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The intravaginal application of misoprostol improves induction of abortion with aglepristone

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Abstract

The aim of the present study was to compare the clinical and endocrinological effects of four different treatments for the induction of abortion in bitches. For this purpose, 28 pregnant bitches between days 25 and 35 of gestation, were randomly assigned to four groups. In *group I* (n = 7), only aglepristone (AGL, 10mg/kg bw, two injections 24 h apart, s.c.) was administered. In *group II* (n = 7), AGL (as in group I), cabergolin (CAB, 5 μg/kg, daily p.o., until completion of abortion) and misoprostol (MIS, 200 μg for bitches with ≤ 20 kg bw, 400 μg for bitches with > 20 kg bw, daily intravaginally, until completion of abortion) were administered. In *group III* (n = 7), AGL (as in group I) and MIS (as in group II) were administered. In *group IV* (n = 7) AGL, (as in group I) and cloprostenol (CLO, 1μg/kg bw, s.c., two injections 24 h apart with the AGL injections) were combined. In all groups, bitches were examined daily, clinically and ultrasonographically to monitor resorptions/abortions. To measure serum progesterone (P4) and total estrogen (TE) concentrations, blood samples were collected in all groups immediately after the first AGL administration and every other day until completion of abortion. No statistical differences were found between groups concerning the duration until completion of abortion following treatment (n.s.); however, in Group III, 6 d after the start of treatment all pregnancies were terminated whereas in Group I, II and IV, only 57.1% (4/7), 85.7 % (6/7) and 42.8 % (3/7) of pregnancies were terminated. In the latter groups, all pregnancies were terminated between days 8 and 10 after the start of treatment. In Group IV, P4 concentrations on days two and one before the beginning of abortion and the day the abortion started was significantly lower than in the other groups ($P < 0.01$). No statistical differences were found between groups for TE concentrations ($P > 0.05$). In Groups I, II and III, no severe side effects occurred. Severe vomiting after each treatment and until the end of abortion was observed in Group IV only. In conclusion, only when a combination of AGL and MIS was used abortion was completed within 6 d in all bitches whereas the additional use of CAB did not improve the treatment.

Keywords: Dogs; Pregnancy termination; Abortion; Aglepristone; Misoprostol

1. Introduction

The search for efficient protocols for pregnancy termination in dogs and cats is an important field in veterinary science. In bitches, termination of pregnancy with drugs is preferred by owners who wish to prevent postoperative occurrence of incontinence, changes in

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coat condition or behaviour. Furthermore, in many kennels the bitch is still excluded from breeding after mismating. However, drugs for termination of pregnancy must be carefully chosen dependent on safety, efficacy, and costs of the drug as well as compliance of the owner [1].

In bitches, the progesterone (P4) antagonist aglepristone (AGL) has been successfully used for termination of pregnancies [2,3] or induction of parturition in female dogs [4–7]. Aglepristone binds with higher affinity to P4 receptors than the endogenous progesterone which leads to suppression of the biological effect of progesterone [2–6]. According to Fieni et al [5] 97.1% of pregnancies were terminated, when AGL was given at a dose of 10 mg/kg body weight (bw) on two consecutive days. After injection of AGL, symptoms of inflammation at the injection site may seldom occur, other side effects were not observed [9]. Injection of AGL does not decrease the plasma P4 concentration, however, decrease of body core temperature, opening of the cervical canal and behavior are the same as during normal parturition [10,11].

In bitches, prolactin receptor antagonists like cabergoline or bromocriptine can be used to induce abortions, particularly during late pregnancy [12]. These antiprolactins stimulate dopamine receptors in the pituitary lactotroph cells which consecutively prevents the release of prolactin secretion; since prolactin is a luteotropic hormone, one effect of the antiprolactin is suppression of P4 production. A uterine or cervical effect is not known. Onclin et al [13] reported that when cabergoline (CAB) was injected subcutaneously for 5 d starting at day 40 of gestation, plasma P4 concentrations decreased to < 2 ng/ml and fetal expulsion occurred 60–132 h after the last injcetion of AGL. Cabergoline has only mild side effects, such as vomiting, anorexia, polydipsia, however, less than bromocriptine [14].

During a previous study, two different protocols were used to even accelerate termination of pregnancies; since it is important to start the treatment immediately after the diagnosis of pregnancy to induce resorption instead of abortion, treatment started before day 30 of gestation. We either used a combination of AGL and CAB, or AGL alone. It was found, that the administration of AGL and CAB terminated pregnancies significantly quicker than AGL alone (6.8 vs 10.6 d) [15]. This was not comparable to the results from Galac et al [16] who observed completion of abortion 4 to 7 d after the start of treatment, defined as complete loss of all fetuses. However, in the cited study, AGL was injected at day 30 after ovulations and in 5 bitches only. In our study, most bitches received AGL before day 30 of gestation, making a direct comparison difficult. Further studies to improve and accelerate fetal resorption in bitches seemed therefore useful.

Prostaglandins have been successfully used for the induction of abortion during mid-pregnancy; however, subcutaneous injections for 6 d and longer and at least twice daily have been recommended [17,18]. Furthermore, natural as well as synthetic prostaglandins cause side effects, such as tachycardia, hypersalivation, defecation, urination, emesis, and local pruritus at the injection site [18,19,20]; the use in bitches should therefore be restricted. To increase the luteolytic effects of CAB, prostaglandins and CAB have been used in combination and resorptions/abortions were successfully induced from day 25 of pregnancy on. Some researchers combined the prostaglandins cloprostenol (CLO) or alphaprostol given on alternate days with daily CAB administrations [12,21]. The effect was satisfying, however, severe side effects were observed. Onclin and Verstegen [12] reported that the combination of CAB and one injection of CLO (5 μg/kg) at the beginning of the treatment (day 28 after LH peak) or two injections (1 μg/kg) at days 28 and 32 induced resorptions in all bitches, but with less side effects when the lower prostaglandin dose was used. In the present study, we investigated, whether Misoprostol (MIS), a PGE1 analogue, could improve the course of resorption/abortion with fewer side effects than cloprostenol or alphaprostol. Misoprostol causes relaxation of the cervix and stimulation of uterine contractions [22] after selective binding to EP-2/EP-3 receptors. The softening effect on the cervix is neither osmotic nor via the nitric oxide–cGMP system [23]. During recent years, MIS proved to be effective for termination of pregnancies in women. Vaginal administration of MIS successfully terminated pregnancy after the second half of gestation [24,25,26]. The cervical administration proved to be more efficient than the oral treatment [27,28,29]. In women, mild diarrhoea is the major adverse reaction reported for MIS. Nausea and vomiting may occur but usually resolves 2 to 6 h after administration of MIS [28,29].

In goats, parturition was successfully induced with a combination of PGF2α and MIS [30]. In heifers [31], sheep [32], mares [33] and bitches [34] MIS has been tested for the induction of parturition and abortion, respectively. In one study, MIS was used in combination with CAB for the termination of pregnancies in