Because pregnancy is easy to detect during the preossification period, that is the best time for abortion induction.

The advantages of prostaglandin analogs over natural prostaglandins include a higher affinity for corpus luteum receptors, lower affinity for smooth-muscle receptors, and longer duration of action.

When using cloprostenol, a dosing error could have fatal consequences.

The preossification period begins at the time of fetal attachment and ends at fetal ossification, approximately 40 to 42 days after the luteinizing hormone (LH) peak. This is the optimum time for abortion induction because pregnancy is easy to detect and most abortions during this period result in resorption, which is safest for bitches and more acceptable to owners than an abortion by fetal expulsion. Safe and reliable protocols for abortion induction during this period of pregnancy have recently been described (Table 1). Synthetic or natural prostaglandins (PGs), antiprolactin drugs (e.g., bromocriptine, cabergoline, metergoline), inhibitors of progesterone secretion (e.g., epostane), or inhibitors of progesterone action (e.g., mifepristone, aglepristone) are suitable for abortion induction. However, because of the side effects of PGs and the limited availability of some compounds, a combination of synthetic PGs and antiprolactinic agents is preferred. This combination has been described as balanced luteolysis.

ABSTRACT: The best time for inducing abortion in bitches is approximately 28 days after the luteinizing hormone surge (25 days after the first fertile mating). At this time, pregnancy can be easily confirmed, thereby avoiding unnecessary treatments. This is one of the major advantages of inducing abortions in the preossification period. Because it is almost impossible to accurately confirm pregnancy during preattachment, nonpregnant bitches are often treated. Once pregnancy has been confirmed, a safe approach for termination can be chosen.

Compendium July 2002  Abortion in Bitches  557

www.VetLearn.com

ABORTION INDUCTION PROTOCOLS IN THE PREOSSIFICATION PERIOD

Prostaglandins

As diestrus progresses, the corpus luteum (CL) becomes more sensitive to PGs, making luteolysis induction easier during the preossification period. PGs induce abortion by producing vasoconstriction, which reduces CL blood flow, causes cellular degeneration, and interrupts progesterone synthesis and production. After PG administration, myometrial contractions increase because of a double mechanism, including a direct effect on the myometrium; however, the luteolytic effect reduces progesterone levels simultaneously, thus increasing myometrial tone. During the preossification period, PGs can be given over a shorter duration with a lower dose.

Natural Prostaglandins

Because CL sensitivity to exogenous PGs progressively increases during preossification, lower doses can be given and hence fewer side effects are observed. Many protocols have been described, most of which suggest dosages from 0.1 to 0.25 mg/kg SC bid for 4 to 6 days. Other protocols recommend lower dosages, even as low as 20 to 30 µg/kg SC tid to qid. Administering lower doses on the first day and progressively increasing them to effect tend to minimize side effects. Close monitoring of induction efficacy by checking progesterone levels or by ultrasonography is highly recommended.

Synthetic Prostaglandins

Fieni and colleagues administered cloprostenol (2.5 µg/kg SC q48h three times) to 67 pregnant bitches (mean gestation stage, 35.5 days after mating). After one treatment, 53 of the 67 bitches (79.1%) aborted; and after a second treatment to the remaining 14 bitches, 9 more (92.5%) aborted. In this trial, administering a mixture of atropine sulfate (0.025 mg/kg), prifinium bromide (0.1 ml/kg), and metopimazine (0.5 µg/kg) for 5 days significantly increased the abortion rate. Other protocols recommend lower dosages, even as low as 20 to 30 µg/kg SC tid to qid. Administering lower doses on the first day and progressively increasing them to effect tend to minimize side effects. Close monitoring of induction efficacy by checking progesterone levels or by ultrasonography is highly recommended.

Table 1. Recommended Protocols for Abortion Induction in the Preossification Period

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Efficacy</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural PGF$_{2alpha}$</td>
<td>0.1–0.25 mg/kg SC q12h for 4–6 days</td>
<td>High (80%–100%)</td>
<td>Excessive salivation, vomiting, defecation, urination, anxiety, pupillary dilation followed by constriction</td>
<td>Monitor progesterone levels to confirm abortion; use the lowest possible dose on the first day, and progressively increase it to minimize side effects</td>
</tr>
<tr>
<td>Cloprostenol</td>
<td>1–2.5 µg/kg SC q24–q48h for 5 days</td>
<td>High (100%)</td>
<td>Excessive salivation, vomiting, defecation, urination, anxiety, pupillary dilation followed by constriction</td>
<td>Monitor progesterone levels to confirm abortion; cloprostenol has fewer side effects than natural PGF$_{2alpha}$</td>
</tr>
<tr>
<td>Combinations of low-dose PGs and dopamine agonists</td>
<td>Cabergoline (5 µg/kg/day PO for 5 days) plus cloprostenol (1 µg/kg SC q48h)</td>
<td>High (100%)</td>
<td>Few or none</td>
<td>Start induction on day 25 after LH peak or 20 to 28 days after first mating; monitor progesterone levels to confirm abortion</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine (30 µg/kg PO tid) plus two injections of cloprostenol (1 µg/kg on days 28 and 32 after LH peak)</td>
<td>High (90%–100%)</td>
<td>Few</td>
<td>Start induction on day 25 after LH peak or 20 to 28 days after first mating; monitor progesterone levels to confirm abortion</td>
</tr>
<tr>
<td></td>
<td>Bromocriptine (10 µg/kg PO tid) plus PGF$_{2alpha}$ (100 µg/kg SC tid)</td>
<td>High</td>
<td>Few</td>
<td>Administer bromocriptine until abortion is clinically evident; administer PGF$_{2alpha}$ until 2 days after abortion begins</td>
</tr>
<tr>
<td>Progesterone antagonist (aglepristone)</td>
<td>10 mg/kg SC (two doses, 24 hours apart)</td>
<td>High (94.8%)</td>
<td>None</td>
<td>Not available in many countries</td>
</tr>
</tbody>
</table>

*Estrumate® (cloprostenol 250 µg/ml; Schering-Plough Animal Health) must be diluted in saline at a ratio of 1:10 (1 ml of Estrumate® to 9 ml of saline solution). From this solution, administer 1 ml/10 kg (2.5 µg/kg) or 1 ml/25 kg (1 µg/kg). Do not reuse the solution.
mg/kg) prevented the occurrence of side effects in 39 of the 67 bitches (58.2%).

When using synthetic PGs, it is important to realize that mistakenly using doses suggested for natural prostaglandin F<sub>2α</sub> (PGF<sub>2α</sub>) or inaccurately diluting commercial preparations of cloprostenol could result in the death of a patient.

An alternative method for administering cloprostenol to dogs has been described.<sup>11</sup> Calcium cloprostenol (2.2 to 5.2 µg/kg/day) was administered SC by miniosmotic pumps for 7 days in 13 bitches, all of which eventually aborted. The only side effects (lethargy and vomiting on days 0, 1, and 2) occurred in one bitch that received the higher dose (5.2 µg/kg/day).

Intravaginal administration of PGs has recently been described.<sup>12</sup> Ten pregnant bitches received either a synthetic PGF<sub>2α</sub> gel (luprostiol) or natural PGF<sub>2α</sub> at 0.15 mg/kg/day intravaginally. A stable gel formulation containing 38 mg of PGF<sub>2α</sub> and 100 g of gel was made based on triacetin and fumed silica (6%). For the synthetic analog, a similar gel was used: triacetin and fumed silica (5.8%) with 54 mg of luprostiol. All bitches aborted, and side effects were moderate.

**Natural Versus Synthetic Prostaglandins**

Synthetic PGs have been tested for use in dogs.<sup>10,13,14</sup> The advantages of PG analogs over natural PGs include a higher affinity for receptors in the CL, fewer effects on smooth muscle, and longer duration of action. These properties improve the efficacy of PG analogs, allowing them to be used at lower doses, less frequently, and with fewer side effects. Only the PG analog cloprostenol has been sufficiently studied<sup>10,15</sup> to be recommended in practice.

Because the half-life of PGF<sub>2α</sub> in dogs is thought to be only seconds or minutes,<sup>16</sup> administration of multiple doses per day is needed. Cloprostenol is considered to have a half-life of at least 12 to 14 hours and a much stronger luteolytic effect than PGF<sub>2α</sub>. In hamsters, cloprostenol is approximately 200 times more active than natural PGF<sub>2α</sub> with regard to its luteolytic effect, while its action on smooth muscle fibers is less.<sup>17</sup> Therefore, it can be used in much lower doses than natural forms of PGF<sub>2α</sub> and is associated with fewer effects on smooth muscle and reduced side effects.

**Side Effects of Prostaglandins**

The side effects of PGs are related to their smooth-muscle stimulant properties. Therefore, in theory, synthetic analogs that have higher affinity for CL receptors than for smooth-muscle receptors tend to cause fewer side effects. The toxicity and side effects of PGF<sub>2α</sub> have been characterized and include salivation, vomiting, hyperpnea, ataxia, and pupillary dilation followed by constriction.<sup>18</sup> A median lethal dose of 5.13 mg/kg was determined, and 75% of deaths occurred within 12 hours of treatment. Shille and colleagues<sup>13</sup> found a slight but consistent increase in liver-enzyme concentrations in serum 24 hours after injecting a synthetic analog of PGF<sub>2α</sub>.

Side effects of PGs are dose dependent: Lower doses (0.1 mg/kg or less) are mainly associated with defecation, while hyperpnea, anxiety, salivation, and vomiting are frequently observed with medium doses (0.1 to 0.20 mg/kg). These effects are usually evident 10 to 20 minutes after administration and last for about 15 minutes. Side effects tend to disappear over the course of therapy. After two or three doses, side effects are limited to slight hyperventilation, slight hypersalivation, and (rarely) vomiting. With proportionate doses relative to size, small and medium-sized bitches tend to experience more side effects than do large bitches.<sup>13</sup>

Preadministering atropine and walking the bitch after the injection may help reduce side effects. In our experience, administering the lowest possible dose on the first day of treatment and progressively increasing it helps minimize side effects. Close monitoring of the treatment response (with ultrasonography or by measuring progesterone levels) is always advisable. It is noteworthy that most bitches return to estrus earlier than expected after PG treatment, probably related to a shorter duration of diestrus.<sup>19–22</sup>

**Prostaglandin and Prolactin-Secreting Inhibitor Combinations**

Combinations of PGs and prolactin-secretion inhibitors reduce progesterone release by a double mechanism of action: a direct local effect of PGs on steroidogenesis and an indirect effect due to withdrawal of pituitary prolactin support.<sup>13,22</sup> Lower doses of PGs can be used with these combinations, resulting in fewer or no side effects. Different combinations have been proposed<sup>24–27</sup>; however, cloprostenol with oral cabergoline appears to be the combination of choice.

Gerstenberg and Nöthling<sup>24</sup> reported that preadministration of metergoline reduced the number of PGF<sub>2α</sub> injections necessary to induce and complete abortion to an average of 4.8 compared with 8 to 14 injections for conventional regimens. They also proposed that preadministration of metergoline allows a faster and easier abortion without mammary development and lactation.

Onclin and colleagues<sup>25</sup> reported on use of the dopamine agonist cabergoline with a synthetic analog of PGF<sub>2α</sub>, either cloprostenol or alphaprostol. In five animals, alphaprostol (20 µg/kg/day SC) combined with cabergoline (1.65 µg/kg/day SC) was injected for
5 days starting at day 32 after LH peak. In two separate groups of five animals, cloprostenol at doses of 2.5 and 1 µg/kg/day was used in combination with the same dosage of cabergoline (1.65 µg/kg/day) starting from day 25 after LH peak. Pregnancy was terminated in all dogs. Side effects were observed in bitches that received cabergoline along with alphaprostol and the higher dosage of cloprostenol. No side effects were observed with the cloprostenol (1 µg/kg/day) and cabergoline (1.65 µg/kg/day) combination.

More recently (in an attempt to describe an easily applicable protocol for use in practice), Onclin and Verstegen described the administration of oral cabergoline (5 µg/kg/day) and cloprostenol (1 µg/kg SC q48h) for inducing abortion. This combination, starting from day 25 after LH surge (20 to 28 days after first mating), induced abortion by resorption in 100% of bitches within 5 to 8 days. The only side effect was a bloody vaginal discharge in some bitches. This combination is also effective after day 40 following the LH surge, but abortion by fetal expulsion is often observed. In practice, the day of mating is known more often than the day of LH surge; therefore, induction should be started as soon as pregnancy can be confirmed because this corresponds approximately to day 25 after LH surge.27

Because oral cabergoline is not available in all countries, some protocols using bromocriptine have been described. One study examined treatment with bromocriptine (30 µg/kg PO tid for 10 days) and cloprostenol (2.5 µg/kg SC at the beginning of induction or 1 µg/kg SC on days 28 and 32 after LH surge). The group treated with the higher dosage of cloprostenol experienced side effects within 10 minutes after injection; no side effects were observed in the group receiving the lower dosage of cloprostenol. All bitches in both groups aborted. The animals’ subsequent fertility was not impaired; all returned to estrus and became pregnant when mated. The combination of cabergoline and a synthetic PGF2α analog (luprosti) absorbed in a fumed silica and triacetin has recently been described.29 This regimen appears to be safe, fast, and effective for abortion induction in bitches. Another protocol calls for bromocriptine (10 µg/kg PO tid until abortion is clinically evident) combined with PGF2α (100 µg/kg SC tid until 2 days after abortion begins).30

**Glucocorticoids**

Dexamethasone induces abortion in bitches; however, its mechanism of action is unknown. Intramuscular injections at 5 mg/kg q12h for 10 days starting at day 30 to 45 of pregnancy can be used for abortion induction. In one study, oral dexamethasone (0.2 mg/kg bid or tid for 5 days starting at day 35 of pregnancy followed by another 3 to 5 days during which the dose was progressively reduced to zero) induced abortion in all bitches (n = 20).31 Polyuria/polydipsia was observed in all bitches and resolved after the drug regimen.

**Gonadotropin-Releasing Hormone Antagonists**

Gonadotropin-releasing hormone antagonists act by decreasing concentrations of circulating gonadotropins, causing luteolysis and decreasing progesterone concentrations. However, they are not effective in early pregnancy when the CL is not dependent on the support of pituitary LH. Detirelix (a single injection of 2 mg/kg after day 20 of diestrus) is reportedly an effective abortifacient; however, this compound is not commercially available.33

**THE POSTOSSIFICATION PERIOD**

The postossification period begins when fetal ossification occurs (approximately 40 to 42 days after LH peak) and ends at parturition. All the protocols described for the preossification period are applicable in the postossification period. However, because the fetal skeleton is developed in the postossification period, abortions induced during this time cause fetal expulsion (sometimes of live fetuses). Therefore, abortion induction during this period is not recommended because it is traumatic for the bitch and owner.

**MONITORING ABORTION INDUCTION**

If abortion is induced in the preossification period, ultrasonography at day 5 to 7 after induction is recommended. Signs of abortion include changes in fetal anatomy, placental detachment, and/or fetal resorption. Pregnancy termination, as monitored by ultrasonography, is always sudden.2 If ultrasonographic equipment is not available, measuring serum progesterone is a reliable alternative; plasma progesterone concentrations below 1 to 2 ng/ml for more than 2 days indicate pregnancy termination.2

**CONCLUSION**

In recent years, knowledge of the mechanisms controlling luteal function in dogs has increased, especially regarding the luteotrophic role of prolactin. This knowledge, together with new drugs, has improved the management of mismating and unwanted pregnancies in bitches (Figure 1). Although estrogens have been widely used in the past, they are no longer recommended because of their potential deleterious side effects and the fact that many bitches are not pregnant at the time of treatment. If used, however, a low-dose regimen using estradiol benzoate is recommended. The concept of balanced luteolysis introduced by Verstegen appears to be highly promising for mismating and termination of
pregnancy. Although antiprogestogens are highly effective and safe for this purpose, there are still some concerns regarding their potential for human abuse. Whichever method is selected, the response should be closely monitored by ultrasonography or serum progesterone measurement to confirm the efficacy of the regimen and identify possible complications.

REFERENCES


In dogs, the median lethal dose for natural PGF$_{2\alpha}$ is ___ mg/kg.

a. 5.13
b. 1
c. 10
d. 20
e. 2

3. Side effects of PGs include

a. salivation
b. vomiting
c. defecation
d. hyperpnea
e. all of the above

4. The side effects of PGs

a. are related to their smooth-muscle stimulant properties
b. are dose-dependent
c. appear 10 to 20 minutes after administration
d. last for about 15 minutes
e. all of the above

5. What is the reason for combining PGs and dopamine agonists?

a. to reduce progesterone release by a double mechanism of action
b. to avoid pregnancy detection
c. to reduce the PG dose
d. a and c
e. none of the above

6. What is the preferred synthetic analog of PGF$_{2\alpha}$?

a. alphaprostol
d. all of the above
c. large doses of PGF$_{2\alpha}$ are required.
d. a and b
e. none of the above

7. Abortion induction is not recommended in the post-ossification period because

a. abortion occurs by fetal expulsion.
b. live fetuses may be expelled.
c. large doses of PGF$_{2\alpha}$ are required.
d. a and b
e. none of the above

8. After abortion induction with PGs, bitches return to estrus

a. when expected.
b. earlier than expected in most cases.
c. later than expected.
d. at varying times but usually when expected.
e. at varying times but usually later than expected.

9. Most protocols for abortion induction with natural PGF$_{2\alpha}$ recommend doses of ___ mg/kg.

a. 0.1 to 0.25
d. 2.5
b. 1 to 2
e. none of the above
c. 2

10. The side effects of PGs

a. can be minimized by walking the bitch after the injection.
b. can be minimized by using the lowest possible dose the first day.
c. cannot be minimized.
d. a and b
e. none of the above