Use of prostaglandins and bromocriptine mesylate for pregnancy termination in bitches

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Objective—To assess the efficacy and safety of 2 protocols using bromocriptine mesylate and prostaglandins to terminate unwanted pregnancy in bitches.

Design—Prospective randomized single-blind controlled study.

Animals—Thirty-four healthy crossbred and purebred bitches referred for possible pregnancy termination. Seven additional pregnant bitches were used as controls.

Procedure—Pregnancy was assessed by ultrasonographic examination from day 25 after mating in all bitches. Of the 34 bitches, 25 were pregnant and were randomly allocated to a treatment group. Group-1 dogs (n = 12) received a combination of increasing amounts of bromocriptine mesylate (15 to 30 µg/kg [6.8 to 13.6 µg/lb], PO, q 12 h) and dinoprost tromethamine (0.1 to 0.2 mg/kg [0.045 to 0.09 mg/lb], SC, q 24 h). Group-2 dogs (n = 13) received a combination of increasing amounts of bromocriptine mesylate (the same schedule as group-1 dogs) and cloprostenol sodium (1 µg/kg [0.45 µg/lb], SC, q 48 h). Both groups were treated until pregnancy termination.

Results—Treatment success was 100% in both groups. Days of treatment required for pregnancy termination did not significantly differ between groups (5.0 ± 0.6 vs 3.7 ± 0.6 days, group-1 and group-2 dogs, respectively) although adverse effects only developed in group-1 dogs. At the end of the protocols, pseudopregnancy was observed in 3 of 12 and 6 of 13 group-1 and group-2 dogs, respectively. Pregnancy termination was followed by a mucoid sanguineous vulvar discharge for 3 to 10 days.

Conclusions and Clinical Relevance—Results of this study indicate that protocols that combine the use of bromocriptine mesylate and prostaglandins for the termination of unwanted pregnancy in bitches are efficient and safe. The use of bromocriptine mesylate and cloprostenol had the best results and could be easily used on an outpatient basis. (J Am Vet Med Assoc 2002;220:1017–1019)

Unwanted pregnancy in bitches is a commonly encountered problem in the practice of veterinary small animal medicine. Protocols that use estrogen have been reported to interrupt unwanted pregnancy in bitches, but they have not found wide acceptance because of adverse effects. Estrogens are not 100% effective for this purpose and can cause bone marrow hypoplasia. In conjunction with progesterone, estrogens can also cause cystic endometrial hyperplasia and are not 100% effective for this purpose and can cause bone marrow hypoplasia. In conjunction with progesterone, estrogens can also cause cystic endometrial hyperplasia. Antiprogestagens such as aglepristone, which appear as the best option because of their safety for this purpose, are not available in most countries.

Prostaglandin F₂α is luteolytic and abortive in bitches. Prostaglandin F₂α prevents the synthesis of progesterone by activating a protein kinase-C, which inhibits progesterone synthesis and opens Ca²⁺ channels so that Ca²⁺ influx causes apoptosis in the corpora lutea. Prostaglandins (PG) also have an evacuating effect on the uterus. Female dogs, in comparison to most other species, are more resistant to the luteolytic effects and are particularly susceptible to their adverse effects. Protocols that use PG, therefore, usually require an unsuitable number of injections and can cause salivation, vomiting, diarrhea, and hyperpnea.

A form of PGF₂α, dinoprost tromethamine, is marketed for use in small animals in most countries. Synthetic analogues, including cloprostenol sodium, are commercially available for use in large animals. Synthetic analogues, in comparison to natural forms, have the advantage of much stronger luteolytic and fewer nonspecific smooth muscle effects. They can therefore be used in lower dosages, which reduces their adverse effects.

Use of various combinations of PGF₂α and dopaminergic agonists has been reported to successfully interrupt pregnancy from day 25 of the estrous cycle without the adverse effects found with estrogen treatment. Prostaglandins and dopaminergic agonists synergistically decrease serum progesterone concentrations. Prostaglandins have a direct action on the corpus luteum, whereas dopaminergic agonists act indirectly on the corpus luteum by decreasing the main luteotropic hormone, prolactin. Information from most studies, however, have been derived using a limited number of laboratory Beagles.

Availability in the veterinary market of the 2 most commonly used dopaminergic agonists, namely bromocriptine mesylate and cabergoline, is limited in most countries in North and South America. Although cabergoline is more potent and has fewer adverse effects than bromocriptine mesylate, its routine indication is often restricted because of cost. Therefore, the purpose of the study presented here was to assess the efficacy and safety of 2 protocols using bromocriptine mesylate and prostaglandins to terminate unwanted pregnancy in bitches.

Materials and Methods

Animals—Thirty-four healthy crossbred and purebred bitches, 1 to 11 years of age and weighing 6 to 28 kg (13.2 to 61.6 lb), were referred to the Institute of Theriogenology of the National University of La Plata from August 1999 to June 2001.
small animals

for possible pregnancy termination. During the same period 7 pregnant bitches with the same age and body characteristics were used as controls. Throughout the study, bitches remained in their normal surroundings (home) except at the time of injections and examinations. All the owners signed consent forms.

Procedure—Confirmation or absence of pregnancy was determined by ultrasonographic examination from day 25 after mating in all bitches.12 Findings on ultrasonographic examination were also used to define gestational age. Pregnant bitches were randomly allocated to a treatment group. Group-1 dogs (n = 12) received a combination of increasing amounts of bromocriptine mesylate and dinoprostone tromethamine. Group-2 dogs (n = 13) received a combination of increasing amounts of bromocriptine mesylate (the same schedule as group-1 dogs) and cloprostenol (Appendix). For injection, cloprostenol was diluted 10-fold in physiologic saline (0.9% NaCl) solution. One hundred-microgram bromocriptine mesylate tablets were manufactured for this study. Both treatments were continued until pregnancy termination (abortion or resorption), which was confirmed by ultrasonography. After pregnancy termination, the same dosage of PG was continued for 2 days. The 7 pregnant bitches used as controls received no treatment.

Ultrasonographic monitoring—Bitches were monitored every other day by ultrasonography until pregnancy termination and then for an additional 48 hours. Control dogs were monitored with the same frequency until parturition and then 48 hours later. Diameter of gestational sacs, heart rate, anatomy of fetuses, and the attachment of the placenta were assessed.14 Resorption was defined as the death of all embryos or fetuses, a decrease of volume of fetal amniotic fluid, cardiac arrest, and homogenization of the embryonic or fetal structures and resorption. Abortion was defined as the expulsion of fetuses with uterine vacuity.12,14

Statistical analyses—The proportion and percentage of bitches referred that were pregnant and had treatment success (pregnancy termination) were calculated. Data were analyzed by least squares analysis, using the general linear model procedure for days of treatment required.4 The mathematical model included the main effect of treatment and gestational age as a covariable. The rate of adverse effects and mammary gland changes (enlarged mammary glands or milk secretion) in bitches were analyzed by categoric data analysis.9 To further characterize the study, gestational age was correlated either with days of treatment required and with the appearance of resorption or abortion.1 The results are expressed as least squares means (± SEM).10 The level of significance was set at P < 0.05.

Results

On the basis of ultrasonographic findings, 25 of 34 (73.6%) dogs that were referred for possible pregnancy termination were 25 to 42 days pregnant, whereas the remaining 9 (26.4%) dogs were not pregnant. The pregnant control dogs had normal ultrasonographic findings throughout gestation and whelped healthy litters.

Treatment success for termination of pregnancy was 100% in both groups. Of the 12 group-1 dogs, 8 terminated pregnancy by abortion, and 4 terminated pregnancy by resorption. Of the 13 group-2 dogs, 11 terminated pregnancy by abortion, and 2 terminated pregnancy by resorption. Days of treatment required for pregnancy termination did not significantly differ between treatment groups (5.0 ± 0.6 vs 3.7 ± 0.6 days, group-1 and group-2 dogs, respectively). Days of treatment for pregnancy termination ranged from 3 to 10 days and from 1.5 to 10 days for group-1 and group-2 dogs, respectively. Abortion was preceded by a sequence of events similar to that of normal parturition, such as signs of anxiety and nesting, whereas there were no prodromal signs with resorption. One of the group-2 dogs had a split abortion that occurred during 2 days of treatment (days 3 and 10). When both treatments were analyzed together, correlations between gestational age and days of treatment and between gestational age and abortion were not significant (r = –0.35, P = 0.08 and r = 0.37, P = 0.06, respectively).

Adverse effects were only observed in group-1 dogs, whereas they were absent in group-2 dogs (P < 0.001). They appeared 30 minutes after injection of dinoprostone tromethamine and lasted a few minutes. They were mild and did not lead to termination of pregnancy in any instance. They consist of vomiting, nausea, retching, and hyperventilation. At the end of the protocols mammary gland milk secretion and overt signs of pseudo-pregnancies were observed in 3 of 12 and 6 of 13 group-1 and group-2 dogs, respectively. Mammary glands were enlarged in 3 group-1 and 2 group-2 dogs. Pregnancy termination was followed by a mucoid sanguineous vulvar discharge for 3 to 10 days in all dogs. None of the dogs has had uterine problems after treatment.

Discussion

Termination of unwanted pregnancy by medical intervention in dogs is a problem, because reliable methods that are free of adverse effects are available in only a limited number of countries. In a previous study,19 60% of dogs that had mated accidentally were not pregnant. In the present study, > 25% of the dogs referred for possible pregnancy termination were not pregnant. Findings in both studies clearly demonstrate that pregnancy termination should only be initiated after pregnancy has been positively determined.

Protocols for pregnancy termination that combine the use of dopaminergic agonists and PG allow a reduction in the amount of PG used and, therefore, its adverse effects. Although we used a lower bromocriptine mesylate dosage, our results (100% efficacy) were in line with those of a previous study in 5 laboratory beagles in which a similar protocol was used.12 Even with a lower cloprostenol dosage, we obtained the same results as in another study.8 In that same study, administration of a combination of dinoprostone tromethamine and bromocriptine mesylate for a set time of 5 days had a 100% failure for pregnancy termination in 6 bitches. By contrast, our results using the same PG emphasizes the importance of extending treatments until the desired effect is achieved (pregnancy termination) instead of using a fixed-time protocol.

Although not significantly different, the protocol used in group-2 dogs was shorter than the protocol used in group-1 dogs. Furthermore, failure to find the expected negative correlation between gestational age and days of treatment was probably the result of the number of dogs included in our study, as a propensity was shown in this aspect. Later in pregnancy, termination has been reported to be shorter and associated with abortion rather than resorption in laboratory experiments.11 Also, an inclination for abortion in late pregnancies was found in our study. Although resorption is
usually much more acceptable by owners than abortion, aborted fetuses were rarely observed as dogs devoured fetuses and membranes as they were expelled.

Vomiting and diarrhea are usually associated with treatment with bromocriptine mesylate, but neither was observed in this study, whereas adverse effects could be clearly related to dinoprostone tromethamine. Administration of exact dosages PO at feeding time along with the gradual increasing dosage scheme could have prevented the usual digestive adverse effects of bromocriptine mesylate. Adverse effects of dinoprostone tromethamine were transient, and vomiting was nonproductive and self-limiting, as the PG was administered SC as far from feeding time as possible. Similar to findings in another study, no adverse effects were associated with the SC administration of a potent and long acting form of PG, cloprostenol, every 48 hours. Signs of overt pseudopregnancy in some of the dogs of our study after treatment and pregnancy termination may have been the result of an abrupt increase in serum prolactin concentrations caused by a treatment-induced decrease in progesterone production.

Results of this study indicate that these protocols that combine the use of bromocriptine mesylate and PG for pregnancy termination are efficient, without compromising the health or the reproductive future of dams. Moreover, the protocol using cloprostenol could be easily used on an outpatient basis, as bromocriptine mesylate is administered PO by owners, and SC injections of cloprostenol and follow-up are conducted every other day. Except the dog with the split abortion that occurred on 2 days of treatment, no dog required more than 3 visits to the clinic. For bitches in which ovariohysterectomy is not an option and in countries where availability of other safe drugs is restricted, the use of cloprostenol with bromocriptine mesylate provides a good alternative to terminate unwanted pregnancies without adverse drug effects.

References

Appendix

Dosage protocols for termination of pregnancy in group-1 and group-2 dogs

<table>
<thead>
<tr>
<th>Days</th>
<th>Group 1 (n=12)</th>
<th>Group 2 (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bromocriptine mesylate (PO, q 12 h)*</td>
<td>Dinoprostone tromethamine (SC, q 24 h†)</td>
</tr>
<tr>
<td>1</td>
<td>15 µg/kg (6.8 µg/lb)</td>
<td>0.1 µg/kg (0.45 µg/lb)</td>
</tr>
<tr>
<td>2</td>
<td>20 µg/kg (9.09 µg/lb)</td>
<td>0.15 µg/kg (0.70 µg/lb)</td>
</tr>
<tr>
<td>3</td>
<td>25 µg/kg (9.09 µg/lb)</td>
<td>0.2 µg/kg (0.09 µg/lb)</td>
</tr>
<tr>
<td>Remaining</td>
<td>30 µg/kg (13.6 µg/lb)</td>
<td>0.2 µg/kg (0.09 µg/lb)</td>
</tr>
</tbody>
</table>

*Administered orally with food at feeding time. †Administered subcutaneously as far from feeding time as possible.