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Comparative efficacy of therapeutic protocol of mismating in canines

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Abstract
The unplanned mating of stray dogs is one of the major reason for increasing population of pet dogs The study was carried out at the Department of Teaching Veterinary Clinical Complex, College of Veterinary Science and Animal Husbandry, Anjora, Durg, Chhattisgarh, India during June to November, 2023 in twelve female dogs to evaluate the efficacy of estradiol benzoate in mismating in dogs to prevent pregnancy. The information of mismated female dogs regarding breeding records, day of mismating, history of proestrual bleeding and mating history were collected by owners and dog breeders. Physical examination including rectal temperature, heart rate and respiration rate were recorded as early as possible after mating. Based on the starting of treatment postmating, mismated dogs were allocated into 3 groups. All the affected dogs were given three doses of estradiol benzoate (Injection PREGHEAT, Virbac, 2 ml, 1 mg/ml) intramuscularly at dose rate of 0.02 mg/kg body weight at alternate days. Group I, II and III includes affected dogs with their first dose of estradiaol in between 1-3, 4-6 and 7-12 days postmating, respectively. The comparative efficacy of estradiol benzoate administered between day 1 to day 15 post mating was evaluated in terms of conception rate between different groups. The confirmation of pregnancy was done by transabdominal ultrasonography on 30 days postmating. Group I and II shows 100% efficacy of estradiol benzoate while group III is limited to 50% efficacy of estradiol treatment for mismating. Dogs were effectively and safely treated from conceiving and getting pregnant with three dosage of 0.02 mg/kg of Estradiol benzoate within 7 days postmating in mismated dogs.

Keywords: Termination of pregnancy, estradiol, mismating, ultrasonography

1. Introduction
One of the most common "reproductive" concern from dog and cat owners is unplanned mating or mismating or pregnancy termination. The unplanned mating of stray dogs is one of the major reason for increasing population of pet dogs (Parmar *et al*., 2021) [10]. The estrous period in dogs is about 10 days which provides a long mating period of 1 week after the start of estrus (Tsutsui *et al*., 2006) [16]. Therefore, the probability of pregnancy is high when misalliance occurs. Longer estrus periods along with bitches' promiscuous behaviour greatly enhance the risk of mismating in dogs (Bisla *et al.,* 2018) [1] Additionally, the estrus-bitch's roaming behaviour and propensity to accept a male dog greatly enhance the possibility of mismating (Sarkar *et al*., (2021) [12].
There are two different concepts for therapeutic managment for accidental matings of bitches whose owners are unwilling to pursue surgical treatment. First approach is related to the earliest prevention of nidation and implantation after mating and second approach should be related to the termination of pregnancy in mid gestation. Due to ethical considerations, prevention of nidation and implantation is requested by many owners.
If the animal is a potential breeder, there are drugs that can halt or prevent conception. The primary elements that should affect the use of these drugs are cost, convenience, safety, efficacy, and adherence to therapy. Oestrogens have been the sole pharmaceutical option for treating mismating for over 20 years. They are taken between 1 and 5 days after breeding in an effort to interfere with embryonic implantation (Eilts, 2002) [3]. Two drugs that can be given during estrus to prevent pregnancy are oestrogens and tamoxifen. Some of the oestrogens that are utilised are diethylstilbestrol (Bowen *et al*., 1985) [2], mestranol (Kennelly 1969) [8],

estradiol cypionate (Bowen *et al*., 1985) [2], and estradiol benzoate (Sutton *et al*., 1997) [13]. Although, when used appropriately, injectable oestrogens can prevent pregnancy, their continuous use is not recommended because of the significant risk of severe side effects, including pyometra and possibly fatal suppression of the bone marrow (Weiss and Klausner 1990) [17]. The only medication that has been shown to be somewhat safe and effective at low dosages is estradiol benzoate. Pyometra was shown to be 8.7% common in the four months following the administration of modest dosages of estradiol benzoate in a retrospective research conducted in the United Kingdom. In contrast, the condition was assessed to be less than 2.0% common in a clinical setting (Romagnoli, 2018) [11].

In the early stages of diestrus, prostaglandins (PGs) have also been utilised to stop mismatched bitches from getting pregnant. However, in the early diestrus phase, the canine corpora lutea were resistant to the luteolytic impact of PGF2α, and contradictory efficiency findings were found. Moreover, the use of prostaglandins in mismated bitches is hampered by the fact that they are linked to notable adverse effects and necessitate repeated doses over a comparatively extended duration (Johnston *et al*., 2001) [6].

Dog misalliance can be treated by ovariectomy or antiprogesterone treatment (Fieni *et al*., 2001) [4]. Throughout the gestation period, CL secretes progesterone (P_4), which is necessary for the maintenance of canine pregnancy. Synthetic steroids known as progesterone receptor antagonists attach to P_4 receptors with a high degree of affinity, blocking P_4 from having any biological effects (Hoffman and Scheuler, 2000) [5]. Accessible in certain American and European veterinary markets as a pregnancy termination indication, Aglepristone has demonstrated efficacy and safety in the early and midgestational phases of dog pregnancies (Kanca *et al*., 2008) [7]. However, due to the high expense of therapy, the product's application in early pregnancy prevention is severely restricted. It is still quite expensive. The purpose of this study was to examine the efficacy and side effects of estradiol benzoate administered on different days after mating to prevent conception in mismated dogs.

The study was carried out at the Department of Teaching Veterinary Clinical Complex, College of Veterinary Science and Animal Husbandry, Anjora, Durg, Chhattisgarh, India during June to November, 2023. Twelve female dogs were presented with complaint of mating with stray dogs within 15 days post mating. The information of mismated female dogs regarding breeding records, day of mismating, history of proestrual bleeding and mating history were collected by owners and dog breeders. Physical examination including rectal temperature, heart rate and respiration rate were recorded as early as possible after mating. Based on the starting of treatment postmating, mismated dogs were allocated into 3 groups. All the affected dogs were given three doses of estradiol benzoate (Injection PREGHEAT, Virbac, 2ml, 1 mg/ml) intramuscularly at dose rate of 0.02 mg/kg body weight at alternate days. Group I, II and III includes affected dogs with their first dose of estradiaol in between 1-3, 4-6 and 7-12 days postmating, respectively. The comparative efficacy of estradiol benzoate administered between day 1 to day 15 post mating was evaluated in terms of conception rate between different groups. The confirmation of pregnancy was done by transabdominal ultrasonography on 30 days postmating in all the mismated dogs.

Table 1: Treatment protocol of different groups

Groups	Experimental Animals	Days on which doses of estradiol given after the day of mating (Day 0)		
		1st dose of estradiol	2nd dose of estradiol	3rd dose of estradiol
I	D1	3rd day	5th day	7th day
	D2	1st day	3rd day	5th day
	D3	1st day	3rd day	5th day
	D4	1st day	3rd day	5th day
II	D5	5th day	7th day	9th day
	D6	4th day	6th day	8th day
	D7	5th day	7th day	9thday
	D8	6th day	8th day	10th day
III	D9	9th day	11th day	13th day
	D10	9th day	11th day	13th day
	D11	7th day	9th day	11th day
	D12	15th day	17th day	19th day

Statistical analysis

The conception rates of canines were evaluated in terms of percentage and comparison between different groups were done.

Results and Discussion

Group I and II shows 100% efficacy of estradiol benzoate while group III is limited to 50% efficacy of estradiol treatment for mismating. However, it is not worth to say the treatment to be 100% effective (effective to the tune of 75.00%) which raised a sense of doubt with respect to fertilization taking place or not, while attempting prevention of conception (Parmar *et al*., 2021) [10].

The length of the estrus cycle in the bitches is approximately 2 months, which in comparison to the other species is relatively long. The average bitch ovulates once or twice per year. Unique to the dog we find an inter-estrus interval (IEI), the time from onset of one proestrus cycle to the next, that includes proestrus, estrus, diestrus and anestrus. This interval usually ranges within 16-56 weeks, yet individual variations may be seen. During manipulation of the estrous cycle it is therefore the shortening and lengthening of IEI that is altered. Nowadays manipulation of the estrous cycle has become a common request of dog owners for different reasons.

Estrogen is a steroid compound, primarily synthesized by the ovaries (Sontas *et al*., 2009) [14]. The most common reason for the use of estrogens in small animal practice, is the immediate treatment of unwanted matings. The estrogens will prevent conception by the closure of the tubal-uterine junction or their effect on the oviduct and uterus. Today, the use of estrogens for mismating is no longer recommended because the development of estrogen-induced myelotoxicity (EIM) and

pyometra following the use of estrogens for the management of diseases and for experimental purposes has been reported. There are no safe and efficacious doses of estrogens existing, and most mismated dogs are reported to be nonpregnant at the time of examination. EIM can show clinical signs which may include complete loss of appetite, uni- or bi-lateral epistaxis, depression, petechial hemorrhages, vulvar edema, pale mucous membranes and vaginal bleeding. For hematologic changes the most typical ones are nonregenerative anemia, thrombocytopenia, and leukocytosis followed by a leukopenia (Sontas *et al.*, 2009) [14].

Safe and effective termination of pregnancy is possible in both dogs and cats by administration of estradiol benzoate at dose rate of 0.20 mg/kg intramuscularly, three times in alternate days as early as possible after mating (Tsutsui *et al*., 2006) [16]. The adverse effects of estradiol at this dosage (panting, trembling, nausea, and diarrhea) are mild (Bowen *et al.*, 1985) [2]. Only estradiol benzoate is considered to be reasonably safe and effective at low doses (Whitehead, 2008 and Tsutsui *et al.*, 2006) [18, 16]. In certain European countries, a compound containing estradiol benzoate is marketed for veterinary treatment in mismated bitches (Sutton *et al.*, 1997) [13]. Since oestrogens causes endometrial hyperplasia, pyometra, and bone marrow aplasia in bitches, they have long been regarded as potentially harmful medications for small animals (Teske, 1986) [15].

For the treatment of mismating as well as the early termination of an undesired pregnancy in bitches, numerous medication combinations are available. These drugs generally causes a number of adverse effects. In female dogs, dexamethasone at a dose of 0.02 mg/kg orally, can also be used to effectively end a pregnancy. The negative consequences of corticosteroid administration, such as panting, polyuria, and polydipsia are normally seen. Combination drug protocols have been shown to reliably terminate pregnancy with minimal adverse effects, shortest treatment times and highest success rates; however, their cost and requirement for compounding are drawbacks. The combination drug protocols include cabergoline 5 mcg/kg, PO, divided every 24 hours for up to 10 days and cloprostenol 1 mcg/kg given subcutaneously twice at 28 and 32 days after the LH surge (Onclin *et al.*,1995) [9]. Antiprogestins, such as aglepristone, are still available and safe for termination of pregnancy (Fieni *et al*., 2001) [4].

Fig 1: Ultrasonography showing non gravid uterus

Fig 2: Ultrasonography showing gravid uterus

Table 3: Finding of ultrasonography for pregnancy diagnosis

Groups	Animals	Pregnancy diagnosis	Conception rate
I	D1	Non pregnant	0%
	D2	Non pregnant	
	D3	Non pregnant	
	D4	Non pregnant	
II	D5	Non pregnant	0%
	D6	Nonpregnant	
	D7	Nonpregnant	
	D8	Nonpregnant	
III	D9	Nonpregnant	50%
	D10	Pregnant	
	D11	Nonpregnant	
	D12	Pregnant	

Conclusion

Dogs were effectively and safely treated from conceiving and getting pregnant with three dosage of 0.02 mg/kg of Estradiol benzoate within 7 days postmating in mismated dogs. Group I and II showed 100% efficacy to treatment given within 7 days post mating, while group III showed 50% efficacy to treatment given after 10 days of mating. It indicates that the early administration of estrodial benzoate results in successful embryonic degeneration by delaying the embryo's passage through the uterine tube.

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