting or reformulating some of the drugs to facilitate accurate dosing of smaller animals. In most cases, these are experimental and extra-label uses of drugs, and the documentation of consent via a signed release-form or consent-form is important from a legal standpoint.

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