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Case Study

TERMINATION OF PREGNANCY IN BITCHES

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ABSTRACT
Veterinarians are often consulted for preventing and terminating unwanted pregnancies in dogs. This is for being unintended mating at too young or old age and for reproductive management of valuable bitches or to help preventing pet over-population and abandonment the other reasons include disproportionate size of mating partners or unwanted or accidental mating; however, inducing abortion is not an ideal method of population control (Abhilash.*et al*, 2012). Regardless of what treatment is used for pregnancy termination it is most important to diagnose that the bitch is actually pregnant before treating for mis mating. Post-coital douches are of no value to prevent unwanted pregnancy. Sixty percent of mis-mated bitches do not conceive, hence confirmation of an undesired pregnancy is advised before proceeding for instituting a therapeutic approach since only 40% of bitches presented for misalliance were actually pregnant (Reddy *et al.*, 2014). In past, the treatment for preventing pregnancy due to mismating was by administration of natural or synthetic estrogen within 1 to 5 days of breeding but its side effects and unreliable therapeutic outcome limited its use now a day's anti progesterone, dopamine agonists, prostaglandin and glucocorticoids are used for safe and effective pregnancy termination (Palmer and Post, 2002).
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KEYWORDS: ECP, Estrogen, Prostaglandins analog, Mifepristone, Cabergoline, Bromocriptine, Dopamine Agonists, Dexamethazone.

INTRODUCTION

Veterinarians are often consulted for preventing and terminating unwanted pregnancies in dogs. This is for being unintended mating at too young or old age and for reproductive management of valuable bitches or to help preventing pet over-population and abandonment; however, inducing abortion is not an ideal method of population control (Fernando, 2002).The other reasons include disproportionate size of mating partners or unwanted or accidental mating (Abhilash *et al.*, 2012). Regardless of what treatment is used for pregnancy termination it is most important to diagnose that the bitch is actually pregnant before treating for mismatings. Post-coital douches are of no value to prevent unwanted pregnancy (Davidson, 2013). Sixty percent of mis-mated bitches do not conceive, hence confirmation of an undesired pregnancy is advised before proceeding for instituting a therapeutic approach since only 40% of bitches presented for misalliance were actually pregnant (Reddy *et al.*, 2014). In past, the treatment for preventing pregnancy due to mismating was by administration of natural or synthetic estrogen within 1 to 5 days of breeding but its side effects and unreliable therapeutic outcome limited its use (Palmer and Post, 2002).

Early Pregnancy Detection

Abdominal palpation can be a valuable method of detecting pregnancy if performed 26 to 28 days after mating. Now a day, Tran's abdominal ultrasonography is method of choice for early pregnancy detection where, embryonic vesicle can be visualized as early as day 19 after the LH peak. Embryos can be detected by day 24, and heartbeat can be detected by day 24 or 25. If ultrasonographic equipment is not available, an ELISA test for canine relaxin can be conducted as soon as day 21 after breeding (Fernando, 2002). Examination of vaginal smear is a diagnostic tool for evaluating mating and to find the stage of the cycle. The presence of sperm or sperm head confirms mating whereas absence of sperm indicates that a fertile breeding attempt was futile. (Abhilash.*et al*, 2012)

Drugs used for termination of pregnancy in bitches

Several medications have been used to terminate the unwanted pregnancies, although none of the drug has been found to work in all cases. Three primary classes of drugs have been used in pregnancy termination viz. estrogen, prostaglandin and glucocorticoids.

Estrogens or Synthetic Estrogenic Compounds-

Estrogens are steroid compounds, synthesized primarily by the ovaries, and to a lesser extent by the testicles, adrenal cortex, and placenta. Other sites of estrogen production include liver, muscle, fat, and hair follicles. The immediate precursors to the estrogens are androstenedione or testosterone, and estradiol 17β and estrone are the main endogenous estrogens in most species. Natural estrogens such as estradiol, estrone, and estriol are produced from natural sources such as ovary of female, urine of pregnant animals, adrenals and testes of males. Synthetic estrogens exerting the same effect as natural estrogens including diethylstilbestrol (DES), ethinyl estradiol, and esters of estradiol such as benzoate, cypionate, propionate, valerate,

enanthate, and undeclynate are produced from coal tar derivatives and other steroids (Roberts, 1986). Estrogens are necessary for many physiological actions in the body including: normal growth and development of female gonads; development of secondary sexual characteristics including duct growth of the mammary glands (Hassan *et al*., 2009). In general, there are few drugs used to terminate pregnancy in bitches during estrus. Estradiol cypionate (ECP), estradiol benzoate, and diethylstilbestrol (DES) were used extensively for this purpose (Valerie, 2009). Mechanism of Action Estrogen is interfering transportation time in oviduct and tightens the utero-tubular junction, resulting in implantation failure or embryonic death. Dose - 0.01 mg/kg I/M or S/C. Repeat on 3rd, 5th and 7th day after mating 0.1-3 mg/kg for one injection within 4 days of mating.

Estradiol Cypionate (ECP)

Estradiol cypionate is probably the only standard drug that increases the tubular motility to facilitate rapid transport of the fertilized eggs in the oviduct and uterus and thus prevents implantation (Johnny, 2002). Dose - dose is 44 mcg/kg (0.02 mg/kg) - not exceeding a total dose of 2 mg and given once intramuscularly during estrus. It is important that the dog is not allowed to mate again. It is not effective if used during proestrus or diestrum. Tsutsui *et al*., 2006 demonstrated that a single treatment of estradiol benzoate at 0.2 mg/kg on 5th day post ovulation effectively prevented pregnancy without causing any side effects. They indicated that side effects would be more common in animals treated with repeated administration of estradiol benzoate. The dog may show side effects such as continued estrous signs, due to estrogen influence, cystic endometrial hyperplasia, pyometra or bone marrow suppression (Hasan *et al*., 2009).

Conjugated Estrogen

Conjugated oestrogens can be used for the treatment of misalliance in dogs within 5 days following breeding. They are mainly isolated from mare's urine and hence it can be called as conjugated equine oestrogen. These are most commonly used for the treatment of osteoporosis, atrophic vaginitis with a dose schedule of 1.875mg daily for 3 days for pregnancy termination (Abhilash.*et al.*, 2012).

Prostaglandins and its analogues

Briles and Evans 1982 in his study reported that PGF2α given intramuscularly to pregnant beagle bitches from day 33 to day 53 of gestation can be used to terminate gestation. Similarly, Wichtel *et al.,* 1990 successfully terminated pregnancy in four of the four bitches that received PGF2α 125 µg/kg bid sub cutaneously.

Safe and effective termination of pregnancy is possible in the bitch by administration of Prostaglandin $F_{2\alpha}$ (natural hormone) at 0.1 mg/kg, SC, tid for 48 hr followed by 0.2 mg/kg, SC, thrice in a day. Synthetic prostaglandins (cloprostenol 1–3 mcg/kg every 12–24 hr to effect) more specifically target the myometrium, causing fewer systemic adverse effects, and are currently preferred for pregnancy termination (Davidson, 2013).

Natural Prostaglandin

Prostaglandins are found to be highly effective for termination of pregnancy in bitches after 30 days of gestation. Its use prior to 30 day is not recommended. Prostaglandin administration has certain side effects. To minimize side effects after administration of drug, the dog should be observed for 30 minutes for any side effects. The dog should be fed 1-2 hours after prostaglandin injection so as to avoid vomiting. Most of the animals treated will exhibit some of the side effects like panting, respiratory distress, excess salivation, vomiting, defecation, stranguria and urination. Normally these side effects start within 30 seconds to 3 minutes and usually persist for 5-20 minutes. Side effects are usually severe during the first few injections and side effects will be diminishing after each subsequent injection. It has been observed that pre treatment concentration of plasma progesterone was more than 6ng/ml plasma progesterone which reduced to less than 2.0 ng / ml after pregnancy termination and (Feldman *et.al,* 1993). Most preferred treatment protocol is 0.1 mg/kg s/c every 8 hours for 2 days and then 0.2 mg/kg given s/c every 8 hours until abortion complete, the average time required was approximately 5-7 days (Feldman et.al, 1993 and Renukaradhya *et al*., 2008).

Prostaglandin analogs

It has greater luteolytic effect at relatively low doses and decreases the occurrence of myometrial contractions and severity of side effects compared to natural prostaglandins. It has much greater affinity for the prostaglandin receptors and has a longer half life than natural prostaglandin. It can be given at a dose rate of 2.5µg/Kg body weight subcutaneously every 48 hours for 3 to 4 times (Reddy *et.al*, 2010).They further, observed that in order to reduce side effects of PG, atropine sulphate can be given at the rate of 0.04 mg/kg body weight subcutaneously 10-15 minutes prior to the administration of drug. The side effects noticed were transient panting, trembling, nausea, and mild diarrhea**.**

Dexamethazone

Dexamethasone administered at beginning of mid-gestation can terminate pregnancy in dogs, presumably by activating endogenous mechanisms similar to those involved in parturition. It can result in the production of oestrogen and prostaglandin by the fetoplacental unit. Single dose of glucocorticoids is not efficacious in the bitch. It can be given at a dose rate of 200µg/kg body weight for 7 days and then at a tapering dose of 10-20 µg/kg for next 3 days (Wanke *et al.,* 2002). Pregnancy can also be reliably terminated in the bitch by administration of dexamethasone at 0.2 mg/kg, PO, bid to effect. The owner should be informed for probable adverse effects of corticosteroid administration like panting, polyuria, polydipsia (Davidson, 2013). Advantages of such a therapy for pregnancy termination include the fact that it involves only oral administration of a relatively inexpensive drug; however repeated administration and high doses make the method impractical.

Dopamine Agonists

Maintenance of canine pregnancy is dependent on functional corpora lutea (CL) throughout gestation. Luteal function in the dog is thought to depend on pituitary support, rather than uterine or placental influences. The 2 hormones principally responsible for maintenance of the canine CL are luteinizing hormone (LH) and prolactin (PRL).The LH peak of estrus is sufficient to establish

luteal function for approximately 4 wk. Prolactin becomes the dominant luteotropin during the 2nd half of gestation (Johnston *et al*., 2001). Dopaminergic agonists are ergot derivative alkaloid compounds that exert an antiprolactinergic effect. The ability of dopamine agonists to inhibit prolactin secretion makes them optimal for milk suppression, either during overt pseudopregnancy episodes or in the post-partum period. It is well known that prolact in is luteotropic hormone required during the second half of canine luteal phase. Therefore, anti-prolactins can also be used to suppress luteal function in progesterone dependent conditions such as pyometra, unwanted pregnancy and mammary tumors. Two of the most widely used dopamine agonists in dogs are bromocriptine and cabergoline, which have a direct action on D2-dopamine receptors of the lactotrophic cells of the anterior pituitary gland (Abhilash *et al*., 2012**).**

Bromocriptine

Bromocriptine mesylate at a dose of 30-100 mcg/kg administered orally twice daily for five to six days at 35 to 40 days of gestation causes abortion in three to five days. Bromocriptine may cause dogs to vomit and have inappetence, and it has not been widely accepted however, the long-term effects of bromocriptine on reproduction also have not been fully studied (Hoskins, 2002). It has been reported to be an effective abortifacient after 35 days of gestation but not prior to day 30. Two different treatment protocols have been adopted. In one protocol 0.1mg/kg body weight daily or BID for 6 consecutive days beginning on day 30 of gestation. In the second protocol, 0.03 mg/kg twice daily for 4 days beginning after day 30 of gestation has been reported. The common side effects for use of Bromocriptine are inappetence, anorexia, vomiting and depression. Further the drug is not 100% effective in terminating pregnancy. Emesis is presumably due to interaction with dopaminergic elements in the emesis centre 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. Because of above reasons the drug has not been used extensively.

Cabergoline

It is a long acting dopamine receptor agonist and prolactin inhibitor. It is highly effective orally and parenterally. A dose of 5µg/kg once daily cause a sharp decline in serum prolactin concentration and result in abortion without much side effects (Reddy *et.al*, 2010). The common side effects by use 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.

Combination of prostaglandin and dopamine agonis

Simultaneous administration of prostaglandin and dopamine agonist is found to be highly effective. Therapy begins 28 days after first breeding. Cloprostenol is administered subcutaneously on alternative days at a dose rate of 1 µg/kg and the drug has to be administered three times. Oral cabergoline has to be given at a dose rate of 5µg/kg body weight for 9 days. This regimen reduces the adverse effects of prostaglandin therapy alone and increases the efficacy of prolactin antagonists. When bitches were treated for approximately 9 days, 100 percent bitches showed resorption and generally there were no side effects except sanguineous vaginal discharge (Onclin *et al.*, 1995).

Anti progesterone therapy

Anti-progestins are synthetic steroids that bind with great affinity to progesterone receptors, preventing progesterone from exerting its biological effects. After administration of the drug peripheral progesterone concentration remains unaltered but its action is blocked. In dogs, the anti-progestins mifepristone and aglepristone have been used for experimental and clinical purposes, including pregnancy termination and management of pyometra (Fieni *et al.*, 2001)

Mifepristone

Mifepristone is a progesterone and glucocorticoid antagonist. It is more potent as an anti-progestin than as an anti-corticoid. In pregnant bitches, mifepristone is able to interrupt early pregnancy in 80 percent of cases without any major side effects. To improve its efficacy, mifepristone is currently used in combination with low doses of prostaglandin analogs such as misoprostol. The efficacy of combined treatment (mifepristone plus misoprostol) is 96 percent effective in humans. The drug acts as a progesterone receptor antagonist at uterine level independent of any additional effects on luteal function. Premature cessation of luteal function may occurr secondary to pregnancy termination or may represent a luteolytic effect of treatment independent of pregnancy status. Mifepristone has been demonstrated to induce direct luteolysis and has an anticorticoid activity in bitches. This drug is orally active and has been shown to be safe and effective in terminating pregnancy after 30 days of gestation. The treatment protocol involved oral administration of drug at the rate of 2.5 mg/kg twice daily for 4-5 days or until abortion or resorption occurred (Concanoon *et.al*, 1990). In a trial by Reddy *et al.*, 2014; Mifepristone was given at a dose rate of 3mg/kg body weight twice daily orally, or in 250 ml of DNS I.V., chlorpheniramine maleate @0.5 mg/kg body weight, Cefpodoxime 5@ mg/kg body weight and melonex suspension, @0.5 mg/kg body weight was given orally for five days for effective pregnancy termination in bitches. Antibiotic administration was stopped after day 5 and nutritional supplements were given .The animals became normal within one week. On first day of treatment animal was dull and there was no signs of any discharge from vulva of animal.

Aglepristone

Aglepristone does not modify plasma concentrations of progesterone, prostaglandins, oxytocin or cortisol within 24 hours after its administration but induces an increase in concentrations of prolactin within 12 hours in bitches treated at mid pregnancy (Galac *et al.*, 2000). This is a relatively new antiprogesterone drug developed for animal use. Aglepristone can be used any time up to day 45 for safe and effective termination of pregnancy in bitches (Fieni *et al.*, 2001). Aglepristone acts like a progesterone antagonist, at the uterine level and do not have direct and immediate luteolytic properties. Termination of pregnancy occurs in the presence of high plasma progesterone concentrations. There is mammary gland congestion,

shortening of the inter-oestrous interval and prolactin release seems to prove a direct or indirect action of aglepristone on hypothalamic-pituitary axis. The drug can be administered at a dosage of 10mg/kg body weight (0.33ml/ kg/day) subcutaneously twice at 24 hour interval. Efficacy of treatment for termination of pregnancy is reported to be 95 percent. No side effects were observed except mammary development and lactation (Baan *et al.*, 2005). As an abortifacient, Aglepristone (RU 46534) is a competitive progesterone antagonist. It binds to progesterone receptors without inducing the molecular cascade associated with progesterone. Its affinity to PRs is higher than progesterone; 3.12, 3.8, and 9.26 times greater in the bitch, doe rabbit, and queen, respectively. Aglepristone can therefore be used in various progesterone dependent physiological or pathological conditions, with the aim of blocking the action of progesterone. The early administration of aglepristone at 0 to 25 days after mating always resulted in prevention of pregnancy. Late administration of aglepristone at day 26 to 45 after mating induced resorbtion or abortion within seven days in 96 percent of cases. Irrespective of the stage of pregnancy, treatment with aglepristone has no apparent negative effects on subsequent fertility. Aglepristone is a safe and relatively effective means of treating pyometra (Gogny, and Fieni, 2015).

Gonadotropin releasing hormone (GNRH) antagonist

Gonadotropin releasing hormone (GnRH) antagonists are particularly useful when a rapid inhibitory effect on the gonadal axis is required. Valiente *et al*., 2009; performed a study to test the efficacy and clinical safety of a low and high dose of the third generation GnRH antagonist, acyline, on pregnancy termination in female dogs. The effect of the antagonist on the progesterone (P4) serum concentration was also described. Twenty one mid pregnant bitches were randomly assigned to a single subcutaneous (SC) dose of a placebo (PLACE; n = 7), a low (ACYL; 110 µg/kg; n = 6) or high (ACYH; 330 µg/kg; n= 8) dose of acyline. The animals were followed for 15 days. All ACY treated but no placebo treated animals terminated their pregnancy by abortion ($p < 0.01$). The ACYL and ACYH groups interrupted their pregnancy 7 ± 1.9 and 6.4 ±1.3 days after treatment, respectively ($p = 0.7$). A significant interaction between treatment and day was found ($p < 0.01$) for P4 serum concentrations when PLACE was compared with both ACY groups. No difference was found for this hormone between both ACY groups ($p > 0.05$) where P4 diminished throughout the study. The decreasing rate varied among animals and was closely related to the time of abortion when P4 reached basal concentrations. In PLACE animals, gestation progressed normally and P4 did not change throughout the study ($p > 0.05$). None of the bitches presented side effects. It was concluded that acyline safely terminated mid pregnancy by permanently decreasing P4 serum concentrations.

Pregnancy termination in dogs with novel nonhormonal compounds

Resorption of the products of fertilization was induced in bitches given (subcutaneously) single or multiple doses of the non-hormonal compounds L-10492 and L-10503 during the first half of gestation; also resorption or expulsion of the conceptus was induced when these compounds were given during the latter part of pregnancy. The smallest doses were required at a time immediately after implantation of the fertilized ova in the uterus. Effectiveness and appearance of side effects were dose-dependent. These consisted of decreased appetite, loss of body weight, and diarrhea (feces sometimes containing streaks of blood). Bitches which had aborted returned to estrus within normal intervals of time, exhibited normal mating behavior, and were fertile. They had normal deliveries and lactation, and the pups were normal. The mechanism of action does not involve effects on nidation and the compounds were not luteolytic, but probably involved the uteroplacental complex (Galliani and Lerner 1982).

Progesterone Synthesis Inhibitors

Progesterone production can be blocked by use of certain enzymes. Epostane is one of such enzyme inhibitor that has no intrinsic oestrogenic, androgenic or progestogenic activity. The enzyme When administered subcutaneously at the onset of metoestrus (dioestrus), it prevent or terminate pregnancy. It can be given at a dose rate of 5mg/kg body weight orally for 7 days (Keister *et. al*, 1989). Progesterone production can be blocked by the hydroxyl steroid dehydrogenase isomerase enzyme inhibitors, which prevent the conversion of prognenelone to progesterone. Prognenelone is biologically inactive, and therefore progesterone support for the pregnancy is lost, resulting in resorption or abortion (Gilian, 1998).

Embryotoxic Agents

Several novel embryotoxic agents such as phenyltriazole isoindole and isoquinoline compounds have been evaluated in the bitch. They are most effective when given around the time of implantation and often only a single administration is required. A single sub- cutaneous or intra muscular injection *of 2-(3 ethoxy-phenyl)-5, 6-dihydro-striazole [5, 1-a] isoquinoline (DL 204-IT)* dissolved or suspended in an oily vehicle is sufficient. The optimal time of treatment was found to be day 20 of gestation, at which time the smallest effective dose was 6.25 ng/kg (Galliani *et al.*, 1982). However many of these agents have toxic side effects including vomiting, diarrhoea, weight loss, pyrexia, lethargy and immunosuppression.

Tamoxifen Citrate

It acts as an antiestrogen in premenopausal women but has estrogenic activity in dogs. It may interfere with zygote transport and/or implantation. Relatively high doses of drug are given twice daily during proestrus, oestrus, and early metoestrus. The drug was effective in preventing or terminating pregnancy if administration began during proestrus or estrus or on day 2 of estrus. Efficacy was much poor in the treatment commenced on day 15 onwards. It can be given at a dose rate of 1mg/kg orally twice a day for 10 days. A high incidence of pathological changes in the bitch's reproductive tract is induced by tamoxifen, including ovarian cysts and endometritis, and the compound is of little value for potential breeding animals (Bowen *et al.*, 1988).

Termination of pregnancy by Mifepristone and Misoprostol

A trial has been reported on termination of human pregnancy at the Department of Obstetrics and

Gynecology Masaryk University and University Hospital Brno from 1/ 6/2014 to 30/ 6/2015 using 600 mg of mifepristone (Mifegyne) and 400 µg of misoprostol (Mispregnol). The patients were monitored for subjective perception of medical termination of pregnancy (pain, nausea, vomiting, and satisfaction with this method) and objective process (hospitalization, surgical intervention). The view of patients was found by the phone questionnaire .The results were, complete abortion without a surgical intervention in 103 patients. Nausea, pelvic pain, and intensity of bleeding were evaluated as suitable. Only 1 patient (0.9%) was hospitalized for nausea and 1 patient (0.9%) was hospitalized in case of need for an emergency curettage and transfusions. Some kind of contraception after the medical termination of pregnancy started using 98.0% of women. The satisfaction rate of this method was high 101 patients themselves declared satisfied, 66.7% very satisfied, 24.3% rather satisfied. Medical termination of pregnancy has good efficiency; we consider it safe with minimum side effects and is well evaluated by patients. (Frank.*et al* 2015)

- Administration of PGF2 alpha SC and misoprostol (Prostaglandin E; PGE) intravaginally.
- Two types of luteolytic prostaglandin F2 alpha: the natural PGF2 alpha dinoprost tromethamine (Lutalyse ®) and the synthetic PGF2 alpha cloprostenol (Estrumate ®).
- Several commercial preparations of prostaglandin E are available; both PGE1 and PGE2 are available. PGE1 preparations are significantly less expensive than PGE2 products. Misoprostol (PGE1) has been shown to successfully induce pregnancy termination, especially when used concomitantly with PGF2 alpha administration.
- Combination therapy shortens the period of treatment time as compared to the use of PGF2alpha alone.

Lochia noted after a mean of 2.5 days of treatment, initiation of abortion after a mean of 3.5 days and completion of abortion after a mean of 5 days (Davidson, 2013). The administration interval between mifepristone and misoprostol is usually about 36-48h, which might affect a owners choice of method of termination. Unwanted outcomes such as uterine bleeding, painful cramps and psychosocial issues which may occur during this long interval can be altered by a shorter administration interval. A shorter interval will be cost effective as it saves both owner's and clinician's time and other resources. If the waiting time interval between therapeutic interventions could be reduced without compromising efficacy, it will potentially improve compliance, patient acceptability and quality of care. A systematic review of randomized controlled trials published from 1999 to 2008 was conducted to assess the evidence for a shorter mifepristone and misoprostol administration interval at first trimester medical termination. The primary outcome measure was complete abortion without the need for a surgical procedure. In future this protocol may be tried and tested for effective termination of pregnancy in bitches.

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