INTRODUCTION

Canine reproductive physiology has unique characteristics that make extrapolation from farm animals (horses, cows, sheep, goats, pigs) unsuccessful in this species. Domestic bitches are nonseasonally monoestrous. Bitches ovulate only once or twice per year with few exceptions. The period from the onset of proestrus to the onset of the next proestrus is referred to as the interestrous interval (IEI). Unique to dogs, the IEI includes proestrus, estrus, diestrus, and anestrus. During anestrus, neither the ovary nor the pituitary are quiescent. The IEI averages 31 weeks with a typical range of 16 to 56 weeks. However, the IEI may be more or less frequent depending on the duration of anestrus, which varies between and within individual bitches. Estrous cycle manipulation in dogs is used for both shortening and lengthening the IEI, depending on the desired outcome. This review focuses on shortening the IEI for purposes of estrus induction.

In the bitch, progression from early to late anestrus is characterized by a higher amplitude and a greater number of hypothalamic gonadotropin-releasing hormone (GnRH) pulses. The GnRH pulse frequency is significantly increased during late anestrus. The sensitivity of the pituitary to GnRH and the indirect response of the ovary to...
GnRH also changes from early to late anestrus, with both a significant increase in pituitary sensitivity to GnRH (as expressed by circulating luteinizing hormone [LH] concentrations) and an increase in ovarian responsiveness to LH and follicle-stimulating hormone (FSH). Serum FSH concentrations are increased throughout much of canine anestrus, but are significantly higher during late anestrus compared with during mid and early anestrus. Conversely, LH concentrations are low except near the end of anestrus. An increase in plasma FSH concentration is critical for the initiation of folliculogenesis and, consequently, for the termination of anestrus in dogs. In most domestic mammals, FSH is regarded as the most important factor in the early stages of follicular development, whereas LH is regarded as the primary regulatory factor in the more mature follicles. It has been suggested that, for canine anestrus to end, an increasing plasma FSH concentration must exceed some threshold level of enough sensitive antral follicles to result in the progression of these follicles to the pre-ovulatory stage. FSH induces expression of LH receptors in the ovarian granulosa cells. After initial follicle recruitment, LH is progressively able to replace FSH in the support of follicular maturation. In fact, supraphysiologic doses of LH alone administered to bitches in anestrus will induce follicle growth and proestrus.

**PATIENT EVALUATION OVERVIEW**

Methods for inducing estrus in bitches need to be safe and reliable. Methods for estrus induction in bitches include the use of dopamine agonists (bromocriptine, cabergoline, metergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, and leuprolide), and exogenous gonadotropins (LH, FSH, human chorionic gonadotropin [hCG], equine chorionic gonadotropin [eCG], and human menopausal gonadotropin). These methods vary greatly in their efficacy of inducing estrus as well as in the pregnancy rates after the induced estrus. In addition, the applicability of some of these methods for clinical practice is questionable. Indications for inducing estrus include management of prolonged anestrus (prolonged IEI) in conjunction with routine breeding management when breeding opportunities are missed or after conception failure, or if a particular mating must be timed around the availability of the stud dog or whelping around a certain time of the year (eg, before hunting season). Estrus induction is most successful in fertile females that are at least 120 days from the onset of their last proestrus. Although several studies have demonstrated that ovulation can be induced after diestrus termination, bitches rarely become pregnant from this approach. In the dog, histologic changes similar to endometrial involution are not complete until 135 days after the last proestrus, regardless of whether the bitch was pregnant or not.

**PHARMACOLOGIC OPTIONS FOR ESTRUS INDUCTION**

**Dopamine Agonists**

Dopamine agonists are ergot derivatives that inhibit prolactin secretion by directly stimulating dopamine receptors. In species other than the dog, dopamine agonists inhibit gonadotrophin secretion during anestrus and dopamine antagonists induce reproductive activity. In the bitch, however, dopamine agonists induce the onset of estrus. It was previously believed that prolactin inhibition was necessary for canine estrus induction to occur. However, Beijerink and colleagues (2003) demonstrated that bromocriptine shortens the IEI in the bitch, even when the dose is so low that it does not lower the plasma prolactin concentration. In addition, bitches treated with low doses of a serotonin receptor antagonist (metergoline) had reduced prolactin concentrations, but did not go into estrus. These observations suggested that dopamine agonists induce estrus with another mechanism other than via lowering plasma prolactin.
prolactin concentration. Kooistra and coworkers (1999) reported that follicle development and resulting estrus induction with bromocriptine was associated with an increase in plasma FSH concentration without a concomitant increase in plasma LH concentration. The dopamine agonist–induced increase in the basal plasma FSH concentration was similar to what is observed during physiologic late anestrus. In the mare, dopamine receptors are present in the ovary and, in rats, dopamine agonists and antagonists directly affect ovarian steroidogenesis. It is not known if there is a direct gonadal effect of dopamine agonists in the dog. However, it should be noted that prolonged cabergoline administration during proestrus and estrus does not affect follicular development.

The pregnancy rate after estrus induction using dopamine agonists varies depending on dose, treatment duration, and stage of anestrus. Several estrus induction protocols using dopamine agonists have been reported (Table 1). Within the United States, the most common dopamine agonist treatment used is cabergoline at a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Protocols using dopamine agonists for estrus manipulation in the bitch</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Zoldag et al, 2001</td>
<td>48</td>
</tr>
<tr>
<td>Verstegen et al, 1999</td>
<td>5</td>
</tr>
<tr>
<td>Verstegen et al, 1999</td>
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<tr>
<td>Verstegen et al, 1999</td>
<td>5</td>
</tr>
<tr>
<td>Gobello et al, 2002</td>
<td>5</td>
</tr>
<tr>
<td>Rota et al, 2003</td>
<td>12</td>
</tr>
<tr>
<td>Gunay et al, 2004</td>
<td>13</td>
</tr>
<tr>
<td>Cirit et al, 2007</td>
<td>28</td>
</tr>
<tr>
<td>Cirit et al, 2007</td>
<td>10</td>
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<td>Cirit et al, 2007</td>
<td>19</td>
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<tr>
<td>Cirit et al, 2007</td>
<td>8</td>
</tr>
<tr>
<td>Nak et al, 2012</td>
<td>20</td>
</tr>
<tr>
<td>Kusuma &amp; Tainturier, 1993</td>
<td>10</td>
</tr>
<tr>
<td>Kusuma &amp; Tainturier, 1993</td>
<td>10</td>
</tr>
</tbody>
</table>

**Abbreviations:** IM, intramuscularly; PO, per os; ISD, once per day.

- a Human chorionic gonadotropin 500 IU administered IM in late proestrus to induce ovulation.
- b Human chorionic gonadotropin 500 IU administered IM on the first and third days of estrus to induce ovulation.
- c Dose appears to be 1000X but reported three times in reference at this amount.
dosage of 0.005 mg/kg administered once daily orally until 1 to 2 days after the onset
of induced proestrus. Cabergoline (available as Dostinex [Pfizer] and in generic forms)
is a human product containing 0.5 mg of cabergoline per tablet and sold at about $10
per tablet. Aside from the cost, cabergoline can be difficult to dose accurately, espe-
cially in small animals. For accurate dosing in dogs, tablets can either be com-
 pounded into the appropriate-strength capsules or a portion of the tablet can be
crushed and diluted with fluid just before dosing. Ciirt and coworkers (2007)
observed that a 0.5 mg Dostinex tablet completely dissolves in 50 mL of distilled water
at room temperature, producing a solution that is 0.01 mg of cabergoline/mL. It was
reported by Persiani and colleagues (1994) that the relative bioavailability of tablets
versus an aqueous solution of cabergoline was 99% and the pharmacodynamics and
relative bioavailability was not influenced by formulation (tablet vs solution). However,
cabergoline is inactivated over time in aqueous solutions containing water, such that
the cabergoline solutions should be prepared fresh daily and used within 15 minutes of
preparation. McLean and coworkers reported that cabergoline could be stable for
28 days if compounded in acidic fluids (1% acetic acid solution).

There are 2 prominent side effects with dopamine agonists: coat color changes and
vomiting. Approximately 25% of bitches that received cabergoline for 14 to 45 days
developed coat color changes beginning the second week of administration and lasting
until the next coat shedding. Of these, fawn-colored bitches developed a yellowish
coat color whereas Argentine boarhounds became black spotted, mainly on their
extremities. In previous untreated estrous periods, these bitches had shown no
cr colors changes. These authors postulated that a color shift in certain hair coats
of particular breeds could be mediated through inhibition of melanocyte-stimulating
hormone secretion. Transient coat color changes should be considered a possible
side effect when planning long-term treatment with dopamine agonists in dogs.

Vomiting was a frequent side effect (3%–25% of cases) with bromocriptine or
cabergoline occurring within 1 hour after the first treatment. Vomiting
 tends to be a less common side effect after cabergoline when compared with
bromocriptine, probably because cabergoline binds more specifically to dopamine
type-2 receptors in the hypothalamus and pituitary gland. It is important to note
that Gunay and colleagues did not observe any side effects of vomiting when
they administered cabergoline to German Shepherds using a much higher dose of
cabergoline (6 mg/kg) than the optimal effective dose (0.005 mg/kg) as determined
by dose response. Beginning with lower doses of bromocriptine initially can result
in habituation, which will almost completely eliminate emesis as a side effect of
treatment. It should be noted that even very high doses of metergoline do not
induce vomiting in bitches.

Gonadotropin-Releasing Hormone and Gonadotropin-Releasing Hormone Agonists

GnRH is a hypothalamic decapeptide that mediates the synthesis and release of pitu-
tity LH and FSH. In the bitch, progression from early to late anestrus is characterized
by a higher amplitude and a greater number of GnRH pulses, and an increase in pitu-
tity sensitivity to GnRH. Different approaches have been investigated to directly
stimulate the activity of the pituitary with GnRH and GnRH agonists to induce estrus
(Table 2). Pulsatile administration of GnRH at doses of 0.0002 to 0.0004 mg/kg at
90-minute intervals is sufficient to obtain increases in LH similar to the endogenous
pulses that normally occur at the end of proestrus. By making molecular changes to
native GnRH, more than 700 GnRH agonists have been synthesized that have an
increased receptor affinity and enhanced stability. High rates of fertile estrus induction
were reported with less than 0.0024 mg/kg/d of lutrelin for more than 8 days.
Table 2
Protocols using GnRH and GnRH agonists for estrus manipulation in the bitch

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Estrus Induction Protocols</th>
<th>Pregnancy Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanderlip et al, 1987</td>
<td>8</td>
<td>GnRH 0.000040–0.000430 mg/kg IV every 87 min for 9 d</td>
<td>37.5</td>
</tr>
<tr>
<td>Cain et al, 1988</td>
<td>8</td>
<td>GnRH 0.000096–0.000139 mg/kg IV every 90 min for 11–13 d</td>
<td>87.5</td>
</tr>
<tr>
<td>Concannon et al, 1997</td>
<td>36</td>
<td>GnRH 0.000015–0.000500 mg/kg IV every 90 min for 7–9 d</td>
<td>33</td>
</tr>
<tr>
<td>Rota et al, 2003</td>
<td>10</td>
<td>Buserelin 0.0015 mg/kg SQ TID for 11 d and 0.00075 mg/kg SQ TID for 3 d</td>
<td>20</td>
</tr>
<tr>
<td>Inaba et al, 1998</td>
<td>18</td>
<td>Leuprolide 0.10 mg/kg SQ once&lt;br&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>78</td>
</tr>
<tr>
<td>Hatoya et al, 2006</td>
<td>7</td>
<td>Leuprolide 0.0036 mg intranasal spray once daily until onset of proestrus up to 14 d</td>
<td>42.9</td>
</tr>
<tr>
<td>Concannon, 1989</td>
<td>24</td>
<td>Lutrelin 0.0017–0.0025 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>37.5&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>6</td>
<td>Lutrelin 0.0024 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>33.3</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>20</td>
<td>Lutrelin 0.0018 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>35</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>6</td>
<td>Lutrelin 0.0012 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>33.3</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>18</td>
<td>Lutrelin 0.0006–0.0024 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>88.9</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>7</td>
<td>Lutrelin 0.0002 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>57.1</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>24</td>
<td>Lutrelin 0.0006–0.0024 mg/kg/d SQ for 7–8 d via osmotic mini pump</td>
<td>16.7</td>
</tr>
<tr>
<td>Concannon et al, 2006</td>
<td>6</td>
<td>Lutrelin 0.048 mg/kg/d SQ for 12–14 d via osmotic mini pump</td>
<td>0</td>
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<tr>
<td>Kutzler et al, 2001</td>
<td>7</td>
<td>Deslorelin 2.1 mg SQ once over the shoulder blades</td>
<td>43&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kutzler et al, 2002</td>
<td>6</td>
<td>Deslorelin 2.1 mg vestibular submucosa once</td>
<td>67</td>
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<tr>
<td>Kutzler et al, 2002</td>
<td>5</td>
<td>Deslorelin 2.1 mg vestibular submucosa once</td>
<td>40</td>
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<tr>
<td>Volkmann et al, 2006</td>
<td>3</td>
<td>Deslorelin 2.1 mg vestibular submucosa once</td>
<td>67</td>
</tr>
<tr>
<td>Volkmann et al, 2006</td>
<td>10</td>
<td>Deslorelin 1.05 mg vestibular submucosa once</td>
<td>70</td>
</tr>
<tr>
<td>Kutzler et al, 2002</td>
<td>5</td>
<td>Deslorelin 1.5 mg IM once</td>
<td>60</td>
</tr>
<tr>
<td>Walter et al, 2011</td>
<td>11</td>
<td>Deslorelin 4.7 mg SQ medial side of the leg once</td>
<td>63.6</td>
</tr>
<tr>
<td>Fontaine et al, 2011</td>
<td>6</td>
<td>Deslorelin 4.7 mg SQ ventral abdomen close to the umbilicus once&lt;br&gt;&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25</td>
</tr>
<tr>
<td>Fontaine et al, 2011</td>
<td>23</td>
<td>Deslorelin 4.7 mg SQ ventral abdomen close to the umbilicus once&lt;br&gt;&lt;sup&gt;d&lt;/sup&gt;</td>
<td>78.3</td>
</tr>
<tr>
<td>Von Heimendahl et al, 2012</td>
<td>16</td>
<td>Deslorelin 4.7 mg SQ ventral abdomen close to the umbilicus once</td>
<td>68.8</td>
</tr>
<tr>
<td>Borges et al, 2015</td>
<td>19</td>
<td>Deslorelin 4.7 mg SQ ventral abdomen close to the umbilicus once</td>
<td>36.8</td>
</tr>
<tr>
<td>Borges et al, 2015</td>
<td>17</td>
<td>Deslorelin 4.7 mg SQ ventral abdomen close to the umbilicus once</td>
<td>70.6</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscularly; IV, intravenously; SQ, subcutaneously; TID, 3 times per day.

<sup>a</sup> Fertirelin 0.003 mg/kg IM given on the first day of estrus to induce ovulation.
<sup>b</sup> Premature luteal failure.
<sup>c</sup> Administered 80 to 160 days after their previous estrus.
<sup>d</sup> Administered 200 to 590 days after their previous estrus.
However, reduced efficacy occurred at doses of 0.0048 mg/kg/d owing to a failed or insufficient LH surge at the end of proestrus. Concannon and colleagues concluded that the dose of GnRH agonist needed to be sufficiently large enough to stimulate the initial increase in LH and FSH but modest enough to not excessively downregulate the spontaneous preovulatory surge and be administered for at least 10 to 13 days.

Increases in GnRH do not need to be pulsatile to induce estrus. Constant infusion or release of a GnRH agonist (lutrelin, deslorelin, leuprolide) via a subcutaneous osmotic mini pump or implant resulted in similar estrus induction and pregnancy rates as GnRH pulsatile infusion, provided that the GnRH agonist therapy is discontinued. According to Concannon and colleagues, GnRH agonist needs to be administered for at least 10 to 13 days, but removed shortly before or at the time when the LH surge typically occurs, to prevent downregulation. A single injection of leuprolide (0.1 mg/kg subcutaneously) induced estrus in prepubertal bitches as well as bitches 120 and 150 days postpartum. An intranasal spray containing a GnRH agonist (Leupron Depot, Takeda Chemical Industries, Osaka, Japan) used to induce estrus produced no negative clinical effects and seemed to cause little stress to the animals. As mentioned, prolonged administration of GnRH agonists results in pituitary overstimulation, downregulation of GnRH receptor transcription in the pituitary, suppression of LH (and in some species FSH) secretion, decreased luteal responsiveness to LH, and decreased progesterone secretion. Premature luteal failure resulting in a shortened diestrus with subsequent pregnancy loss has been reported with GnRH agonist therapy for estrus induction.

The GnRH agonist that has been most widely studied in canine estrus manipulation is deslorelin. Deslorelin is a D-Trp⁶-Pro⁹-des-Gly¹⁰GnRH agonist with 2 amino acid substitutions. Veterinary clinical applications of deslorelin in bitches were first introduced by Trigg and colleagues (2000) during an investigation for a novel contraceptive (Suprelorin), which is now commercially available in Europe, Australia, and New Zealand. Preliminary investigations with this product demonstrated that it induced estrus in all anestrous bitches treated initially, which was followed by prolonged estrus suppression. Administration of a 2.1-mg deslorelin implant resulted in reliable, rapid, and synchronous estrus when administered to anestrous bitches or to diestrous bitches after termination of diestrus using prostaglandin F-2α in. Although all of these methods resulted in rapid and dependable estrus induction in bitches, pregnancy rates (fertility) varied from 8% to 100% depending on the stage of estrous cycle in which the induction was initiated and the protocol used. GnRH and GnRH agonists are not approved for use in bitches in the United States. Although readily available, the extralabel use of a GnRH agonist (Suprelorin-F, Virbac Animal Health, Fort Worth, TX) in species other than ferrets is strictly prohibited.

Gonadotropins

Both LH and FSH are follicotrophic in the dog; administration of pharmacologic doses of either LH or FSH alone induces estrus (Table 3). However, an estrus induction protocol established with combined dosages of FSH and LH designed to resemble the gradual increase of endogenous FSH coincidentally with the LH increase during proestrus was not successful. The LH potency within purified or partially purified FSH products used may interfere with endogenous LH release. Bouchard and coworkers demonstrated that LH cross-reactivity from contamination of porcine-derived FSH lasts 48 hours after administration. In addition, acute allergic reactions have been reported after intravenous administration of LH (5 mg) in 2 bitches.

In addition to exogenous pituitary gonadotropins, eCG (formerly known as pregnancy mare serum gonadotropin) and human menopausal gonadotropin have been
used for estrus induction in bitches (see Table 3). The most widely studied gonadotropin for estrus induction in the dog is eCG, with protocols ranging from daily to weekly injections using either subcutaneous or intramuscular routes of administration. Studies using eCG have generally been more successful for estrus induction in bitches than those using FSH. Bitches treated with eCG at a dose of 20 IU/kg subcutaneously for 5 consecutive days with an additional 500 IU subcutaneously per bitch of hCG on the last day of treatment had similar estrus induction and ovulation rates to cabergoline treated bitches.61

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Estrus Induction Protocol</th>
<th>Pregnancy Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verstegen et al,14</td>
<td>16</td>
<td>LH 0.1 IU/kg TID for 7 d</td>
<td>37.5</td>
</tr>
<tr>
<td>Shille et al,58 1984</td>
<td>5</td>
<td>FSH 0.77–1.1 mg IM once</td>
<td>40</td>
</tr>
<tr>
<td>Shille et al,58 1984</td>
<td>4</td>
<td>FSH 0.077–0.11 mg to 1.23–1.78 mg IM SID</td>
<td>50</td>
</tr>
<tr>
<td>Nickson et al,66 1992</td>
<td>18</td>
<td>eCG 187 MU IM once</td>
<td>50</td>
</tr>
<tr>
<td>Hancock &amp; Rowlands,1949</td>
<td>9</td>
<td>eCG 200–300 IU SQ once or 100 IU SQ</td>
<td>11.1</td>
</tr>
<tr>
<td>Thun et al,97 1977</td>
<td>6</td>
<td>eCG 15.6–35.7 IU/kg SQ for 10 d</td>
<td>50</td>
</tr>
<tr>
<td>Thun et al,97 1977</td>
<td>7</td>
<td>eCG 15.6–35/7 IU/kg SQ for 10 d</td>
<td>57</td>
</tr>
<tr>
<td>Thun et al,97 1977</td>
<td>12</td>
<td>eCG 1.25–2.8 IU/kg SQ for 10 d</td>
<td>58</td>
</tr>
<tr>
<td>Archbald et al,88 1980</td>
<td>8</td>
<td>eCG 44 IU/kg SID IM for 9 d</td>
<td>60</td>
</tr>
<tr>
<td>Archbald et al,88 1980</td>
<td>5</td>
<td>eCG 44 IU/kg SID SQ for 9 d</td>
<td>60</td>
</tr>
<tr>
<td>Allen,99 1982</td>
<td>4</td>
<td>eCG 21.2–26.9 IU SQ every 48 h for a total of 5 injections (1250 IU total)</td>
<td>25</td>
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<tr>
<td>Renton et al,100 1984</td>
<td>3</td>
<td>eCG 500 IU SID SQ until onset of proestrus or up to 10 d</td>
<td>0</td>
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<tr>
<td>Chaffaux et al,101 1984</td>
<td>5</td>
<td>eCG 27.8–41.6 IU/kg SID IM for 10 d</td>
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<tr>
<td>Chaffaux et al,101 1984</td>
<td>15</td>
<td>eCG 27.8–41.6 IU/kg SID IM for 10 d</td>
<td>20</td>
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<tr>
<td>Nakao et al,1985</td>
<td>11</td>
<td>eCG 44 IU/kg SID IM for 9 d</td>
<td>13</td>
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<td>Arnold et al,102 1989</td>
<td>17</td>
<td>eCG 20 IU/kg SID IM for 10 d</td>
<td>0</td>
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<tr>
<td>Arnold et al,102 1989</td>
<td>6</td>
<td>eCG 20 IU/kg SID IM for 5 d</td>
<td>50</td>
</tr>
<tr>
<td>Kusuma &amp; Tainturier,39 1993</td>
<td>10</td>
<td>eCG 33.3–71.4 IU/kg SID IM until proestrus or up to 9 d</td>
<td>0</td>
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<tr>
<td>Weilenmann et al,74 1993</td>
<td>14</td>
<td>eCG 20 IU/kg SID IM for 5 d</td>
<td>43</td>
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<tr>
<td>Wanke et al,103 1997</td>
<td>10</td>
<td>hMG 1.7 U/kg SID IM for 9 d</td>
<td>40</td>
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<tr>
<td>Nak et al,88 2012</td>
<td>19</td>
<td>eCG 20 IU/kg SID IM for 5 d</td>
<td>0</td>
</tr>
<tr>
<td>Stornelli et al,62 2012</td>
<td>15</td>
<td>eCG 50 IU/kg IM once</td>
<td>80</td>
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</tbody>
</table>

**Abbreviations:** eCG, equine chorionic gonadotropin; FSH, follicle-stimulating hormone; hMG, human menopausal gonadotropin; IM, intramuscularly; IV, intravenously; LH, luteinizing hormone; SQ, subcutaneously; SID, once per day; TID, 3 times per day.

- Mouse units.
- Human chorionic gonadotropin 50 MU IM at time of eCG injection.
- Human chorionic gonadotropin 500 IU IM or SQ on the 10th day of treatment.
- Human chorionic gonadotropin 500 IU IM on the second day of estrus.
- Premature luteal failure.
- Gonadoliberin 0.05 mg IM on the 10th day of treatment.
- Human chorionic gonadotropin 500 IU IM on the fifth day of treatment.
- Human chorionic gonadotropin 500 IU IM on the seventh day of treatment.
A protocol using 50 IU/kg (intramuscularly once) of eCG combined 7 days later with 500 IU (intramuscularly once) of hCG induced normal and fertile estrus (the mean interval from treatment to estrus was 4.0 ± 0.4 days) with an 80% pregnancy rate (12/15) and no reported side effects. Although eCG induces follicular development and in some bitches allows spontaneous ovulation, not all animals will ovulate spontaneously with a single eCG dose. Hence, the use of hCG after eCG treatment is often recommended. However, the administration of hCG for the induction of ovulation is controversial and several groups have reported no benefit or serious side effects. The administration of hCG has no positive effects on ovulation rates, pregnancy rates, or number of offspring per pregnancy when administered at the onset of or during estrus. In fact, treatment with hCG on the first and third days of estrus significantly prolongs behavioral estrus and lowers serum progesterone concentration of day 5 of estrus. Volkmann and coworkers found similar results when hCG was administered to bitches after day 40 of gestation, in that after an initial increase in serum progesterone concentrations, hCG dramatically suppressed progesterone secretion. In addition to a reduction in ovulation and pregnancy rates, Kusuma and Tainturier (1993) reported both prolonged proestrus and shortened estrus (with concomitant shortened estrus) in bitches treated with hCG in late proestrus. Nevertheless, Wright (1972) reported that ovulation in the bitch occurs 26 to 30 hours after the administration of hCG and that eCG-induced bitches treated with hCG at the onset of estrus had better ovulatory responses than those only treated with eCG.

Although widely available around the world under the brand name of Folligon (Intervet, Osaka, Japan), eCG is not commercially available in the United States except in combination with hCG (PG600; Intervet). This product contains 80 IU eCG and 40 IU hCG per milliliter. Nickson and associates (1992) demonstrated that a single 5-mL injection of PG600 was highly effective at inducing proestrus in bitches (17 of 19). Unfortunately, the ovulation rate was poor (8 of 19); superovulation may have occurred and pregnancy rates were not reported. However, others have reported 50% to 84% whelping rates when eCG and HCG are given in combination to induce estrus in bitches.

Numerous side effects have been reported with eCG, from immune-mediated reactions to sudden death. The most frequent problems encountered with eCG arise from the unpredictability of an individual bitch’s response both in the number of follicles that develop and in the potential for premature luteal failure. Premature luteal failure with subsequent shortening of diestrus and pregnancy loss is a frustrating sequela of eCG use in canids. In 1 study, treatment with eCG was followed by a progressive decline in progesterone concentrations to less than 1 ng/mL between 38 and 40 days after estrus. Histologically, luteal cells from corpora lutea formed in bitches after eCG treatment have reticulated and vacuolated cytoplasm compared with luteal cells from corpora lutea of normal, nonfertile estrous cycles that have compact and granulated cytoplasm. Premature luteolysis of induced corpora lutea have also been reported in ewes, beef cows, and dairy cows. In ruminants, pretreatment with a progestin before ovulation induction increases luteal weight and secretion of progesterone. However, bitches pretreated with megestrol acetate (2.2 mg/kg orally once daily for 8 days) before undergoing an estrus induction with eCG (44 IU/kg intramuscularly once daily for 9 days) were not prevented from undergoing premature luteolysis as progesterone values were less than 1 ng/mL by 50 days after estrus in all eCG-treated bitches. It is of interest to note that such premature luteal regression seems to be independent of the presence or absence of the uterus. This was demonstrated after hysterectomy of normal, nonpregnant bitches on day 4 of estrus during a noninduced cycle. Hysterectomy resulted in premature regression of
the corpora lutea. The authors speculated that a luteotrophic factor of uterine origin, which may be active in the normal cycle of the bitch at 24 days of diestrus, may be involved in luteal maintenance.

**SUMMARY**

Although many methods of estrus induction exist for both canids and felids, success (induction of estrus, ovulation, pregnancy, and delivery of offspring) rates vary between and within various protocols. Knowledge of the strengths and weakness of each regimen will assist the veterinarian in making a selection that will be best suited for the patient and client. Long-acting preparations (eCG, GnRH agonist implants) are convenient for the owner and less stressful for the patient, but are associated with premature luteal failure and subsequent reduced pregnancy rates. For these reasons, practitioners should use dopamine agonists when needing to induce estrus in the bitch.

**REFERENCES**


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