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Combination of dopamine agonist and prostaglandin administration for pregnancy termination in bitches – a novel approach

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ABSTRACT

Pregnancy termination is a required procedure in companion animal practice. In healthy bitches with confirmed pregnancy, good results are obtained with the combination of prostaglandin F₂ and dopamine agonist, followed by regular sonographic examination until confirmed abortion. The aim of this study was to establish a simple and easily applicable procedure, with different dynamics of application of dinoprost and cabergoline. Dinoprost was administered intramuscularly in the vestibule of vagina. Twenty bitches were divided into four equal groups. Group A received dinoprost and cabergoline daily; group B received dinoprost every 48 h and cabergoline daily; group C received dinoprost daily and cabergoline every 48 h, and group D received both cabergoline and dinoprost every 48 h. The treatment lasted until abortion was sonographically confirmed. The pregnancy was successfully terminated in all bitches, and side effects appeared in 90% animals, though they were of strong intensity in only 15% of bitches. Dinoprost administered intramuscularly was effective with fewer undesirable, strong, systemic side effects. Drug administration every 48 h also induced abortion, with negligible side effects, but with slightly longer duration of treatment. This combination could be interesting in cases with time-limited owners and in countries where other drugs are unavailable.

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Bitch; cabergoline; prostaglandin; ultrasound; pregnancy termination; mucosa

Introduction



Postcoital contraception and pregnancy termination are often required procedures in companion animal veterinary practices. Owners decide to terminate pregnancy due to several reasons such as: unwanted pregnancy, age of the dam, health issues, or offspring of small breeding value (Gracin Crnković 2009; Reddy et al. 2014). There are several methods for pregnancy termination which have been reviewed recently (Fraser 2018). The best, and only reliable one, is surgical ovariohysterectomy (OVH), but it is not applicable in the bitches intended for breeding. Pharmacological methods are not permanent, and there are several medications that can be used for either pregnancy termination or induction of abortion, in different stages of pregnancy (Gogny and Fieni 2016; Efenđić et al. 2018). It is advised to use medications that induce abortion after positive pregnancy diagnoses, avoiding blind treatment of non-pregnant bitches (Feldman et al. 1993). Abortion may be induced using only one substance or a combination of two or more substances. In healthy bitches with confirmed pregnancy, good results were obtained with a combination of either natural or synthetic analogues of prostaglandin F_{2α} (PG) and dopamine agonist (cabergoline or bromocriptine), followed by regular sonographic examinations until confirmed abortion (Onclin et al. 1995; Hettling 1998; Onclin and Verstegen 1999; Aslan et al. 2001; Palmer and Post 2002). The advantages of their simultaneous administration are the use of lower doses with fewer

side effects (Onclin and Verstegen 1996). Most side effects are the consequence of PG administration (Aslan et al. 2001; Feldman and Nelson 2004; Kowalewski 2017), and their non-specific effects on smooth muscles (Fraser 2018). Prostaglandins are usually applied in higher dosages or in a repetitive manner, intramuscularly or subcutaneously at least twice a day (Wanke et al. 2002; Root Kustritz 2010; Kowalewski 2017).

The aim of this study was to establish a simple procedure that is easily applicable, especially in countries where aglepristone and other progesterone blockers are not available. Special attention has been given to different dynamics of application of PG and cabergoline, and PG was administered intramuscularly in the vestibule of vagina, in order to avoid or minimize systemic side effects. Duration of the treatment and duration of side effects, their nature and intensity, as well as clinical manifestation of the pregnancy termination were also observed and analysed.

Material and methods

Archive data from research conducted at the Clinic for Obstetrics and Reproduction, Faculty of Veterinary Medicine, University of Zagreb, Croatia and Veterinary practice Jastrebarsko, Croatia were used. The research was conducted on 20 mated bitches of different breeds and age, ranging from 1 to 6 years, in good general health status, in which, according to

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the owner's consent, abortion was induced after positive pregnancy diagnoses. The pregnancy was confirmed by sonographic examination 30–35 days after the first mating, based on the finding of anechoic gestational sac with a visible foetal cardiac action, but without any further measurements to confirm gestational age. The pregnancy was terminated with the combination of dinoprost, natural PG analogue (Dynolitic®; Pharmacia Upjohn, Animal Health Division, Puurs, Belgium) in the dose of 250 µg/kg administered intramucosally in the vestibule of vagina, and dopamine agonist cabergoline (Galastop®, Vetem, Milano, Italy), administered per orally in a dosage of 5 µg/kg. Intramuscular administration was performed by inserting the tip of the needle at the sharpest, almost parallel angle into the vaginal mucosa. Bitches were divided into four groups of five animals (Table 1). Group A received both dinoprost and cabergoline once a day; group B received dinoprost every 48 h and cabergoline once a day; group C received dinoprost once a day and cabergoline every 48 h, and group D received both cabergoline and dinoprost every 48 h. Sonographic examinations were performed every 48 h, on days in which PG was administered to all bitches. The treatment lasted until abortion was sonographically confirmed.

Treated bitches were observed daily, either personally or by communication with the owner, especially regarding side effects and possible vaginal discharge and/or foetal expulsion. Data about the duration of treatment and duration of side effects, their nature (vomiting, panting, tremor, drooling, and defecation) and intensity were recorded. Based on intensity, side effects were scored as mild (+; drooling, tremor, tachypnea); moderate (++, vomiting) and strong (+++; uncontrolled defecation and urination, diarrhoea, ataxia, disorientation). Owners were informed about the possibility of side effects and their nature and received detailed instructions about their pet's care.

All animals were handled in strict accordance with good animal practices as defined by the relevant national and/or local animal welfare bodies. The research protocol and animal management were in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes.

Statistical analysis of collected data was performed with software package SAS 9.4 (Statistical Analysis Software, SAS Institute Inc., Cary, USA). Days of treatment duration and duration of side effects were characterized by PROC MEANS (*i.e.* descriptive statistics). Duration of the treatment and influence of group, breed, age, and duration on intensity of side effects, and the influence of these effects on the duration of side effects, were analysed using module PROC GLM. Results were expressed as least square means ± standard error of the mean (LSM ± SE). PROC LIFETEST was used to calculate median days of pregnancy termination treatment and median days of duration of side

effects. Procedure PROC FREQ with Chi-square option was used to analyse the differences between the severity of side effects, vaginal discharge and foetal expulsion between groups. A statistically significant *P* value was set at <0.05.

Results

Pregnancy was successfully terminated in all treated bitches (Table 2), with side effects appearing in 90% of them (Table 4). No statistically significant differences were observed in the days of duration of treatment for pregnancy termination or in the duration of side effects between groups (Table 3), and other observed parameters had no effects on treatment or side effects, respectively.

The majority of bitches, except two bitches from group B, had some side effects, mostly of mild or moderate intensity (Table 4), including: tremor, drooling, panting and gastrointestinal symptoms. The bitches in group C had the strongest side effects. Brownish vaginal discharge appeared in the majority of bitches, with the exception of two bitches each in groups A and B, while foetal expulsion occurred in two bitches each in groups A and B, and in one each from groups C and D.

Discussion

The aim of this study was to establish a procedure to induce abortion of unwanted pregnancy in bitches based on different dynamics of PG and cabergoline application, and intramucosal administration of PG in the vestibule of the vagina, in order to avoid or minimize systemic side effects. There are numerous reports in the literature about methods for induction of abortion in bitches as reviewed in Eilts (2002), Wanke et al. (2002), Weibe and Howard (2009), Fraser (2018) and Špoljarić et al. (2018). In cases where aglepriston and other medications are not available, the combination of PG and cabergoline remains the best solution. PG is known for its luteolytic effect that causes progesterone decline and enhances myometrial contractions (Feldman and Nelson 2004). Progesterone and prolactin are both necessary for pregnancy maintenance in a dog (Verstegen-Onclin and Verstegen 2008; Concannon 2011; Kowalewski 2017). Progesterone is the of *corpus luteum* (CL) origin, since the dog is void of placental steroids, unlike all other domestic animal species (Kowalewski 2017). Prolactin is known for its luteotrophic effect, and is the cause of increased progesterone concentration after days 25–28 of pregnancy (Okkens et al. 1990; Concannon 2011). The combination of PG and cabergoline has shown good results in pregnancy termination, due to their luteolytic and antiprolactinemic effects. Exogenously administered PG can directly cause CL regression, depending on the type and dosage, and of CL age (Aiudi et al. 2006; Verstegen-Onclin and Verstegen 2008), while cabergoline induces luteolysis by inhibiting prolactin secretion (Onclin et al. 1993; Feldman and Nelson 2004).

All administered protocols were efficient in terminating pregnancy, and these results are in concordance with numerous results in the literature, where termination was confirmed sonographically (Onclin et al. 1995; Onclin and Verstegen 1996; Wanke et al. 2002; Feldman and Nelson 2004). Even

Table 1. Protocols used for inducing abortion in bitches.

Pregnant bitches ^a	Treatment	
Group	cabergoline (<i>p/o</i>)	dinoprost (<i>i/mucosal</i>)
A	daily	daily
B	daily	every 48 h
C	every 48 h	daily
D	every 48 h	every 48 h

^aEach groups consisted of five animals.

Table 2. Clinical data of bitches treated for pregnancy termination.

Case No.	Breed	Age (y)	Days from first mating	Group of treatment	Days of pregnancy termination (d)	Duration of side-effects (d)	Side effects severity	Pregnancy termination	Vaginal discharge	Foetal expulsion
1	Samoyed	3	31	A	7	7	+	Yes	Yes	No
2	Pug	4	32	A	6	6	++	Yes	Yes	No
3	Mixed-breed	4	30	A	7	7	++	Yes	Yes	No
4	Mixed-breed	2	30	A	9	9	++	Yes	No	Yes
5	Dobermann	5	30	A	5	5	+++	Yes	No	Yes
6	Mixed-breed	2	32	B	8	8	+	Yes	Yes	No
7	German boxer	2	30	B	6	6	++	Yes	No	Yes
8	Illyrian shepherd dog	2	30	B	8	2	-	Yes	Yes	No
9	Labrador retriever	6	30	B	11	7	++	Yes	Yes	No
10	Mixed-breed	3	30	B	12	0	-	Yes	No	Yes
11	Cocker spaniel	3	30	C	5	5	+++	Yes	Yes	No
12	Shar-pei	1	30	C	9	9	++	Yes	Yes	No
13	German shepherd dog	2	30	C	11	11	+++	Yes	Yes	Yes
14	Mixed-breed	4	35	C	8	4	++	Yes	Yes	No
15	Labrador retriever	4	30	C	9	6	+	Yes	Yes	No
16	German shepherd dog	1	30	D	11	7	+	Yes	Yes	No
17	Pug	2	34	D	10	3	+	Yes	Yes	No
18	German boxer	2	33	D	9	2	+	Yes	Yes	Yes
19	Mixed-breed	5	30	D	7	3	++	Yes	Yes	Yes
20	Mixed-breed	2	30	D	12	1	+	Yes	Yes	No

though there were no statistically significant differences in the duration of treatment or side effects, some differences were observed in the intensity of side effects. Usually, side effects are evident after every PG administration, in a duration of up to 1 h, and mostly include symptoms categorized as strong (Onclin et al. 1995; Onclin and Verstegen 1996; Wanke et al. 2002; Feldman and Nelson 2004; Riquelme and Ruiz 2018). In this study, only 15% of bitches experienced strong side effects, likely due to intramucosal application, which thus avoids major systemic distribution of PG as in intramuscular or subcutaneous administration, as shown in Špoljarić et al. (2012). This was observed especially in groups where PG was applied every 48 h. Furthermore, this can be explained by the less frequent regime of PG administration (Wanke et al. 2002). These results confirm that most side effects in protocols based on a combination of PG and dopamine agonist, are the result of PG administration, rather than the dopamine agonist. The advantage of a 48 h regime is the reduced time that owners had to bring their animal to the veterinary hospital, and the reduced price of treatment. The negative side is the duration of treatment, which was longest in the group D, where both PG and cabergoline were administered every 48 h, since PG demands repeated

Table 4. Distribution of side effect intensity per group.

Group	Side effect intensity									
	none		mild		moderate		strong		total	
	n	%	n	%	n	%	n	%	n	%
A	0/5	0	1/5	20	3/5	60	1/5	20	5/5	100
B	2/5	40	1/5	20	2/5	40	0/5	0	3/5	60
C	0/5	0	1/5	20	2/5	40	2/5	40	5/5	100
D	0/5	0	4/5	80	1/5	20	0/5	0	5/5	100
total	2/20	10	7/20	35	8/20	40	3/20	15	18/20	90

treatment to induce luteolysis in bitches (Kowalewski 2017). The treatment lasted somewhat shorter, but not significantly, in group B, where cabergoline was applied every day. This daily administration likely induced faster luteolysis. Daily administration of PG and cabergoline resulted in the shortest duration of treatment, which was accompanied with daily side effects, as seen in group A.

Foetal expulsion was not expected, and the reason for the expulsion of foetuses four bitches could be more advanced pregnancy than claimed by owners, since during the examination no parameters for foetal age prediction were measured. Foetal expulsion can be expected when treatment starts after day 40 of pregnancy (Wanke et al. 2002; Feldman and Nelson 2004). This emphasizes the need for accurate pregnancy diagnoses in the beginning of the second trimester, to prevent undesirable events for the owners, such as the unpleasant sight of an aborted foetus. However, Feldman and Nelson (2004) observed foetal expulsion in bitches treated with natural PG only.

Table 3. Duration of treatments of pregnancy termination and duration of side effects, showed as median, confidence intervals (95% CI), mean and standard error of the mean (SE).

Group	Duration of treatment				Log-Rank	Wilcoxon
	median	95% CI	mean	SE		
A	7.0	5.0–9.0	6.8	0.66	$p=0.09$	$p=0.11$
B	8.0	6.0–12.0	9.0	1.09		
C	9.0	5.0–11.0	8.4	0.97		
D	10.0	7.0–12.0	9.8	0.86		
Group	Duration of side effects				Log-Rank	Wilcoxon
	median	95% CI	mean	SE		
A	7.0	5.0–9.0	6.8	0.66	$p=0.12$	$p=0.12$
B	6.0	0–8.0	4.6	1.53		
C	6.0	4.0–11.0	7.0	1.30		
D	3.0	1.0–7.0	3.2	1.01		

*Each groups consisted of five animals.

Conclusions

In conclusion, as already known, the PG and dopamine agonist combination is effective in causing pregnancy termination in bitches. PG can be equally effectively administered intramucosally to avoid undesirable, strong, systemic side effects. Drug administration every 48 h also induced abortion, with negligible side effects, but with slightly longer duration of treatment. This combination could be interesting in cases where owners are time-limited, and in countries where other drugs for successful pregnancy termination are unavailable.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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