

Comparison of three methods for termination of pregnancy in cats using a dopamine agonist and prostaglandin F_{2alpha}

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Abstract

This study compared the effect and efficacy of a natural prostaglandin F_{2alpha} (PGF) a dopamine agonist (cabergoline; CBR), or the combination of PGF and CBR in pregnancy termination in domestic cats. after pregnancy confirmation by palpation and ultrasonography. Treatments on 15 cats (in two trials) were initiated between day 35 - 41 after first mating. Animals were assigned randomly to one of three treatment groups: CBR was given orally (n=10; 50 mcg/cat/day) for five consecutive days (day 0 to 5); PGF (n=10; 2.5 mg/cat/day, s.c.) for five consecutive days; or CBR and PGF (n=9, one cat was eliminated from the study). The queens were monitored by ultrasonography on days three and five during treatments and every day after completion of the treatments for three days to assess pregnancy status and fetal viability. The percentage of cats aborted was different ($P < 0.05$) among treatments. In the CBR group, six of ten cats aborted within three days after the last dose. Three days after the completion of the initial treatment, the only observed side effect was a mild bloody vaginal discharge. In the PGF group, only one of ten cats aborted during the three-day period following the completion of PGF treatment. Ultrasonography revealed viable fetuses (presence of heart beat) during and after treatment in the nine cats that did not lose their pregnancy. All nine cats in the CBR + PGF group aborted within three to six days after the initiation of the treatment (five cats after two doses, three cats after three doses, and one cat after five doses). These results indicate that a combination of CBR and PGF is a quick and effective method for pregnancy termination in cats. At 35 to 41 days after mating, treatment with CBR (at the above dose) alone was less effective in pregnancy termination compared with CBR+ PGF. Furthermore, PGF treatment alone, at least at this dose, was not effective in pregnancy termination in cats during 35-41 days after mating.

Keywords: Abortion; pregnancy; cat; cabergoline; prostaglandin F_{2alpha}

Introduction

Current practical methods to terminate pregnancy after unwanted mating in cats include PGF administration, use of a dopamine agonist such as CBR, or progesterone receptor antagonist.¹ Prostaglandin F_{2α} has been reported to induce abortion by causing a premature luteolysis and thus cessation of progesterone secretion in dogs.² High and low doses of PGF successfully induced abortion in bitches when administered between 35-55 days of pregnancy.² However, using PGF as an abortifacient in cats is controversial and results are highly variable. For instance, administering natural PGF successfully terminated pregnancy in four queens at 33 days of gestation.³ Also, it has been shown that PGF (0.5 to 1.0 mg/kg) injected after day 40 of pregnancy induced abortion in queens.⁴ However, using a similar treatment regimen, it was reported that PGF (400 mcg/kg BW) induced luteolysis in cats, but without subsequent abortion.⁵

Prolactin is a luteotropic hormone in dogs and cats. Inhibition of pituitary prolactin release by the dopamine agonist (CBR) initiated abortion through a marked suppression of plasma progesterone.⁶ It has been shown that daily administration of CBR during mid-pregnancy was effective in pregnancy termination in 80% of treated queens.³ These results were similar to others who recorded 92.3% abortion in queens treated orally with CBR on day 40 of pregnancy.⁶ However, in feral cats, it has been shown that oral administration of CBR (5 to 15 mcg/kg/ BW) for four to nine days during estimated 36-41 days of pregnancy, resulted in 100% abortion at 40.5 ± 6.19 days of pregnancy.⁷

The abortion success rate of progesterone receptor antagonist treatment is reported to be only 67%.¹ In another study, two cats were treated with CBR (15 µg/kg; daily, orally) combined with alfaprostol (10 µg/kg; every other day, s.c.) starting on day 45 after mating. This treatment was not successful, although the cats were treated seven and eight times, respectively.⁸

Modification of the above protocols by combining PGF and CBR might provide a more effective approach for termination of pregnancy. For instance, in dogs, the combination of low dose of PGF and oral CBR was shown to induce abortion in 100% of the treated bitches.^{9,10} Moreover, it was reported that the combination of a synthetic PGF and CBR treatment during mid-gestation induced abortion in all five treated queens with minor side effects¹¹.

The results of termination of unwanted pregnancies with dopamine agonist or PGF in cats are inconsistent (0 to 100% success rate) and the research on use of pregnancy with dopamine agonist and PGF combined is limited. Moreover, to our knowledge, the effect of dopamine agonist, PGF and their combination on pregnancy termination in cats has not been compared in side by side studies. The objectives of the present study were to simultaneously compare the efficacy and clinical properties of CRB, natural PGF, and their combination in termination of pregnancy in queens, and to observe any side effects of these treatments.

Materials and methods

Animals

The Virginia Tech Institutional Animal Care and Use Committee approved all the procedures used in these experiments. Fifteen adult female cats (18.1 ± 0.6 months old) with average body weight of 4.2 ± 0.7 kg were used in two trials. Cats were group housed, fed once a day with a commercial dry feline diet (Feline Maintenance,[®] Hill's Pet Nutrition, Topeka, KS), and given access to water *ad libitum*. Cats were exposed to a lighting schedule of 10 h dark and 14 h light. When estrous behavior was observed, all queens were left with a fertile male cat for five days. Estrous behavior and occurrence of mating was monitored three times daily. The date of the first successful mating was recorded. In both trials, all queens were bred by the male during the five-day period. All queens were housed together during pregnancy and after abortion. On day 25-28 after first mating, pregnancy was confirmed by abdominal palpation and a real time ultrasound scanner, equipped with a 5 MHz transducer probe (Aloka Co., SSD-500, Mure, Mitaka-shi, Tokyo, Japan). To estimate the stage of pregnancy, ultrasound images were used and fetal size was measured by an experienced veterinarian to better estimate the age of conceptus.¹² Thirty days after the completion of the first trial, a second trial was conducted using the same animals and using the same procedures as in trial one. None of the queens in trial two received the same treatment as in trial one. However, in the second trial, one cat was eliminated from the study due to respiratory problems unrelated to the experiment.

Treatment

Treatments were initiated between day 35 - 41 after first recorded mating and ten days after pregnancy was confirmed. Animals were assigned randomly to one of three treatment groups. An oral formulation of CBR (50 mcg/mL; Galastop[®], Vetem, Centralvet, Milan) at a daily dosage of 50 mcg per cat (approximately 12 mcg/kg BW) was used. Natural PGF (Lutalyse[®], Zoetis, Florham, NJ) was administered s.c. at a daily dosage of 2.5 mg per cat (approximately 0.6 mg/kg BW). After detection of pregnancy, and between day 35-41 after mating, cats were randomly divided into three treatment groups. Group 1 received oral CBR (50 mcg per cat; n = 10) for five consecutive days or less if abortion had occurred earlier; Group 2 received (s.c.) 2.5 mg per cat of PGF for five days or less if abortion had occurred earlier (n=10); Group 3 received both oral CBR (50 mcg per cat) and PGF (2.5 mg per cat, s.c.) for five days or less if abortion had occurred earlier (n=9). To examine fetal presence and viability, the queens were monitored by ultrasonography on day 3 and 5 after initiation of treatment during treatments and every day after completion of the treatments for three days. The presence of potential side effects after daily treatment (tachypnea, prostration, vocalization, and emesis) was monitored and recorded.

Statistical analysis

Data from both trials were analyzed by GENMOD procedure on SAS.¹³ The full statistical model included the effects of treatment (CBR, PGF or CBR + PGF), trial (trial 1 and trial 2) and two-way interactions. Statistical significance was defined as $P \leq 0.05$. If the treatment was significant, preplanned contrasts were carried out to compare the proportion pregnancy loss means among treatments (CBR + PGF vs. CBR and vs. PGF and CBR vs PGF).

Results

There was no effect of trial or trial by treatment interaction. There was an effect of treatment on percentage of cats which lost their pregnancy ($P < 0.05$). Pregnancy losses were 100% (9/9) and 60% (6/10) for CBR + PGF and CBR groups, respectively, and were greater ($P < 0.05$) than the PGF group (10%, 1/10; Table). In the CBR group, oral administration of CBR for five days induced abortion in six of ten cats (60%) within three days after the completion of the treatment. In four of these six cats, abortion involved the observed expulsion of fetuses. In the other two cats, no fetus expulsion was observed. Ultrasonography conducted on day five after start of the treatment indicated the presence of non-viable fetuses as no heartbeats were detected. Oral CBR did not produce any side effects except hemorrhagic vulvar discharges were noticed in all queens on day four and five of treatment.

In the PGF group, subcutaneous administration of PGF failed to induce abortion within eight days after the initial treatment period except in one of ten cats. That one abortion occurred at the end of eighth day. In both trials, during the treatment period (five days) and three days after the last injection, ultrasonography revealed normal fetuses that appeared viable as evidenced by heartbeats. Side effects occurred in the queens approximately ten minutes after drug administration and included tachypnea, vocalization, and emesis. After the third injection, queens seemed to adapt to the drug and side effects diminished considerably by the fourth and fifth injection. There were no signs of a hemorrhagic vulvar discharge in the cat that lost its pregnancy and other cats in this group.

In the CBR + PGF group, a combination of PGF and CBR resulted in a rapid loss of pregnancy in all cats (100%) within 3-6 days after initiation of treatment, which was greater ($P \leq 0.05$) the other two treatment groups. Five cats aborted by day 3 (after two doses), three cats aborted by day 4 (after three doses), and one cat aborted on day 6 (after five doses) after the start of the treatment. Abortion involved observed expulsion of fetuses in all cats. The side effects observed with this treatment group (CBR + PGF) were similar to those observed in CBR and PGF groups, including occasional emesis, prostration, and vocalization. Furthermore, hemorrhagic vulvar discharge was observed.

Because we wanted to terminate pregnancy in the 13 cats that remained pregnant (four cats in the CBR group and nine cats in the PGF group), on day 9 and 10 after treatment initiation, these cats received two doses of CBR + PGF which resulted in abortion in all 13 cats, two days (four cats) or three days (nine cats) after the last dose. Abortion involved observed expulsion of fetuses in 12 cats. The side effects were similar to those observed in CBR + PGF treated cats.

Discussion

To our knowledge, this is the first study that simultaneously examined the effect of the dopamine agonist CBR, PGF, and their combination for inducing abortion in cats. It was reported that a combination of CBR and synthetic PGF resulted in termination of pregnancy in all cats (five cats) compared with controls.¹¹ However, in the present study, abortions occurred within 3-6 days after the start of treatment. In contrast, in the previous study,¹¹ abortion occurred within 9 ± 1 days. The differences between the present experiment and the previous report could be attributable to CBR treatment protocol, the type and regimen of PGF used, and (or) the stage of gestation at when treatment was initiated. In the previous study,¹¹ synthetic PGF (cloprostenol) was administered every two days (4-5 injections) starting on day 30 after mating whereas in the present study, we administered natural PGF (dinoprost tromethamine) daily between day 35-40 after mating. Moreover, we administered CBR for

only five consecutive days, whereas, in the previous study, CBR was administered every day for a mean of 11 days.

Five doses of CBR (50 mcg per cat) induced abortion in only six of the ten cats three days after the completion of the treatment. The results are in accord with previous findings⁷ that recorded about 92% abortion rate in queens treated orally with CBR on day 40 of pregnancy. Furthermore, the daily use of CBR injections from day 30 after mating terminated pregnancy in 80% of the treated cats.³ These results, however, are different from others who showed that 4-9 days of CBR treatment at an average of 36-41 days of estimated pregnancy, resulted in 100% abortion at 40.5 ± 6.19 days after mating.⁷ It should be noted in that study, confirmation of pregnancy and abortion was solely based on changes in behavior, body confirmation, and clinical and social interaction.⁷ The findings of this experiment combined with others^{3,6,7} indicate that oral administration of CBR can be effective in inducing abortion in cats; however a longer treatment period (>5 days) may be required in order to reach 100% efficacy.⁷

The mechanism of action by which CBR induced pregnancy loss cannot be derived from this study as no blood hormones were measured. Corpora lutea are necessary to maintain pregnancy in the second half of gestation in cats.¹⁴ Furthermore, prolactin is an essential luteotropic hormone in cats and it appears to act by sustaining corpus luteum lifespan and function after 25 days of gestation in cats.¹⁴ There is substantial evidence that CBR is an ergoline derivative with potent, selective and long-lasting inhibitory activity on prolactin and can inhibit prolactin secretion in cats.^{3,14} Therefore, CBR-induced inhibition of prolactin causes a substantial decrease in luteal progesterone and pregnancy loss.^{3,11,14} In the current study and the previous studies pregnancy loss occurred between seven and ten days after initiation of oral CBR treatments.^{11,14} It is hypothesized the delay between luteolysis induced by CBR and abortion may be due to slower rate of decline in progesterone (through indirect inhibition of prolactin), as well as existence of small amount of progesterone from the cat's placenta in second half of pregnancy that is limited in duration. This small amount of progesterone may delay pregnancy loss, but is insufficient to overcome the marked decrease in luteal progesterone caused the luteolytic effect of cabergoline.^{3,14}

In the PGF group, with exception of one queen, subcutaneous administration PGF did not result in abortion within eight days after the first injection. These results were similar to previous research that showed PGF was luteolytic in cats, but did not induce abortion.⁵ Our findings in PGF-treated group are contrary to others,³ which showed that intramuscularly injection of natural PGF successfully (100%) induced abortion in queens (four cats) when administered on day 30 to 33 after mating. The exact reason(s) for the observed difference between the present experiment and the previous study³ is not clear except that PGF was administered intramuscularly during an earlier stage of gestation. Whether the route and time (relative to mating) of PGF treatment contributes to the effectiveness of PGF as an abortifacient drug, requires more research.

It is apparent that the use of CBR alone during day 35-41 of pregnancy has advantages to that of PGF treatment alone as it can induce abortion without noticeable side effects. However, a five-day treatment was not sufficient to produce 100% pregnancy termination. In contrast, the combination of PGF and CBR was 100% effective in pregnancy termination and required a shorter treatment period (three to five days). It is argued that PGF through its direct luteolytic action combined with CBR by inhibiting prolactin have synergistic effect in decreasing progesterone and result in 100% pregnancy termination compared with CBR or PGF alone.¹⁴

These results provide further evidence that a combination of CBR and PGF is a quick and effective method for pregnancy termination in cats during the second half of pregnancy. At 35 to 41 days after mating, treatment with CBR (at the above dose) alone was less effective in pregnancy termination compared with CBR+ PGF. Furthermore, PGF treatment alone, at least at the dose used here, was not effective in pregnancy termination in cats during 35-41 days after mating.

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Table: Effect of treatment with cabergoline (5 days), prostaglandin F_{2alpha} (5 days), or their combination (2 to 5 days) on efficacy of pregnancy termination starting at days 35 to 41 after mating in queens.

Treatment	Dosage	No. of dose	Efficacy Pterm/Trt ^a	Time of pregnancy termination
PGF (n=10)	2.5 mg (s.c.)	5	1/10 (10%) ^a	8 days after end of treatment
Cabergoline (n = 10)	50 mcg (oral)	5	6/10 (60%) ^b	3 days after end of treatment
Cabergoline + PGF (n = 9)	50 mcg & 2.5 mg (oral & s.c.)	2-5 ^c	9/9 (100%) ^c	On day 3 of treatment (n=5); On On day 4 of treatment (n=3); A day after end of treatment (n=1)

^a Pterm/Trt: number of pregnancy termination/number of queens treated.

* ^{a,b,c} Within a column, values with different superscript differ (P \leq 0.05)

