

Pharmacologic Advances in Canine and Feline Reproduction

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Substantial improvements in therapeutic options for companion animal reproduction and gynecologic emergencies have been made over the last decade. New, alternative drug treatments, with fewer side effects and improved efficacy, are available. This has widened the spectrum of therapeutic possibilities for diseases that were previously treated only by surgical intervention. New drugs are available for estrus induction and pregnancy termination, as well as for the treatment of pyometra. This review summarizes the pharmacology and toxicology of reproductive agents currently in use for contraception, pyometra, dystocia, eclampsia, premature labor, agalactia, mastitis, metritis, and prostatic disorders, and compares their efficacy and safety with newer agents. Drug use and exposure during pregnancy and lactation, and subsequent risks to the fetuses, are also explored, with emphasis on antimicrobials, antifungals, anthelmintics, anesthetics, and vaccinations. © 2009 Published by Elsevier Inc.

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The scope of all drugs used in canine and feline reproduction is too broad a topic to be reviewed in one article. There are many good articles already written on a variety of topics such as estrus induction/synchronization and pregnancy termination in canine and feline patients, and these should be referred to for more in-depth discussions.¹⁻¹⁷ In general, drug options in the field of veterinary theriogenology have recently expanded, with new agents available for estrus induction (gonadotropin-releasing hormone [GnRH], dopamine agonists) and pregnancy termination (dopaminergic agonists, antiprogestational agents). However, current lack of availability in the United States and expense have limited the use of these agents. Because of manufacturer discontinuation of some older products and limited availability of newer agents, there has been an overall decline in drug options in some areas such as contraception. However, new therapeutic options for pyometra, dystocia, eclampsia, and premature labor are available and will be discussed. The use of therapeutic drugs during pregnancy and lactation in canine and feline patients has not been currently reviewed, and there is little to no collated information in general for many of these agents. New and potentially less harmful anesthetics, antibiotics, antifungals, anthelmintics, and vaccines that can be used during pregnancy and lactation will be discussed

as well as current treatment concepts for agalactia, mastitis, metritis, and prostatic disorders.

The Canine and Feline Estrous Cycle

To evaluate current pharmacologic interventions in canine and feline reproductive disorders, it is essential to have an understanding of normal reproductive physiology in both species. There are many good textbooks and published articles available on this topic, so only a very brief overview will be discussed below.

The Canine Estrous Cycle

An understanding of the canine time course of ovulation and fertilization and specific changes in the maternal physiology is essential when providing clinical services such as breeding management and determination of gestational time for surgical intervention. Although canine gestational time is consistent with the timing of hormone surges, it is not predictable based on the time from mating. In general, gestation length in dogs is relatively constant when measured from the beginning of ovulation or the ovulatory surge in luteinizing hormone (LH). Because the LH surge can be measured or estimated (via serial serum progesterone levels) with some accuracy, timing events with the LH surge as a reference point (day 0) can be helpful. The LH surge typically triggers ovulation within 2 days of the surge, and, if fertilization occurs, gestation is 64 to 66 days from the LH surge to parturition.

Using the LH surge as a reference point (day 0), proestrus (heat) may occur anywhere from day -25 to day -3 (average, day -9), and estrus occurs anywhere from day -3 to day +6 (average day, 0-1). Mating with the chance of significant fertility starts at day -3, followed by the LH surge and

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onset of peak fertility at day 0. Ovulation may then occur between 38 and 58 hours after the LH surge.

Canine Stages of Pregnancy

To assess the effects of drugs during pregnancy, it is important to have an appreciation for the various stages of embryonic development and the hormonal milieu that occurs during each phase. There are 3 well-defined stages in canine pregnancy as discussed below.

Stage 1: Canine Fertilization to Implantation

- Positive pregnancy difficult to confirm at this stage.
- Implantation at approximately 18 days from the LH surge (day 0 = day of the LH surge).
- Progesterone required for initiation and maintenance of pregnancy.
- Need progesterone level of >2 ng/mL to maintain pregnancy.
- Progesterone maintains endometrial integrity and placental attachment, and inhibits myometrial contractility.
- Corpus luteum relatively refractory to exogenous chemicals/drugs during first 30 days.
- Changes in estrogen:progesterone ratio or decline in corpus luteum progesterone secretion can lead to impaired implantation or abortion.
- Drugs used to terminate pregnancy at this stage include: 1) estrogens: inhibit oocyte transport/embryotoxic effects; 2) prostaglandins: high doses induce luteal arrest; and 3) inhibitors of progesterone secretion (epostane) or progesterone antagonists (mifeprestone, aglepristone).

Stage 2: Implantation to Fetal Ossification

- Positive pregnancy more easily confirmed (approximately 25-30 days with ultrasound).
- Fetal ossification occurs at 40 to 42 days from the LH peak.
- Embryogenesis and fetal growth and development occur rapidly at this stage.
- Exposure to exogenous drugs or chemicals here may result in limb, skeletal, organ, or neurological deformities during this time.
- Prolactin is the main pituitary hormone that sustains corpus luteum steroidogenesis.
- Dopamine antagonists or prolactin-secretion inhibitors can lead to luteolysis, blockade of progesterone secretion, and abortion.
- Abortion induction usually associated with embryonic/fetal resorption.
- Drugs used to terminate pregnancy at this stage include: prostaglandins, dopamine agonists/antiprolactinic agents (bromocriptine, cabergoline), antiserotonergic (methergoline), steroids (dexamethasone), progesterone-secretion inhibitors (epostane)

or progesterone antagonists (mifeprestone, aglepristone), and GnRH antagonists (not available; efficacy remains to be determined).

Stage 3: Fetal Ossification to Parturition

- Fetus is well developed.
- Prostaglandins are the natural inhibiting factors causing luteal functional arrest before parturition.
- Prostaglandins reduce corpus luteum blood supply and luteal steroidogenesis.
- Abortion induction at this stage is likely to result in fetal expulsion.
- After days 50 to 55 from the LH surge, induced abortion may result in premature parturition and delivery of live pups.

The Feline Estrous Cycle

In feline patients, proestrus (0.5-2 days; female is attractive to the male, but will not allow mating) is followed by waves of folliculogenesis or estrous activity (average, 7 days; female has slightly swollen vulva, scant bloody discharge, vocalization, rolling behaviors, reduced appetite, and is receptive to males). The first estrous cycle in cats is at 6 to 12 months on average, but can be as early as 4 months. Cats are seasonally polyestrous and induced ovulators; ovulation will only occur with adequate coital stimulation. Multiple matings in cats can result in multiple ovulations and more than 1 sire in a litter of kittens. If the queen does not ovulate, an interestrus follows for 2 to 3 weeks, and the cycle repeats until fall. If she ovulates without proceeding to fertilization, metestrus or diestrus results for 30 to 40 days; if pregnant, this will last for 60 to 65 days.

Feline Stages of Pregnancy

Generally, cats do not show obvious signs of pregnancy until 5 to 6 weeks of gestation, so most owners may not even recognize that their animal is pregnant. Studies indicate that ultrasound detection of cardiac activity can be used as early as gestational day 16, with fetal morphology seen by day 26 of gestation. Fetal membranes become apparent by 21 days of gestation, and movement is first noted at day 28.¹⁸ Because of the short gestational period in cats, owners or veterinarians may inadvertently administer drugs or vaccines during this time.

Estrus Induction in Canine and Feline Patients

Estrus induction in canine and feline patients has been accomplished with a variety of pharmaceutical agents.¹⁻⁶ Estrus induction is most successful in normal females; its efficacy in bitches and queens with reproductive disorders is unknown. Agents reported to be effective include synthetic estrogens (diethylstilbestrol [DES]), dopamine agonists (bromocriptine, cabergoline), GnRH agonists (lutrelin, buserelin, fertirelin, deslorelin, and leuprolide), exogenous gonadotro-

pins (LH), follicle-stimulating hormone (FSH), human chorionic gonadotropin (HCG), pregnant mare serum gonadotropin (PMSG), and opiate antagonists (naloxone).¹ These agents vary widely in efficacy, success of subsequent fertility, availability, and practicality. Currently, there are no veterinary products labeled for this indication in canine and feline patients. So, although these products are used "off label" with some success, they are still somewhat experimental in nature and not always readily available.

Estrus Induction in Canine Patients

Both LH and FSH appear to be folliculotrophic in the dog, so that administration of either LH or FSH induces estrus. However, protocols mimicking the natural, gradual increase in LH and FSH in canine patients have not been successful.⁶ An estrogen peak approximately 30 days before the onset of estrus is believed to be required to prime the hypothalamus-pituitary-ovarian axis, causing release of LH in a pulsating fashion.^{19,20} Successful induction of fertile estrus in bitches has been accomplished with DES in various doses with or without FSH and LH.²¹⁻²³ Other gonadotropins have been evaluated with limited success.^{13,24-26} PMSG has been effective, but is associated with premature luteal failure, shortened diestrus, and pregnancy loss.²⁷⁻²⁹ Protocols using estrogens for estrus induction in bitches typically also include FSH or PMSG for folliculogenesis and HCG or LH for induction of ovulation.¹

Prolactin inhibition also plays a role in interestrus intervals and is believed to have effects on gonadotropin release and ovarian response to gonadotropins. Suppression of prolactin release by dopamine agonists (bromocriptine, cabergoline) shortens the duration of anestrus and induces estrus in animals with prolonged anestrus.^{30,31} The dopamine agonist, bromocriptine, was the first prolactin inhibitor studied in dogs for estrus induction, but resulted in significant vomiting in dogs.^{25,32} A newer agent, cabergoline (Galastop, Dostinex), has been shown to induce estrus in most bitches (0.005 mg/kg orally daily, until 3-8 days after onset of proestrus or day 40) with fewer side effects.^{3,33} The drug is available in generic form (Par Pharmaceutical, Inc., Woodcliff Lake, NJ), but remains relatively expensive (\$160.00/8 tabs or approximately \$20.00/tab) and difficult to dose accurately in small dogs. Cabergoline is only available as a 0.5-mg tablet that is inactivated over time in aqueous solutions containing water. For accurate dosing of small animals, tablets can either be compounded into the appropriate-strength capsules, or a portion of the tablet can be crushed and diluted with fluid just before dosing. McLean and coworkers also report that cabergoline is stable for 28 days if compounded in acidic fluids (1% acetic acid solution).³⁴

GnRHs have also been shown to be very effective if given in pulsated fashion (0.2-0.4 $\mu\text{g}/\text{kg}$ every 90-minute intervals intravenously [IV] or subcutaneously [SC] for 3-9 days) to mimic the natural cycle, resulting in LH peaks at the end of proestrus. Subcutaneous administration has been noted to be more practical, but availability of the canine analog is problematic.^{35,36} However, protocols using native GnRH or its

agonists via this technique are not practical for clinic purposes because of the expense, time commitment, and lack of availability of analogs. GnRH analogs (lutrelin, deslorelin, leuprolide) can also be administered as long-acting dosage forms via subcutaneous injections, mini pumps, or implants. An intranasal spray (Leuprolode; Takeda Chemical Industries, Osaka, Japan) has been used in one study in 14 anestrus beagle bitches and produced no negative clinical effects, but needs further evaluation.³⁷ Both expense and side effects may limit the use of these products. Side effects have included premature luteal failure, shortened diestrus, and pregnancy loss.^{38,39} Long-term use is also associated with pituitary overstimulation, downregulation of GnRH receptors, suppression of LH, decreased progesterone secretion, and decreased luteal responsiveness to LH.¹

A synthetic, sustained release GnRH analog (deslorelin) was marketed for several years for equine patients and was shown to be effective in canine patients. Ovuplant (Fort Dodge Animal Health, Overland Park, KS) was a biodegradable, subdermal implant containing 2.1 mg of deslorelin. Studies in dogs demonstrated fast, reliable, synchronous estrus.^{39,40} The product was taken off the market in 2005 because of manufacturing difficulties. Currently, no commercially available replacement exists. Compounding pharmacies have attempted to provide deslorelin in various formulations. BET Compounding Pharmacy (Lexington, KY) makes an injectable deslorelin in a proprietary sustained-release vehicle (BioRelease) that contains 1.5 mg/mL of deslorelin. The drug is not Food and Drug Administration (FDA) approved and lacks the stringent oversight of an FDA manufacturer's approved facility.

Because none of the agents discussed above are labeled for use in canine patients in the United States, cabergoline, which is licensed in Europe for estrus induction in bitches, may be the preferred agent. Although generic tablets are available in the United States, costs remain high. Before administration, clients should be counseled on the fact that these are not approved agents in the United States and their use is off label.

Estrus Induction in Feline Patients

Feline infertility may be a result of numerous factors including environmental, behavioral, infectious, neoplastic, or genetic. Before drug therapy, husbandry problems, male infertility, and underlying uterine disease (cystic endometrial hyperplasia) should be ruled out, and anestrus should be proven based on vaginal smears and progesterone plasma concentrations (< 2.0 ng/mL). High LH results suggest ovariectomy or ovarian failure.⁴¹ If anestrus is documented, then the etiology should be evaluated to rule out abnormal karyotype (38XX = normal) and thyroid function ($T_3 = 60\text{-}200$ ng/dL and $T_4 = 1.0\text{-}4.0$ $\mu\text{g}/\text{dL}$). Hypothyroidism in the queen is extremely rare.

If these results are normal, then the patient may be a candidate for estrus induction. In feline patients, induction of estrus can be attempted with FSH at a dose of 2 mg daily intramuscularly (IM) for 3 to 7 days until the onset of estrus. FSH is considered effective treatment if followed by natural mating or ad-

ministration of HCG (150-250 IU) or 25 μ g of GnRH.⁴² More recent protocols that appear effective use 150 IU of PMSG IM followed by 100 IU HCG 84 hours later.⁴³ However, PMSG is not currently available in the United States. Response here is better during the nonbreeding season. In contrast to canine patients, cabergoline has not been shown to be effective in cats for estrus induction.³¹

Contraceptive Measures in Feline and Canine Patients

The best cycle preventive measures not intended for future breeding remain ovariectomy or ovariohysterectomy. Non-surgical contraceptive measures include permanent or temporary pharmacologic measures including chemical castration of males, estrous prevention of females, estrous suppression, and pregnancy prevention, or termination after unwanted mating. For female dogs, few new options are available aside from new brands of progestins previously marketed. Options have actually declined with the removal of mibolerone (Check Drops) from the market several years ago. Androgens, including mibolerone and testosterone, have been noted to have prolonged effects on the predictable return of estrus in bitches, and long-term use, especially with testosterone, can cause permanent anestrus as seen in racing greyhounds.⁴⁴ Although available from some compounding pharmacies, anabolic steroids are not recommended because long-term safety and efficacy have never been documented.

Progestational Agents

The use of progestin administration remains the widest available method of cycle prevention in dogs, but is not recommended for bitches intended for breeding. Progestin administration produces an artificial luteal phase. Megestrol is the most common progestin prescribed. The dose of megestrol acetate in bitches is 0.55 mg/kg/d orally for 32 days for anestrous bitches. Higher doses of 2.2 mg/kg/d for 8 days are given to bitches in proestrus.⁴⁴ Generic progestin formulations include oral megestrol acetate tabs and suspension depot-injectable medroxyprogesterone acetate (MPA), oral MPA, depot-injectable proligestone, and others. Progesterone increases the risk of cystic endometrial hyperplasia, a uterine condition predisposing bitches to infertility and pyometra.

Megestrol acetate (Ovaban) was approved for use in dogs in the United States, but is not indicated for cats. However, megestrol has been administered to cats at doses of 5 mg per cat for 3 days, followed by 2.5 or 5 mg per cat once weekly, which successfully prevents estrus.⁴⁴ Human-labeled implants of levo-norgestrel (Norplant) or generic levo-norgestrel have also been shown to have contraceptive efficacy in female cats, but not dogs.⁴⁵ Depot injections of medroxyprogesterone acetate (Promone) were available on the veterinary market but have largely been removed. Human generic and brand name depot medroxyprogesterone (Depo-Provera) are currently available.

Typically, there is no universally safe or effective dose of any of the progestins in either dogs or cats. Uterine disease or diabetic-like symptoms can occur in both species. In dogs receiving high doses, side effects may include mammary hyperplasia and tumors, elevated growth hormone, insulin-resistant diabetes, acromegalic changes, adrenocortical suppression, reduced cortisol, skin reactions, and increased appetite with weight gain. In cats, spontaneous ovulations can also occur. Caution should be exercised with depot-injectable progestins, because they cannot be discontinued after injection if side effects should occur.

Chemical Castration

Agents such as arginine stabilized zinc gluconate (Neutersol), targeting male dog contraception, were placed on the US market several years ago. When injected into testis, atrophy of the tubules occurs, resulting in sterilization. This agent effectively sterilized males (99.5%), but only reduced testosterone plasma concentrations by 50%. The product is no longer currently available on the US market, where residual testosterone levels and associated behaviors are not considered desirable. The product may have a niche in Third World countries, where surgical intervention is not available and testosterone levels in dogs may still be desired for hunting and protection.

New Therapies (Vaccines/GnRH Agonists)

Other new products targeting contraception are on the horizon, including contraceptive vaccines generating antibodies to LH-releasing hormone. These can be used in both male and female dogs but are not yet available.⁴⁶ Potent GnRH-agonists have recently been approved as male dog contraceptions in New Zealand and Australia, and efforts are underway to obtain approval as a contraceptive in dogs, as well as cats. GnRH agonists (leuprolide, lutrelin, deslorelin) have been shown to suppress gonadal activity in both male and female dogs with few side effects. The agonists act by causing a downregulation of the GnRH receptors. Chronic suppression of LH and FSH concentrations and suppression of gonadal hormone secretion and gametogenesis occur. The final result is a chemical castration of males and a protracted anestrus in females, which is reversible. Clinical trials of 2 products (Suprelorin; Peptech Animal Health, Macquarie Park, Australia, and Gonazon CR; Intervet, Boxmeer, Netherlands) have shown efficacy, but neither is available commercially in the United States. Depot forms of leuprolide acetate (Lupron; Tap Pharmaceutical, Lake Forest, IL) are available on the human market but remain extremely expensive.⁴⁷ Although these products are effective and safer than many other options, their lack of availability and high cost do not make them highly practical.

Mismate or Pregnancy Termination

The termination of pregnancy in the bitch or queen is often requested by owners after unwanted mating. Because an animal is in estrus and has been found together with a male, this

does not suggest that successful mating has occurred. Only 38% of dogs become pregnant after a single mating.⁹ For this reason, therapy should be delayed until unwanted pregnancy is documented at ~30 days. Vaginal cytology can be performed to document estrus by the presence of 90% to 100% cornified, superficial cells. Further identification of sperm cells in a vaginal swab within 48 hours of mating can be used to confirm that mating has occurred.⁴⁸ Unless there is a valid reason for keeping a reproductively intact animal, the veterinarian should highly recommend ovariohysterectomy once the female is in diestrus. This avoids the health risks associated with the products used to terminate pregnancy, as well as the long-term health risks associated with intact animals.

Once pregnancy has been determined, it is essential that the owner understand the risks associated with mismating or pregnancy termination protocols. Drug options currently available for canine and feline patients and their associated risks are shown in Table 1. The majority of drugs used are not labeled for this indication, and may place the animal at increased risk of side effects such as bleeding, infection, or reduced subsequent fertility. Extensive counseling with the owner is required to establish which therapeutic option is best suited for the animal. Treatment options should be assessed by comparing safety, efficacy, cost, and compliance by the owner. Owners should understand that, in all cases, the animal should be confined after treatment and in future cycles to avoid further unwanted pregnancies and prevent increased risk of pyometra with continued mating. All pregnancy termination protocols necessitate monitoring for completion with serial ultrasound.

Termination of Canine Pregnancies

Estrogens

In general, there are few drugs used to terminate pregnancy in bitches or queens during estrus. Estradiol cypionate (ECP), estradiol benzoate, and diethylstilbestrol (DES) were used extensively for this purpose, but are not currently commercially available from manufacturers. Although estrogens are considered unsafe by many individuals, there are only a few published cases to support this.⁴⁸ The use of estrogens during diestrus significantly increases the risk of the animal developing a pyometra and should not be used.⁴⁹ Because of potential side effects (irreversible aplastic anemia, pyometra, prolonged estrus), lack of availability, and better alternatives, the estrogens are no longer recommended for mismatch injections.⁴⁸

Antiestrogens/Dopaminergic Agents/Prostaglandins

The antiestrogen tamoxifen citrate (Nolvadex) and the dopaminergic drug bromocriptine (Parlodel) have also been evaluated as mismatch drugs, but have not been shown to be highly effective.⁴⁸⁻⁵⁰ After confirmed pregnancy, natural prostaglandins, PGF-_{2α} (Lutalyse), may be administered to lyse the corpora lutea, causing pregnancy termination, but are associated with significant side effects (vomiting, diar-

rhea, and, if overdosed, circulatory collapse). Prostaglandins must also be given for a significant length of time (> 7-9 days), and hospitalization is indicated, adding to the overall cost of therapy. Combination therapy with intravaginal misoprostol may reduce the mean time to abortion to 5 days.⁵¹ Synthetic prostaglandins (cloprostenol, fluprostenol) have fewer side effects and a shorter treatment period and are preferred to the natural prostaglandins.

Dexamethasone

Dexamethasone has more recently been administered to terminate pregnancy in bitches between 30-50 days gestation.⁴⁸ When used in pregnancies less than 40 days, only mild side effects are generally seen (mild vaginal bleeding, anorexia, polydipsia, and polyuria). Because of its efficacy, few side effects, low cost, availability, and ease of administration, it has become the agent of choice in many settings. Both tapering doses (see Table 1) or oral doses of 0.2 mg/kg twice per day until fetal resorption occurs can be used.

Cabergoline

Dopaminergic agents, such as cabergoline (Dostinex), are very effective if administered late in pregnancy (> 40 days' gestation), but can be difficult to dose in small animals. Cabergoline is available in generic tablets that contain 0.5 mg of drug. Although the drug is expensive if an entire bottle is purchased, single doses may also be available from outside pharmacies. Cabergoline is not stable in water if allowed to sit, but can be diluted in water just before administration without losing stability.^{14,48,52} Alternatively, cabergoline can be compounded into smaller doses or made into a solution with 1% acetic acid that can be stored refrigerated for up to 28 days.^{34,53} Cabergoline inhibits prolactin and can result in 100% efficacy if administered at 40 days after the LH surge.^{14,52}

Antiprogestational Agents

Antiprogestational agents mifepristone (RU486; Mifeprex; Danco Laboratories, NY) and aglepristone (Alizine; Virbac, Carros, France) are noted to be very effective (100%) in pregnancy termination and lack the severe side effects noted with some other agents (Table 1). These products do not appear to affect long-term fertility, are rapid in onset, and can be given as an outpatient medication.^{54,55} Unfortunately, they are not readily available in the United States and remain very expensive. Mifeprex is available as a 200-mg tablet in the United States but may cost as much as \$90.00/dose for a 10-kg dog. As these agents become more cost effective and availability improves, antiprogestational agents may eventually become the treatment of choice for pregnancy termination.

New Agents

In addition to the above single-agent treatments, many authors have more recently explored combinations of drugs to increase efficacy and reduce side effects of single agent therapies. Many of these combinations have demonstrated

Table 1. Drugs Used to Prevent or Terminate Pregnancy in Canine and Feline Patients

Drug	Mechanism	Dose
Estradiol Cyprionate (ECP)	Estrogen	Dogs: 44 $\mu\text{g}/\text{kg}$ IM \times 1; during day 4 estrus to day 2 of diestrus, toxic at ≥ 100 $\mu\text{g}/\text{kg}$. Cats: 250 $\mu\text{g}/\text{kg}$ IM 6 days after coitus or 0.125-0.25 mg/cat IM at 40 h after coitus. ^{8,49}
PGF- _{2α} (Lutalyse)	Prostaglandin (Luteolytic)	Dogs: Start at 30 days gestation; then 0.1 mg/kg SC every 8 h \times 2 days; then 0.2 mg/kg every 8 h until abortion is complete, may take ≥ 9 days. Cats: Start at 33 days gestation, 2 mg/cat SC \times 5 days or >40 days; give 500 to 1000 $\mu\text{g}/\text{kg}$ \times 2 consecutive days. ⁹
Dexamethasone (Decadron)	Steroid (Progesterone inhibitor)	Dogs: Start at 30 to 50 days gestation; given as a taper; start at 0.2 mg/kg every day orally \times 7 days. day 8: 0.16 mg/kg (AM) and 0.12 mg/kg (PM). day 9: 0.08 mg/kg (AM) and 0.04 mg/kg (PM). day 10: 0.02 mg/kg (AM) or alternatively, give 0.2 mg/kg every day orally \times 10 days. ¹³
Tamoxifen (Nolvadex)	Anti-estrogen (estrogenic)	Dogs: Give 1.0 mg/kg orally every day \times 10 days, starting in proestrus or estrus; or on days 2, 15, or 30 days of diestrus. Not effective \geq day 15 of diestrus. ⁷
Cabergoline (Dostinex)	Prolactin inhibitor	Dogs: Give 5 $\mu\text{g}/\text{kg}/\text{d}$ orally \times 5 days at 40 days after LH surge, less effective if earlier. Cats: Give 25-50 $\mu\text{g}/\text{kg}$ orally at day 42 \times 3 to 5 days. ¹⁴
Bromocriptine (Parlodol)	Prolactin inhibitor	Dogs: Given second half of pregnancy, dose at 62.5 $\mu\text{g}/\text{kg}$ orally every day after 45 days. ¹⁷
Mifepristone (Mifeprex)	Progesterone blocker	Dogs: Given at 2.5 mg/kg orally every day \times 4.5 days; starting at day 32 or 8, 3-20 mg/kg orally \times 1 to 2 doses. ¹⁶
Agelpristone (Alizine)	Progesterone blocker	Dogs: Given at 2-10 mg/kg SC \times 2; 12 h apart at days 0 to 25 or 26 to 45 days. ⁷ Cats: Given at 15 mg/kg SC every 24 h \times 2, starting at 33 days.

equal efficacy and reduced side effects, but increased expense and time commitments. Other new agents, such as the new progesterone synthesis inhibitor Epostane (Sterling Drug Company, Park Ave, NY), have shown promising results. This drug is not currently commercially available in the United States, can be orally administered, has limited side effects, and can be 100% effective if started on day 1 of diestrus and given for 7 days.⁵⁶ Further studies are necessary but appear promising.

Drugs Used to Terminate Feline Pregnancies

Fewer drug protocols have been evaluated in cats (Table 1). Estradiol cyprionate is not considered safe in cats. PGF-_{2 α} has been administered but has significant side effects and the animal must be hospitalized. Both cabergoline and agelpristone are much better tolerated in cats. Agelpristone is not currently available in the United States. Cabergoline is avail-

able in generic tablets (0.5 mg) and can be compounded into smaller-sized capsules for appropriate dosing.

Complications of Pregnancy/Diestrus

Female reproductive emergencies commonly encountered in small animal practice may involve dystocia, eclampsia, pyometra, mastitis, uterine torsion, and uterine prolapse.⁵⁷ The treatment of uterine prolapse, torsion, and closed pyometra typically involve surgical, rather than medical, intervention. New strategies allowing uterine salvage have been attempted, such as in the case of open pyometra. Medical management of dystocias with new protocols for eclolic agents have also been instituted with improved outcomes.

Pyometra

Pyometra (uterine infection) is a medical emergency in both dogs and cats. The risk for pyometra is believed to be

Table 1. Continued

Availability	Potential Side effects	Comments
Not currently	Estrus prolongation, aplastic anemia, metritis, increased risk of pyometra with benzoate or, if given in diesterus, irreversible sterility.	Estradiol benzoate/DES less effective, cheap, considered unsafe due to toxicity, 100% efficacy.
Available	Vomiting, diarrhea, trembling, ataxia, salivation, panting, circulatory collapse, short diestrus, next cycle can abort fetuses for up to 9 days.	Must hospitalize, high side effects, give food 1 h postdose, premed with atropine, 100% efficacy.
Available	Vaginal discharge, polydipsia, polyuria, anorexia, GI upset	Takes 10 to 23 days to work, inexpensive, no later reproductive effects, must continue until fetal death, 100% efficacy 2 days after end of taper, no hospitalization.
Available	Pyometra, endometritis, cystic ovaries	High risk, poor efficacy, can be given at time of mismate, may affect later reproduction, 100% efficacy if given before day 15. Abortion in 7 to 10 days.
Available as 0.5-mg tabs	Vomiting, fetal expulsion if given after day 40, few adverse side effects.	Successful breeding after abortion, expensive, 100% effective if given at ≥ 40 days. Abortion in 7 to 10 days.
Available as 2.5-mg tabs	Vomiting, diarrhea, listlessness, may decrease over time.	Not effective in 50% of cases, not stable in water.
Available as 200-mg tabs	Limited side effects	Expensive, rapid effects if daily $\times 3$ days or 2 to 11 days for 1 to 2 doses.
Europe only	Depression, anorexia, mammary congestion, vaginal discharge pretermination, decreased temperature, painful injections	Not available, rapid effects, 97.7% efficacy, no later reproductive effects.

age related. Dogs that are <10 years of age have a 2% incidence, with an increase of 6% per year, so that by the age of 10 years, about 24% of dogs have pyometra.⁵⁸ Administration of estrogens for the purpose of pregnancy termination has also been associated with an increased incidence of pyometra in dogs. Animals can present with purulent vaginal discharge, vomiting, inappetence, polyuria, polydipsia, lethargy, abdominal distention, uterine rupture, or peritonitis. Septicemia, endotoxemia, tachycardia, tachypnea, fever, or subnormal body temperature may result. Rapid deterioration, sepsis, and death may occur if treatment is not initiated early in the course of the disease.

Pyometra is typically secondary to pathologic changes induced in the endometrium from progesterone exposure over successive heat cycles.⁵⁹ Pyometra in cats is less common, likely because of the fact that they are induced ovulators with more limited progesterone exposure. However, pyometra is common in catteries with intact queen populations. Progesterone causes endometrial hyperplasia, luminal fluid

accumulation, suppressed leukocyte activity, and decreased myometrial activity. Reduced contractility and fluid accumulation favor ascending bacterial infections that are typically due to enteric bacteria. *Escherichia coli* is the most common isolate and is typically the only isolate. Other isolates have included *Streptococcus* spp, *Staphylococcus* spp, *Proteus*, *Klebsiella*, *Serratia*, *Pseudomonas*, *Enterococcus*, and *Salmonella*.⁶⁰

Treatment of pyometra Treatment of pyometra typically involves immediate intravenous hydration and initiation of antibiotic therapy. Ideally, culture and sensitivity should be performed before initiating empiric antibiotic therapy. Most *Escherichia coli* isolates found in pyometra are identical to isolates found in the animal's urine or blood and share the same sensitivity patterns.⁶¹ *E. coli* isolates found in pyometra may be resistant to 2 or more antibiotics.⁶² Ideally, a fluoroquinolone (enrofloxacin, marbofloxacin) in combination with an extended-spectrum penicillin (Timentin) or ampicil-

lin may be administered acutely. Fluoroquinolones penetrate into uterine tissues at concentrations greater than that of plasma.⁶³ Alternative antibiotics that cover *E. coli* include; aminoglycosides, trimethoprim sulfamethoxazole, amoxicillin-clavulanic acid, third-generation cephalosporins, and chloramphenicol.⁶⁰ After stabilization of the patient by correcting hypotension and dehydration, subsequent ovariohysterectomy should be performed. After culture and susceptibility results, antibiotics should be tailored to the specific isolate and patient, and therapy continued for up to 3 weeks.

Open pyometra (draining) has a much more favorable prognosis than closed pyometra. Bitches and queens with good breeding potential (less than 5 years of age, healthy) whose owners decline ovariohysterectomy can be offered new agents and techniques that have been attempted with some success. Naturally occurring prostaglandins (PGF-_{2α}) have been administered to cause luteolysis and evacuation of uterine contents in open pyometra, but should not be used in closed pyometra because of the potential for uterine rupture. PGE (misoprostol) can be administered intravaginally (1-3 μg/kg every 12-24 hours) in an attempt to relax the cervix before PGF-_{2α} administration. Synthetic prostaglandins have been used in canine patients to date, including cloprostenol and alfaprostol. Synthetic prostaglandin are more specific for uterine smooth muscle, causing fewer observed side effects (nausea, diarrhea, cramping, panting). Prostaglandins stimulate uterine contractions and variably relax the cervix, causing evacuation and drainage of purulent uterine contents. The dose of prostaglandin depends on the drug used. The lowest effective dose should be used; this has not been established in all cases. PGF-_{2α} is administered at 0.1 mg/kg SC every 12 hours for 48 hours, then at 0.2 mg/kg SC every 12 hours to effect. Cloprostenol is administered at 1 to 3 μg/kg every 12 to 24 hours. Therapy may be necessary for 7 to 10 days.^{61,64,65} Side effects after the initial doses can include restlessness, panting, vomiting, elevated heart rate, fever, and defecation. To clear the uterus of infected material, prostaglandin administration should be continued as long as abnormal fluid is seen within the uterine lumen ultrasonographically. Progesterone levels should fall to <2 ng/mL.

More recently, antiprogesterins have been evaluated in the treatment of pyometra. The availability of antiprogesterin-based drugs in some countries has completely changed the clinical approach to pyometras in which the only solution has been ovariohysterectomy. Aglepristone (Alizine), an antiprogesterin, has been examined as a treatment for open pyometra in dogs and cats. A dose of 10 mg/kg on days 1, 2, and 7 in combination with antibiotics was successful in treating 21 bitches and 4 cats with only 1 recurrence over a 14-month period of observation.^{60,66-68} No side effects were observed, and 2 of the bitches went on to be successfully bred.⁶⁸ Although the availability and high cost of these agents limit current use of these agents in the United States, with time they may become a valuable tool in the treatment of pyometra.

Typically, animals treated medically for pyometra have a very high incidence of recurrence (70% in 2 years), suggesting that ovariohysterectomy remains the treatment of choice.

Follow-up of animals after acute treatment is important because there is an association between pyometra, proteinuria, and the development of acute glomerular damage in dogs.⁶⁹ Although further study needs to be done on this association, it may be wise to avoid antibiotics that may contribute to further renal damage (aminoglycosides, sulfas).

Dystocia

Dystocia is from the Greek word “dys” meaning “difficult, painful, or abnormal” and “tokos” meaning birth. Dystocia occurs in approximately 5% of bitches and 3% to 5.8% of queens.^{70,71} Most dystocias are due to maternal factors, with primary and secondary inertia being the most common maternal cause, and fetal oversize, death, or abnormal posture being the most likely fetal causes.^{71,72} Veterinary assistance should be sought with any of the following: 1) labor does not begin when expected; 2) stage 2 labor lasts >1 hour without delivery; 3) >1-2 hours have elapsed between deliveries; 4) the dam or neonates show signs of distress, including stillbirth; 5) green-black discharge without immediate delivery; or 6) a significant hemorrhagic vaginal discharge.⁷² Delivery should occur within 12 to 24 hours of the onset of first-stage labor.

Because there are multiple reasons for dystocia in the bitch or queen and many require surgical intervention, the focus here will be on those disorders amenable to drug therapy. The veterinarian must first determine that the cause of dystocia is not obstruction. Uterine rupture may occur if drug therapy is instituted improperly. Manual manipulation and assisted extraction may be all that are required to achieve results. However, obstetrical manipulations are frequently of limited utility in small animals. In all cases of dystocia, uterine (tocodynamometry) and fetal (Doppler or ultrasound) heart rate monitoring permit the best evaluation of the quality of labor, the degree of fetal stress, and the response to medical therapies.

Ecboic Agents Calcium gluconate and synthetic oxytocin remain the drugs of choice for treating dystocias.⁷³ In general, if an interval between pups exceeds 60 minutes, or uterine inertia has been documented with tocodynamometry, calcium gluconate administration should be initiated first. Serum calcium concentrations may be difficult to assess accurately during primary inertia, unless ionized calcium can be measured diagnostically. Despite normocalcemia in many patients, administration of calcium gluconate usually results in improved myometrial tone. Calcium gluconate 10% is commonly used in bitches either IV (0.2 mL/kg) or SC (1 mL/4.5 kg) every 4 to 6 hours. Calcium gluconate 10% can also be given to queens (0.5-1.0 mL per cat SC or IV).⁷³ Intravenous calcium should be delivered slowly over 10 to 20 minutes with both cardiac and respiratory monitoring. If fetal expulsion does not occur with initiation of calcium gluconate, oxytocin may then be administered. If this fails to cause fetal expulsion after 30 minutes, surgical intervention may be indicated.

Oxytocin can be administered via various routes (intravenous, subcutaneous, and intramuscular). Recent data suggest that the ideal administration of oxytocin is by repeat small doses instead of large single doses. Using a tocodynamometer, large doses of oxytocin (5 U) were noted to produce uterine tetany, whereas smaller doses (0.25 U) produced effective contractions.⁷⁴ It is therefore suggested that initial doses of 0.1 U are given IM or SC and increased incrementally every 30 to 40 minutes to a maximum dose of 5 U.^{73,75} This method reduces the associated deleterious side effects of oxytocin (uterine rupture, placental separation, fetal death, maternal vasodilation, and hypotension) and prevents excessive disruption of blood flow to the fetus and placenta.^{75,76}

Although incremental small doses of oxytocin can have improved outcome for dystocia, only one third of canine patients respond to oxytocin, suggesting that calcium depletion also plays a large role.⁷⁷ Hypoglycemia may also contribute to primary inertia (primarily toy breeds) and should be carefully monitored for. In canine patients, hyperglycemia can occur because of high cortisol concentrations, so that glucose should not be administered unless hypoglycemia is documented.^{70,78}

In queens, medical therapy for dystocia is less successful but may be attempted. Dosages of 0.5 to 2 mL of calcium gluconate (10%) can be administered slowly SC or IV with monitoring. Oxytocin may then be administered at 0.10 to 0.25 U SC or IM. If this fails, 0.25 mL of dextrose (50%) diluted to 2.0 mL in sterile water or saline solution can be administered by slow intravenous infusion. Failure of effective labor to begin is an indication for likely surgical intervention.⁷⁹

Eclampsia

Eclampsia is typically a direct result of hypocalcemia. In canine patients, a total serum calcium concentration of <6.5 mg/dL or an ionized serum calcium of <2.4 to 3.2 mg/dL or <0.8 mmol/L (based on ionized serum calcium in dogs being 55% of total serum calcium) confirms the diagnosis.⁸⁰ The normal reference range for total canine serum calcium is 9.7 to 11.5 mg/dL at our institute, but varies dependent on the laboratory used (8.7-12.0 mg/dL). Puerperal hypocalcemia is considered a life-threatening condition typically seen around 2 to 4 weeks after whelping, but can occur in the prepartum period as well. Eclampsia is primarily seen in smaller breeds with large litters. Heavy lactational demands here cause an imbalance in calcium stores that cannot be compensated for by dietary calcium intake. In dogs, hypocalcemia has an excitatory effect on nerves and muscle cells. Bitches may initially develop facial pruritus, panting, or restlessness, which may progress into tremors, twitching, generalized seizures, hyperthermia, tachycardia, polyuria, polydipsia, and vomiting.⁸¹ Behavioral changes may also occur (whining, salivation, aggression, hypersensitivity, disorientation). Hypoglycemia, toxicosis, epilepsy, metritis, and mastitis should be ruled out.

In feline patients, eclampsia occurs less commonly. It may occur in queens nursing large litters, although it has been reported in queens from 3 to 17 days before parturition. Queens may present with acute lethargy, anorexia, trembling, dehydration, muscle fasciculations, weakness, pallor, hypothermia, bradycardia, dyspnea, and/or tachypnea. Diagnosis is based on abnormally low total serum calcium concentrations of <6.0 mg/dL, in combination with clinical symptoms and history.⁸⁰ The normal reference range for total feline serum calcium is 9 to 10.9 mg/dL, but varies (8.7-11.7 mg/dL) dependent on the laboratory used. Ionized feline serum calcium concentrations (0.77 and 1.27 mmol/L) can be obtained, but may not be diagnostic.

Diagnosis is typically based on signs and clinical history, as well as response to calcium supplementation because serum ionized calcium concentrations may not reflect the degree of hypocalcemia. Calcium concentrations fluctuate with serum protein concentration, acid-base status, and other electrolyte alterations. Hypoglycemia may also develop concurrently. Alkalosis exacerbates hypocalcemia, so that the severity of clinical symptoms may not correlate with the serum calcium concentrations.

If animals are seizing, diazepam (1-5 mg IV) may be given acutely. For acute hypocalcemia, 10% calcium gluconate may be administered at a dose of 0.22 to 0.44 mL/kg IV slowly, over 10 to 30 minutes.⁸¹ Rapid neurological improvement should occur in about 15 minutes. An electrocardiogram should be used to monitor for bradycardia or Q-T shortening. If these occur, then the rate should be slowed or discontinued. Hypoglycemia, hyperthermia, or cerebral edema should be treated if necessary. Corticosteroids are contraindicated as they are calciuric.

Once life-threatening signs are controlled, calcium can be added to intravenous fluids and administered as a slow infusion. In queens, 60 to 90 mg/kg/d elemental calcium (or 2.5 mL/kg every 6-8 hours of 10% calcium gluconate) can be administered. In bitches, doses of 5 to 15 mg/kg/h of elemental calcium (or 0.5-1.5 mL/kg/h of calcium gluconate) may be continued IV. Dosing is based on elemental calcium (calcium gluconate 10% contains 9.3 mg elemental calcium/mL, and calcium chloride 27% contains 27.2 mg of elemental calcium/mL). Once stable, doses of calcium gluconate (not calcium chloride) can be diluted in an equal volume of normal (0.9%) saline solution and administered SC 3 times daily.

Serum calcium should be monitored once to twice daily and the dose adjusted as required. Oral calcium can then be given to queens at a dose of 50 to 100 mg/kg/d (elemental calcium) divided 3 to 4 times daily or to bitches at 25 to 50 mg/kg/d (elemental calcium). If symptoms do not resolve and/or calcium serum concentrations fail to rise, vitamin D (10,000-20,000 U/d) supplementation may be required. It is typically recommended to maintain oral supplementation for up to 1 month postpartum. Calcium carbonate tablets contain 260 to 600 mg of elemental calcium per tablet depending on the manufacturer. For severe hypocalcemia, the kittens or puppies should be taken from the mother for at least 12 to 24 hours and fed a milk substitute diet or weaned if old enough.

To suppress lactation, cabergoline may be administered at 5 $\mu\text{g}/\text{kg}$ once daily for 5 days.

Premature Labor

Ovulation timing is necessary to determine the exact due date, otherwise determining premature labor can be difficult. During mid to late pregnancy, uterine activity can be monitored with tocodynamometry (Whelpwise) to alert the owner or veterinarian to problems in high-risk patients (history of pregnancy loss with no etiology identified). Progesterone levels can also be monitored, but can fall precipitously. In bitches, plasma concentrations >2 ng/mL are required to maintain pregnancy. Typical values >20 ng/mL are common. If levels are between 5 and 10 ng/mL, then monitoring may be required. Supplementation may be required to maintain pregnancy if levels drop to 2 to 5 ng/mL.⁸²

Supplementation should never be done during the first trimester because of risks of masculinizing female fetuses. Supplementation can be performed with progesterone in oil (2-3 mg/kg every 24-48 hours IM to maintain a serum progesterone level of 10 ng/mL).⁸² It is important to discontinue treatment 2 to 3 days before parturition to prevent the fetuses from being retained too long.

If premature labor is diagnosed, tocolytic therapy can be administered, targeting uterine contractions. Terbutaline, a β_2 agonist, is the only product that has been used for preterm labor in animals. The injectable form of terbutaline can be dosed at 0.005 mg/lb or 0.01 mg/kg up to every 6 hours in dogs or cats. Doses should be titrated to effect, with careful monitoring for cardiovascular side effects. Adverse reactions to terbutaline may include cardiovascular arrhythmias, pulmonary edema, and hypokalemia.

In humans, tocolytic agents have included betamimetics (terbutaline), calcium channel blockers (nifedipine), oxytocin receptor antagonists (atosiban), magnesium sulfate, nonsteroidal antiinflammatories (indomethacin), and phosphodiesterase inhibitors (sildenafil). An article from the Cochrane Database of Systematic Reviews 2005 suggests that calcium channel blockers (nifedipine) were associated with better neonatal outcome and fewer maternal side effects than betamimetics in humans.⁸³ Mothers receiving terbutaline had significantly higher heart rates, and neonates had a higher incidence of intraventricular hemorrhage.⁸⁴ Indomethacin was found to be associated with an increased incidence of intracranial hemorrhage and renal dysfunction.⁸⁵ Atosiban had fewer maternal side effects than betamimetics, but was not superior to betamimetics or placebo in terms of tocolytic efficacy or infant outcomes.⁸³

Both vaginal and oral sildenafil (Viagra) has recently been evaluated in pregnant human patients to improve uterine artery blood flow, stimulate intrauterine growth, and prevent premature labor.^{86,87} Results, to date, suggest no teratogenic effects observed in mice, rats, dogs, or in pregnant humans receiving sildenafil for pulmonary hypertension.⁸⁷ Sildenafil increased fetal weight in rats.⁸⁷ Vaginal sildenafil increases uterine artery blood flow in pregnant women, and, when

used in combination with vaginal estradiol, there was improved vaginal blood flow and endometrial thickness in all patients.⁸⁶ Although studies have not been done in veterinary medicine for this use, both sildenafil and nifedipine may have efficacy as tocolytic agents in canine patients and would be interesting to explore.

Therapeutic Drug Use in Pregnancy

The use of drugs in a pregnant or lactating animal must be carefully weighed against risks. Although many drugs can be harmful to a growing fetus, particularly in early pregnancy when limb buds are forming and organogenesis is occurring, the risks should not be overestimated. There are many pharmacologic factors that help determine embryo and fetus exposure to drugs including molecular weight, pH, degree of ionization, lipid solubility, protein binding, placental blood flow, and placental surface area. In general, evolution has resulted in an amazing resilience of embryos and fetuses to environmental toxins. For harmful effects to occur, fetal exposure to drugs or toxins must not only take place at a certain gestational time but must also meet an exposure threshold concentration. In human pregnancies exposed to teratogenic agents during the first trimester, $<10\%$ of exposures resulted in abnormal offspring.⁸⁸

Teratogenic Risk Assessment

Many drugs have undergone teratogenic risk assessment for humans.⁸⁹ The FDA classification of drugs used during pregnancy is based on many factors (Table 2). Data here have been primarily collated from human epidemiological studies or in vitro or in vivo mouse or rat studies.⁹⁰ Although extrapolation of data from these categories to canine and feline species is somewhat limited, it does provide some basis as to categories of drugs that should be contraindicated in most species because of direct fetotoxic effects.

In pregnant and lactating animals, the most common drugs prescribed or frequently needed include antibiotics, antivirals, anthelmintics, antifungals, anesthetics, and vaccinations. Because of the many drugs that may be used during pregnancy and lactation, only the above categories of drugs will be addressed in depth. Other information on drugs used more rarely in pregnancy and lactation can be found in Briggs and coworkers.⁹⁰ Because breast milk possesses nutritional and immunologic properties superior to most milk substitutes, weaning of animals, to treat the queen or bitch, is not recommended unless the drugs have a high potential risk to the fetus or litter and are absolutely necessary.

Antimicrobial Therapy During Pregnancy

Antibiotics are the most common class of drugs prescribed during pregnancy. Most antibiotics are in Category B, meaning that they are probably safe (Table 3). Amoxicillin, ampicillin, amoxicillin/clavulanic acid, cephalixin, cefadroxil, clindamycin, erythromycin, and azithromycin are considered safe. Metronidazole should not be used in early pregnancy,

Table 2. FDA Classification of Drug Safety During Pregnancy

Category A:

Controlled studies in animals and humans fail to demonstrate a risk to the fetus in first trimester; fetal harm is remote.

Examples: Levothyroid, thyroid

Category B:

Either animal reproduction studies have not shown fetal risk, or animal reproduction studies showed an adverse effect not confirmed in controlled human studies.

Examples: Acyclovir, cimetidine, cyproheptadine, desmopressin, diphenhydramine, dolasetron, enoxaparin, famotidine, glycopyrolate, insulin, ketamine, lansoprazole, lidocaine, metoclopramide, naloxone, ondansetron, pantoprazole, propofol, ranitidine, sulcrafate, valacyclovir

Category C:

Either animal studies revealed adverse effects and there are no controlled human studies, or no studies (animal or human) are available.

Examples: Acetazolamide, amantidine, angiotensin-converting enzyme inhibitors, aspirin, atropine, baclofen, bismuth subsalicylate, buprenorphine, butorphanol, calcium channel blockers, chloral hydrate, chloramphenicol, cisapride, clomipramine, codeine, corticotropin, cyclosporine, digoxin, diphenoxylate, echinacea, edrophonium, fentanyl, fluoxetine, furosemide, gabapentin, guaifenesin, heparin, hydroxyzine, interferon, mannitol, mexiletine, nonsteroidal antiinflammatories (first trimester), omeprazole, phenylpropanolamine, prednisone, prednisolone, prochlorperazine, promethazine, physostigmine, spironolactone, sufentanyl, sulfonamides, rifampin, theophylline, tramadol

Category D:

There is positive evidence of human and animal fetal risk, but the benefits may be acceptable if needed for life-threatening or serious disease.

Examples: Aminoglycosides, anabolic steroids, androgens, bromides, calcitrol, cytostatic agents, diazepam, epogen, iodine, meprobamate, methimazole, midazolam, nonsteroidal antiinflammatories (second to third trimester), pentobarbital, phenobarbital, potassium iodide, povidine-iodine, tetracyclines

Category X:

Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience. Risk outweighs the benefits. Contraindicated in pregnancy or animals during breeding.

Examples: Ergotamine, estradiol, isotretinoin, leuprolide, misoprostol, sodium iodide

Abbreviation: FDA, United States Food and Drug Administration

Information derived from: Briggs GG, Freeman RK, Yaffe SJ (eds): *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* (ed 5). Baltimore, Williams and Wilkins, 1998, pp 577-578.

but can be used near term. Antibiotics in Category C (unknown or potential concern) include chloramphenicol, clarithromycin, ciprofloxacin (or enrofloxacin), gentamycin, imipenem, pyrimethamine, rifampin, and trimethoprim/sulfamethoxazole (TMS) in early pregnancy. Category D medications (contraindicated unless benefits outweigh risks) include amikacin, tetracycline, doxycycline, and TMS, if near term.

Bacterial infections in bitches during pregnancy and lactation include, but are not limited to, *Brucella canis* spp, *Staphylococcus* spp, *Streptococcus* spp, *Mycoplasma* spp, *Ureaplasma* spp, and *Chlamydia* spp. It is important that antibiotics administered to the lactating or pregnant bitch or queen be carefully selected so that adverse effects such as permanent tooth discoloration and skeletal defects (tetracyclines), impaired cartilage development (fluoroquinolones), bone marrow suppression or autoimmune disorders (sulfas), or severe diarrhea (clindamycin) do not develop in the fetuses or neonates. In some instances (innate or acquired resistance), the benefits of using the above antibiotics may outweigh the risks to the litter. Because of the multiple antibiotics and organisms that may need coverage, culture and sensitivity results should be used to select antibiotics. Indi-

vidual antibiotics and their pregnancy and lactation risk categories are covered in Table 3.

Brucella canis *Brucella canis*, undulant fever, or contagious abortion is the most common cause of infectious abortions in dogs, and its treatment has been considered difficult at best. Seroprevalence rates range from 1% to 6% in many areas of the United States, but may be much higher in the South. In Peru and Mexico, rates have been reported to be as high as 25% in dogs.⁹¹ *B. canis* is a Gram-negative intracellular coccobacillus that is spread by inhalation, oral ingestion, or contact with the fetus or fetal membranes after abortions/stillbirths of infected fetuses. Venereal transmission or transmission through the genital, oronasal, or conjunctival mucosa also occurs.⁹² Abortion occurs between 45 and 59 days of pregnancy. *B. canis* is most prevalent in large breeding kennels where contact with infective discharges or fetal tissues occurs. Because there is no permanent cure for *B. canis*, infected animals must be eliminated from breeding. The infection affects both females and males. Males may develop chronic prostatitis and orchitis/epididymitis, which can continue to shed bacteria for months. Although some dogs may

Table 3. Antibiotic Use in Pregnancy and Lactation

Drug	Species	Results	Human Exposure	Lactation*	Risk†
Amikacin (Amikin)	Mice, rats	Nephrotoxicity in pregnant rats and fetuses, no evidence of impaired fertility or teratogenicity.	No reports linking amikacin to congenital defects in humans, eighth cranial nerve toxicity reported.	Low concentrations in milk, limited oral absorption.	D
Amoxicillin (Amoxi-tabs)	Mice, rats	No adverse effects in up to 10× the human dose.	No evidence supporting fetal harm or reproductive effects.	Excreted into milk in low concentrations.	B
Ampicillin (Polyflex)	Mice, rats, rabbits, guinea pigs	No adverse effects in up to 10× human, reduced uterine contractions with IV infusion in guinea pigs.	No evidence supporting fetal harm or reproductive effects.	Excreted into milk in low concentrations.	B
Azithromycin (Zithromax)	Mice, rats	No adverse effects in doses toxic to the mother.	Limited data available.	Accumulates in milk because of ion trapping.	B
Chloramphenicol (Viceton)	Mice, rats	Chromosomal aberrations in mice, not rats.	No birth defects, but cardiovascular collapse in exposed infants.	Excreted into milk, causing refusal to drink, GI upset, vomiting.	C
Ciprofloxacin (Cipro)	Dogs, rats, mice	No embryotoxic effects, except permanent lesions to cartilage in weight-bearing joints	No proven fetal harm, but safer drugs are available, best to avoid	Excreted into milk in high concentrations; arthropathy risk in pups.	C
Clavamox (Amox/Clav)	Mice, rats, pigs	No adverse fetal effects reported.	Large studies show no adverse teratogenic risks.	Excreted into milk in low concentrations.	B
Clindamycin (Antirobe)	Mice, rats,	No effects on fetuses at doses up to 2× human dose.	No birth defects noted in surveillance studies.	Excreted into milk with at least one case report of bloody stool.	B
Cefazolin (Ancef)	Mice, rats	No adverse effects in up to 25× human dose.	No adverse fetal effects noted.	Excreted into milk in low concentrations.	B
Cefotaxime (Claforan)	Mice, rats	No evidence of impaired fertility or adverse effects.	No adverse fetal effects in low concentrations in early or late fetal in up to 20× human dose.	Excreted into milk.	B
Cefpodoxime (Simplicef)	Rats, rabbits	No evidence of impaired fertility or adverse effects.	No reports of adverse effects on fetuses in up to 2× human dose.	Excreted into milk in low concentrations.	B
Cephalexin (Keflex)	Mice, rats	No evidence of impaired fertility or adverse effects in up to 500 mg/kg.	No adverse effects in second to third trimester. Surveillance study suggests risks of cleft palate, cardiovascular defects during first trimester exposure.	Excreted into milk in low concentrations.	B
Doxycycline (Vibramycin)	Mice, rats	Impaired fetal development, placental anomalies, delayed differentiation in long bones.	Adverse effects in human fetuses to teeth, bones, congenital defects and maternal liver toxicity.	Excreted into milk in concentrations that may result in stained teeth and delayed bone growth.	D

Table 3. Continued

Drug	Species	Results	Human Exposure	Lactation*	Risk†
Erythromycin (Gallimycin)	Rats	No evidence of impaired fertility or adverse effects.	Hepatotoxicity to estolate salt, but no adverse effects throughout pregnancy.	Excreted into milk in moderate concentrations.	B
Gentamycin (Gentaved)	Rats, rabbits	No adverse effects seen at low doses, increased blood pressure, nephrotoxicity, neuromuscular weakness.	No teratogenic risks or structural defects, but can cause eighth cranial nerve toxicity.	Excreted into milk in moderate concentrations, limited oral absorption, but measurable concentrations in offspring.	C
Imipenem	Rats, monkeys, rabbits	Increased abortion at 3× human dose in monkeys.	No teratogenic effects reported in early or late pregnancy.	Excreted into milk in small amounts.	C
Metronidazole (Flagyl)	Mice, rats	No adverse effects with oral doses up to 5× human, fetal deaths with IP dosing.	Conflicting data, may increase risk of cleft lip/palate in first trimester, avoid use in first trimester.	Excreted into milk in high concentrations, withhold feeding for 12 to 24 hours after dose.	B
Penicillin (Bicillin)	Mice, rats, rabbits	No evidence of impaired fertility or adverse effects.	Old data suggest risk of abortions first trimester, new evidence from large studies suggests not harmful, safe.	Excreted into milk in low concentrations.	B
Tetracycline (Panmycin)	Rats, pigs	Embryotoxicity, congenital anomalies, intrauterine death, delayed fibula growth, causing stillbirths, premature births.	Causes pregnancy-related maternal acute fatty liver, renal failure, pancreatitis, hepatocellular injury.	Excreted into milk in low concentrations; potential tooth staining.	D
Ticarcillin/Clavulanate (Timentin)	Rats, mice	No adverse effects on fertility or fetuses.	No reports linking use to any adverse effects.	Excreted into milk in low concentrations.	B
Trimethoprim/sulfamethoxazole (Bactrim)	Rats	Teratogenic effects, cleft palate at high doses.	Congenital, cardiovascular defects. Jaundice, hemolytic anemia, kernicterus, hyperbilirubinemia when exposed near term.	Excreted into milk in moderate concentrations. Avoid with premature, neonates, hyperbilirubinemic.	C or D (if near term)
Vancomycin (Vancocin)	Rats, rabbits	No adverse effects at human doses.	No teratogenic effects, conflicting reports of hearing loss in neonates exposed in utero.	Excreted into milk in high concentrations, not absorbed orally so low risk of systemic effects.	B

*Presence of antibiotics in milk can modify neonatal bowel flora, have direct effects on neonate, and interfere with culture results.

†Pregnancy risk factors (A, B, C, D, X) are defined in Table 2. Categories A and B have limited fetal risks, and Categories C and D have been associated with adverse effects in either animal or human fetuses. Risk factors and other information summarized from Briggs GG, Freeman RK, Yaffe SJ: *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk* (ed 6). Philadelphia, Lippincott Williams and Wilkins.

clear the infection, others may remain bacteremic for years. In large kennels, testing for this organism is recommended on a routine basis, which may help prevent the further spread of disease. Kennels should only be considered clear of disease if all animals test negative for 3 months. Eradication is difficult and may take 5 to 7 months in closed kennels and may never be achieved in open kennels. Privately owned bitches should be tested before each breeding, and stud dogs annually. Even maiden bitches should be tested before breeding because of the potential for oronasal mucosal transmission.

Although uncommon, *Brucella canis* is also a zoonotic disease, so consultation with owners should include discussion of the human risk for infection, particularly in households where small children, pregnant, or immune-suppressed patients reside. Dogs are a natural reservoir of the organism. *B. canis* can live in areas with high humidity, low temperatures, and no sunlight for long periods of time. It can live in water, aborted fetuses, feces, equipment, and clothing for several months. The most common route of human infection is via aerosolization of contaminated dust or dirt, or direct contact with canine abortion products or infected vaginal discharge via mucous membranes or abraded skin. It may also be transmitted via ingestion from contaminated hands or if an infected dog is allowed to lick around the face or mouth.

Treatment of *Brucella canis* Treatment of *Brucella canis* with antibiotics has not been shown to establish a long-term cure to date in canine patients.⁹² Infected animals should be housed separately, neutered, and given antibiotics to prevent shedding and bacteremia. Protocols that have been used have included minocycline (25 mg/kg orally daily \times 14 days) plus dihydrostreptomycin (5 mg/kg IM twice per day \times 7 days). High-dose enrofloxacin (5 mg/kg orally twice per day) for 4 weeks has also been administered successfully to dogs in one kennel in which 12 dogs were found to be positive for *B. canis* by either blood culture or serology. Results here demonstrated equal efficacy to prior studies using streptomycin combined with tetracycline or minocycline, but had fewer side effects. However, none of the dogs in this study showed symptoms of chronic infection, diskospondylitis, ocular infection, or testicular infection.⁹²⁻⁹⁴ Treatment remains challenging, and close monitoring for relapse is necessary.⁹¹

In humans, most protocols call for at least a month of therapy. Humans with *Brucella* spp including *B. canis* have been successfully treated with gentamicin (initially \times 1-2 weeks) in combination with doxycycline (42 days orally).^{95,96} Clinical resolution of *B. canis* ocular inflammation was noted in one canine case using gentamicin SC, with oral ciprofloxacin and doxycycline. With the addition of rifampin, indirect fluorescent antibody titer was reduced by half, and agar gel immunodiffusion test became negative.⁹⁷ A meta-analysis review of human brucellosis cases suggests that higher relapse occurs without the use of an aminoglycoside, and that gentamicin is not inferior to streptomycin. Doxycycline with rifampin was found to be better than quinolones with rifampin. Combination therapy with 2 or 3 antibiotics was

better than single-agent therapy, particularly if an aminoglycoside was included. Optimal treatment was suggested to be doxycycline-aminoglycoside-rifampin, with the aminoglycosides given for 7 to 14 days and doxycycline-rifampin for 6 to 8 weeks.^{98,99}

Because of the intracellular nature of this organism, and the fact that it can be harbored in pharmacologically difficult areas for drugs to penetrate (prostate), neutering, and, at minimum, a month of enrofloxacin (5 mg/kg orally twice per day), should be administered. Animals should be followed up closely, and if they remain culture or serologically positive, a 1- to 2-week course of an aminoglycoside, along with an antibiotic that penetrates intracellularly (doxycycline) and rifampin, may be an effective cure.

Antifungal Therapy in Pregnancy

Systemic Fungal Infections Fungal infections are not common in immunologically healthy animals, but may be more common in pregnant patients because of their altered immune status. Systemic fungal infections including *Histoplasmosis*, *Blastomycosis*, *Coccidioidomycosis*, *Aspergillus*, *Cryptococcus*, and *Candida* have an increased incidence in human patients during pregnancy and may be seen with higher incidence in pregnant animals.¹⁰⁰⁻¹⁰² In humans, diagnosis of disseminated disease was strongly associated with the trimester of pregnancy: first trimester = 50% of cases, second trimester = 62% of cases, and third trimester = 96% of cases.¹⁰³

Antifungal agents used in the treatment of severe systemic fungal infections include fluconazole, itraconazole, ketoconazole, flucytosine, voriconazole, caspofungin, and potassium iodine. Use of these agents during pregnancy has been evaluated in human and animal studies and associated with a significant risk of teratogenic effects.¹⁰⁰ Studies in mice with single-dose exposures to fluconazole and itraconazole showed teratogenic effects to be both concentration and gestational exposure time dependent.^{104,105} In a recent study evaluating outcomes of 229 pregnant women exposed to itraconazole at different stages during pregnancy, there was no difference in major malformations noted in infants, but the rate of pregnancy loss was higher and birth rates were lower in women exposed to itraconazole.¹⁰⁶ Orally administered ketoconazole and flucytosine have been reported to be teratogenic and embryotoxic in animals, and should not be used during pregnancy.¹⁰⁷ Because of the high risk of significant teratogenic effects to the growing fetuses, these agents are primarily placed in Pregnancy Category C. The triazole derivatives (voriconazole, posaconazole, and ravuconazole) are associated with an even greater teratogenic risk, and are placed in Pregnancy Category D. This chemical class has been found to alter normal hindbrain development, resulting in severe teratogenic effects in rodents.¹⁰⁸

Although amphotericin B has multiple side effects associated with its use (nephrotoxicity, hypersensitivity, fever, hypotension, nausea, vomiting) it is the only antifungal agent that has broad-spectrum coverage for most organisms that

cause life-threatening systemic mycosis and has limited teratogenic risk (Pregnancy Category B).¹⁰⁰ Side effects are significantly improved with the use of liposomal amphotericin B, although it is more expensive. Ideally, liposomal amphotericin B would be the drug of choice to use in pregnant animals with life-threatening fungal infections, if the benefits of treatment outweighed the risks.

Microsporium canis

Aside from systemic fungal infections, many large catteries and shelters have a difficult time managing dermatophytosis. *Microsporium canis* is a zoonotic disease that is easily transmitted and highly contagious. The organisms are extremely difficult to eradicate from the environment and are frequently passed onto litters of infected mothers. Multiple antifungal agents (griseofulvin, lufenuron, terbinafine, and so forth) have been used topically and orally for *Microsporium canis* with often limited benefit.^{109,110} Antifungal agents such as griseofulvin have been noted to be extremely teratogenic in cats, resulting in multiple congenital malformations of the brain, skeletal system, optic nerves, heart, and soft tissue.¹¹¹ The risk of treating a pregnant queen for a nonlife-threatening fungal infection with antifungal agents that are highly teratogenic is not worth the benefits in general.

After parturition, effective management of ringworm includes isolation and treatment of the infected animals, removal of all substrates (toys, scratching posts, grooming instruments), removal of all bedding, carpets, food bowls, and decontaminate with either 1:10 bleach in water or 1% formalin. Other antiseptics are ineffective. Heat sterilization may be effective if temperatures reach 43.3°C (110°F). Sprays, fogs, or rinses with enilconazole may be useful for areas with epidemic ringworm. No treatment is 100% effective, and spontaneous recovery can occur without treatment in about 3 months. The mother can be clipped gently, and a 4% lime sulfur solution can be applied by patting with a gauze pad.¹¹²

Itraconazole (10 mg/kg/d × 21 days) is the oral antifungal agent of choice, but can cause nausea, vomiting, and liver impairment. Dosing should not take place until after weaning, and baseline liver enzymes should be evaluated before therapy. Dosing in kittens is difficult because the commercial capsules are only available in a 100-mg strength. This often results in veterinarians having local pharmacies make flavored suspensions of the drug, which are often not stable or not orally absorbed. The drug is very sensitive to pH changes, and even if a stable preparation is made, its absorption is highly dependent on an acid environment. The commercial capsules have limited absorption unless given with an acidic fluid (juice or colas). A commercial solution (Sporonox Oral Solution; Janssen Pharmaceutica, Beerse, Belgium) is available, which is expensive, well absorbed orally on an empty stomach, and stable. The use of oral itraconazole for 21 days in combination with lime sulfur rinses twice weekly appears to be safe and effective for most cats. For severe infections, treatment may take longer (10-49 days).¹¹³ While no treat-

ment protocols exist for young kittens, only severe infections should be treated.

Anesthetic Use During Pregnancy

Pharmacology Cesarean delivery is often performed as an emergency procedure for dystocia when the animal is often exhausted or debilitated. The goal of anesthesia here is to provide adequate and safe anesthesia for the bitch or queen without significant fetal depression. The physiological changes that occur in pregnancy significantly alter the pharmacology of most anesthetics and must be considered carefully when selecting anesthetics. Most anesthetic drugs diffuse across the placenta into the umbilical circulation. Placental transfer of drugs is dependent on lipid solubility, molecular size (< 500 D), degree of protein binding, ionization, and concentration gradient across the membrane. Drugs with high molecular weight, high protein binding, low lipid solubility, and high ionization have limited penetration across the placenta. In general, most anesthetic agents are highly lipophilic and small in molecular weight. Some neuromuscular-blocking agents are extremely large in molecular weight and may not readily cross the placenta.

Once drugs have crossed the placenta, they pass through the fetal liver, then pass to the fetal vena cava via the ductus venosus, where there is a dilutional effect occurring from blood from the caudal portion of the body. This provides some degree of protection to the fetus to high concentrations of drug. Some drugs such as propofol are metabolized and cleared rapidly from the maternal blood, limiting exposure to the fetus. Other drugs such as glycopyrrolate (an anticholinergic), a highly ionized, quaternary ammonium agent, have limited placental passage in pregnant dogs when compared with atropine.¹¹⁴ The maximum fetal to maternal serum concentration ratio was reported as 1.0 for atropine compared with only 0.04 for glycopyrrolate. In addition, given the same dose of drugs, anticholinergic effects in the bitches were greater with glycopyrrolate than with atropine.¹¹⁴

Alternative Anesthetic Techniques

Techniques including epidural anesthesia have been used to circumvent the use of general anesthesia. An epidural often requires further sedation of animals, but avoids anesthetic exposure of the fetuses. It is inexpensive, produces minimal depression in the newborn, and allows the mother to return to preanesthetic alertness rapidly. Clinical expertise in the administration of an epidural is necessary. Lidocaine 2% without epinephrine is the most common local anesthetic administered. If given as an epidural, neonatal blood concentrations should be minor. Disadvantages of epidural anesthesia include respiratory depression or arrest if the epidural block advances to the anterior thoracic or cervical area. Hypotension, bradycardia, hypothermia, cord laceration, spontaneous movements of the head and front limbs, and difficulty in epidural needle placement can occur. If respiratory problems occur, it may not be possible to intubate the mother

without the use of a general anesthetic. General anesthesia therefore remains the technique of choice.^{115,116} After the epidural, incoordination of the dam can be problematic, contributing to trauma of the neonates if adequate supervision is not performed.

Local anesthetics may be used to “field block” or provide regional anesthetic for the dam when transitioning to inhalant anesthesia.¹¹⁵ Typically, lidocaine (0.5%-1%) without epinephrine is injected SC along the incision site. Dilute 2% lidocaine to 0.5% to 1% with sterile water or normal saline solution. The dose should be kept at a range from 0.9 to 1.5 mg/kg. Large doses given for local infiltration may cause significant depression at delivery. Total doses of lidocaine should never exceed 2.3 mg/kg.

Analgesics

Pregnant patients are highly prone to vomiting and possible aspiration during and after anesthesia. Even if food is withheld for several hours, the bitch's or queen's stomach may not be empty, and ingestion of placental material must be considered if she has already delivered one or more fetuses. In this setting, premedication with a low dose of morphine (0.1-0.2 mg/kg) in dogs or meperidine (1-2 mg/kg) in dogs or cats may not only provide analgesia, but may provoke vomiting and ensure gastric emptying. All opioids cross the placenta and can cause significant central nervous system (CNS) and respiratory depression in neonates. Elimination of opioids can take up to 2 to 6 days in neonates. Fentanyl, meperidine, oxymorphone, and hydromorphone in order of increasing duration can be used depending on the duration of desired action. Buprenorphine is not recommended because of difficulty in reversing this agent. Butorphanol can be administered during surgery to achieve mild to moderate levels of sedation and postsurgery analgesia. If significant CNS and respiratory depression occur, naloxone (0.04 mg/kg SC) may be administered to pups.¹¹⁶

Avoiding the use of tranquilizers, sedatives, and analgesics until the neonates are delivered is ideal; using regional anesthesia and narcotics once the neonates are delivered facilitates analgesia for the dam. Airway management with endotracheal tube placement and caution during recovery should be emphasized.

Gastroprotectants

Aspiration prophylaxis is important before anesthesia during pregnancy, because pregnant patients are more likely to experience symptomatic and silent regurgitation. The administration of opioids can also significantly slow gastric emptying. Metoclopramide (Reglan) is indicated in most animals to increase gastric motility and emptying, without increasing gastric acidity. Metoclopramide acts as a dopamine antagonist and inhibits the chemoreceptor trigger zone. It also has the added benefit of inducing prolactin secretion. Doses of 0.1 to 0.2 mg/kg SC or IM can be administered with an onset of action of 10 to 15 minutes. Although other antiemetics may be effective in the bitch or queen, they should not be

used until after the neonates have been delivered. Inhibitors of gastric acid secretion such as famotidine or ranitidine can also be administered to reduce gastric acid secretion and increase gastric pH.^{116,117}

Anticholinergics

Premedication with anticholinergics is somewhat controversial because of their potential for tachyarrhythmias and production of gastric stasis promoting reflux of gastric contents. Anticholinergics have the advantage of reducing salivation and unavoidable excessive vagal tone with uterine traction. Glycopyrrolate (0.01 mg/kg IM or IV) is often the only premedication advised for cesarean section anesthesia.^{116,117} Glycopyrrolate increases gastric pH, causing a decrease in the severity of esophagitis and aspiration pneumonitis if regurgitation and aspiration of vomitus occur.¹¹⁸ Glycopyrrolate is preferred to atropine because of its limited transplacental passage and resultant effect on fetal heart rate.¹¹⁴

Tranquilizers

Phenothiazines are contraindicated in pregnancy because of significant hypotension and reduced blood flow. Severe fetal CNS depression is also seen after premedication with acepromazine, and there is no specific antagonist for reversal. If sedation is required for fractious dogs or cats, the use of a reversible narcotic is advised. Low doses of acepromazine can also be used postoperatively to calm anxious dams and allow milk let-down; the dose should not exceed 0.01 to 0.02 mg/kg.¹¹⁶ Benzodiazepines (midazolam and diazepam) may smooth induction and recovery from anesthesia, but may also cause profound sedation in neonates. Medetomidine (up to 80 µg/kg) has been used in cats to reduce ketamine requirements (< 2 mg/kg), but is not recommended before delivery of neonates. The effects of medetomidine can be antagonized with atipamezole.¹¹⁷

Inhalation Induction

Before induction, a catheter should be placed and IV infusion of a balanced electrolyte solution begun. Preoxygen should be given via face mask for 3 to 5 minutes before induction to prevent arterial desaturation if apnea occurs. Inhalation induction can be introduced gradually with volatile agents into the gas mixture, but is associated with hypoxemia. Gas anesthetics readily cross the placenta and equilibrate with the maternal system. Neonatal depression is equal to maternal depression. Hypotension, reduced uterine blood flow, and fetal acidosis occur with deep maternal anesthesia. Isoflurane, sevoflurane, or desflurane is preferred over halothane because of the faster induction and recovery. The slower speed of induction with gas anesthetics alone increases the risk of vomiting and aspiration before endotracheal intubation can be achieved. Additionally, hypoxemia occurs with mask induction. For this reason, intravenous

induction with a short-acting agent such as propofol followed by intubation is preferred.

Concentrations of isoflurane, sevoflurane, or desflurane are highly dependent on other agents used for premedication and the degree of nitrous oxide used. Isoflurane and other gas anesthetics should be given at the lowest concentration to maintain maternal consciousness (1%-2%). The minimum alveolar concentration of most volatile anesthetics is reduced by approximately 25% during pregnancy. Nitrous oxide can be used to potentiate the effects of gas anesthetics, but its use could potentially result in diffusion hypoxia of pups, so some authors suggest that if nitrous oxide is used, limit administration to 60% or less and discontinue at least 10 minutes before delivery.¹¹⁹⁻¹²¹ In general, anesthetics can be administered with 100% oxygen. Although a light plane of anesthesia is desired, if it is too light, then maternal stress-induced vasoconstriction can adversely affect placental blood flow and cause more damage.

Intravenous Induction This is considered the favored route of induction for cesarean sections. Induction is best with intravenous propofol. It produces rapid induction of basal narcosis for intubation and inhalation. Propofol (4-6 mg/kg IV) should be administered slowly (> 20 sec) to decrease the incidence of apnea. Supplemental doses can be added (0.5-2.0 mg/kg), but high or prolonged doses may cause depression of the fetuses and metabolic acidosis. The drug crosses the placenta, but is eliminated from the plasma rapidly because of extensive distribution and rapid metabolism. Propofol is metabolized primarily in the liver, but extra hepatic metabolism also occurs. It is therefore considered the drug of choice because of rapid recovery. Care should be taken when administering propofol to cats. Only benzyl alcohol-free products should be administered to cats because of its extreme toxicity in cats.

Recent studies comparing the use of propofol with general anesthesia techniques in companion animal cesarean sections demonstrate that propofol followed by isoflurane anesthesia is superior to anesthesia with thiopental.¹²² Administration of propofol IV followed with isoflurane was also found to have increased survival among pups, increased vigor, and increased vocalization.^{123,124}

The above information pertains to anesthetics used for cesarean section and does not apply necessarily to pregnant animals requiring surgery in the early stages of pregnancy. Here, there is a much greater risk of embryotoxicity and teratogenic risk to the fetuses depending on the stage of pregnancy and the exposure time to the anesthetics. Most induction agents, narcotics, and muscle relaxants are devoid of teratogenic fetal effects. To date, in human medicine, parenteral anesthetics including thiopental, etomidate, and ketamine have not been reported to have any negative effects on fetuses. Nitrous oxide, halothane, and isoflurane have had mixed results, with some evidence demonstrating increased incidence of spontaneous abortions and skeletal defects if first-trimester exposure occurs. Isoflurane does produce a

reduction in fetal cardiac output and redistribution of fetal circulation away from the placenta. Fetal sheep have developed hypercarbic acidosis within 1 hour of 1 minimum alveolar concentration isoflurane anesthesia to the mother.¹²⁵

Postdelivery

Anesthesia may interfere with involution of the uterus. Halothane has been associated with a high incidence of uterine hemorrhage after cesarean section, and drugs may be required to promote involution.¹¹⁷ An ecbolic drug such as oxytocin (0.25-2 IU) or ergometrine (up to 0.5 mg) may be administered after delivery of the pups to promote involution and control uterine hemorrhage.¹¹⁷ Additionally, oxytocin promotes milk let-down. Most drugs penetrate into milk and can affect the neonate if given in a very high dose. Further small doses of opioid analgesics (codeine, morphine, fentanyl) or acepromazine may be administered to maintain pain relief and limit anxiety and stress. Nonsteroidal drugs should not be given because of their potential for inhibiting platelet function and potential bleeding as well as effects on neonatal organ maturation and renal function. Benzodiazepines should also be avoided because of neonatal lethargy, weight loss, and sedation. Patients should be kept on a recovery trolley after surgery, until sternal recumbency, in case vomiting occurs.

Immediately after the delivery, neonates should be placed in a dry, clean, warm towel, and fluids should be cleared from the face and mouth with a small suction bulb. Vigorous rubbing can be used to stimulate breathing. A snugly fitting, small face mask can be used to ventilate neonates. Lung expansion is required for surfactant release. Drugs can be delivered to neonatal animals SC, IM, IV, or intraosseously. Sublingual administration of drugs does not result in predictable absorption and is not advised. Doxapram is only useful if barbiturate anesthesia has resulted in respiratory depression. Atropine is contraindicated because fetal bradycardia is the result of myocardial hypoxemia. Positive-pressure ventilation is essential to improve blood oxygen levels. If pups are depressed from benzodiazepines, flumazenil can be given, or if depressed from opioids, naloxone. Neonates should be weighed and encouraged to nurse as soon as possible. Constant supervision is necessary until the bitch or queen has recovered fully (often > 24 hour). Weighing after initial nursing confirms ingestion of colostrum.

Anthelmintic Use During Pregnancy

The use of anthelmintics during pregnancy and lactation in feline and canine patients is not without risk, but appears to have benefits that may outweigh the risks in environments in which high parasitic burdens are noted. Transplacental and transmammary parasite infections may result in significant morbidity in litters with large parasitic loads. Reduced weight gain, severe microcytic hypochromic anemia, eosinophilia from migrating larvae, elevated liver enzymes, pneumonitis, and environmental contamination are the result of parasitized litters left untreated.^{126,127} Although many studies

have evaluated the efficacy of anthelmintics at reducing worm burdens in puppies and kittens, few studies have been done on pregnant animals. To date, only fenbendazole has a specific claim on the prevention of vertical transmission of parasite infections in dogs or cats.

Despite a vast array of new, highly effective parasitacides and very aggressive protocols for deworming, there remain a number of infections that are still prevalent within breeding environments. In canine patients, *Toxocara canis* (canine roundworms), *Ancylostoma caninum* (canine hookworm), *Giardia*, and *Coccidia* continue to be problematic, particularly among large breeding operations.¹²⁸ In feline patients, *Toxocara cati* (roundworms), *Toxoplasma gondii* (protozoan), and *Coccidia* remain problematic.

Toxocara canis Of all organisms, *Toxocara canis*, the canine roundworm, is the most important infection due to fatalities in pups, reactivated infections in dams, and environmental contamination of a potentially zoonotic organism. The lifecycle of *T. canis* may explain the difficulty in eradicating this organism. Large numbers of eggs are produced by the female worm that, once excreted into the environment, may last for years. The larvae of *T. canis* migrate through tissues and become encysted. By mechanisms believed to be hormonally related in late pregnancy, encysted larvae become reactivated during pregnancy and are passed on either transplacentally (98%) or neonatally, via milk (1.5%).¹²⁹ The lifecycles of *T. cati* and *T. leonina* differ in that either no prenatal infection occurs (*T. cati*), or migration is limited to the intestinal wall (*T. leonina*), so that transplacental or transmammary infection does not occur. Because transplacental passage of feline roundworms (*T. cati*), and their reactivation, is not considered significant, worming kittens rather than the queen may be preferred.

In contrast, prenatal infection of pups with *Toxocara canis* leads to patent infection soon after birth, with adult worms being noted at 2 weeks and a large number of eggs passed into feces starting at 16 days.¹³⁰ Therefore, infected pups may not only place the dam at risk of further infection, but may act as a reservoir for oral infection to other canine and paratenic hosts.¹³¹ Although rare, *T. canis* may also infect humans, resulting in “larva migrans visceralis.” The prevention of *T. canis* prenatal infection is therefore critical from both a veterinary and zoonotic aspect.

Treatment of *Toxocara canis* and *Ancylostoma caninum* during pregnancy Although there are no established anthelmintic protocol recommendations in canine or feline patients during pregnancy and lactation, the studies below indicate that many drugs can be used safely and effectively with few, if any, harmful effects to pups or kittens. The use of these drugs may not only protect the dam from pregnancy-induced reactivation of infections, but also reduce overall morbidity of pups or kittens due to heavy worm burdens and decrease environmental egg contamination.

A variety of anthelmintic agents have been evaluated for

use in the treatment of *Toxocara canis* and *Ancylostoma caninum* infections during pregnancy. These include fenbendazole, albendazole, oxfendazole, doramectin, ivermectin, milbemycin, moxidectin, pyrantel pamoate, piperazine, and selamectin. Comparison between agents is difficult to assess because of varying worm burdens, doses, schedules, and environmental contamination rates. Interestingly, no fetotoxic or teratogenic side effects were noted in any published veterinary study located. In human patients, both albendazole and mebendazole have been placed in Category C. Although both have been administered to human patients throughout pregnancy, without obvious teratogenic effects, a dose of albendazole (10 mg/kg to rats on days 9-11) resulted in a decrease in crown-rump length, an increase in fetal resorptions, and craniofacial skeletal malformations compared with those of controls.¹³² Although first-trimester administration is not advised, either albendazole or mebendazole is considered safe according to labeled directions in late pregnancy.

Fenbendazole

In pregnant feline and canine patients, fenbendazole has been administered orally daily to the pregnant queen or dam, starting in late pregnancy, without harm to the fetuses. Burke and Roberson demonstrated the efficacy of fenbendazole granules (50 mg/kg orally once daily starting at 40 days' gestation through day 14 postpartum) against *Toxocara canis* and *Ancylostoma caninum*.¹³³ This resulted in 89% fewer roundworms and 99% fewer hookworms in pups born to medicated dams. Efficacy was shown to be schedule dependent, such that if treatment was stopped the day of parturition, there was only a 64% reduction in roundworms and an 88% reduction in hookworms. A reduction in hookworm burden (85%) of second litter pups to bitches initially treated with fenbendazole but without further treatment was also noted.¹³³ Albendazole and oxfendazole at doses of 100 mg/kg orally, starting at day 30 of pregnancy through days 12 to 18 after parturition, also appear to prevent *T. canis* infections in pups.^{134,135} Fenbendazole is also highly effective (90%-100%) against *Giardia* at doses normally used to also eliminate roundworms, hookworms, whipworms, and tape worms (50 mg/kg orally \times 3 days; nonpregnant animals). Both albendazole and mebendazole and, potentially, fenbendazole, are excreted into human and animal breast milk (2%-10%), but the negligible bioavailability of the parent drugs suggests that clinically significant amounts do not occur.^{136,137} Ideally, because fenbendazole is labeled for use in pregnancy, this may be the preferred drug in pregnant animals.

Pyrantel Pamoate

Pyrantel pamoate can also be used in pregnant animals, but is not labeled for use. It has been assigned to Category C in humans and does not appear to be teratogenic in either rats or rabbits at oral doses up to 1000 to 3000 mg/kg.¹³⁸ How-

ever, a study looking at pyrantel pamoate (5 mg/kg) and piperazine (100 mg/kg) was less effective against *Toxocara canis* (83.5% and 82.5%, respectively) when compared with fenbendazole.^{133,139} Increased efficacy was noted when directly administered to pups at ages 10, 20, and 30 days (94%-98% efficacy at 35 days).

Ivermectin

Because of the time commitment required in the above worming protocols, large breeding operations have looked for alternative therapies. With the advent of the macrocyclic lactones, several drugs have now been shown to be effective after either injection (ivermectin, doramectin) or topical treatments (selamectin, moxidectin). Treatments using ivermectin or doramectin (1 mg/kg SC on day 30 postconception or on days 40 and 50 postconception) both failed to prevent postnatal infections in pups from either *Toxocara canis* or *Ancylostoma caninum*, suggesting that timing may be critical.^{140,141}

Payne and Ridley demonstrated that treatment with ivermectin (300 µg/kg SC on days 0, 30, and 60 of gestation) significantly reduced *Toxocara canis* worm burden (90%) in pups, and egg production into the environment by 99.8%.¹⁴² An additional injection, 10 days after whelping, was 100% effective in eliminating eggs and adult worms. The injectable cattle solution (Ivomec; Merial Essex, UK) (1% or 10 mg/mL = 10,000 µg/mL) was used off label for this study. The authors suggest that side effects were minimal with this protocol, with injection site irritation after subcutaneous inject being the primary side effect. The authors suggest that the protocol is simple (every 30 days) and inexpensive (65 cents/dose for a 70-lb dog). Ivermectin has been classified as Category C in humans, and the drug crosses into human breast milk. Used inadvertently in 203 first-trimester human pregnancies, there were no adverse sequelae.^{143,144} Ivermectin was shown to only be teratogenic at doses that were maternotoxic in mice, rats, and rabbits.¹⁴⁵

Selamectin

Selamectin is another macrocyclic lactone that is commercially available for dogs as a topical spot-on (Revolution) treatment. Payne-Johnson and coworkers examined the efficacy of the selamectin in pregnant and lactating dogs in the treatment and prevention of *Toxocara canis* and flea (*Ctenocephalides felis*) infestations.¹⁴⁶ Selamectin (6-12 mg/kg) was administered topically to dams at 40 and 10 days before parturition, and 10 and 40 days after parturition. Efficacy of selamectin against naturally acquired *T. canis* infections based on egg counts from dams was 99.7%, compared with vehicle controls. Fecal egg counts in pups were reduced by ≥96% on the 24th and 34th days after birth. Adult worm counts were reduced by 98.2% in pups. Percent reduction in geometric mean flea counts for selamectin-treated dams and pups was ≥99.8% throughout the study. No adverse reactions or mortalities were noted in either the dams or pups during the study. Selamectin was therefore considered safe and effective when administered topically to dams, at a min-

imum dose of 6 mg/kg, at 40 and 10 days before parturition and 10 and 40 days after parturition.

Moxidectin

Another macrocyclic lactone, moxidectin (1 mg/kg SC on day 55 postconception), was reported to have 100% efficacy in dams and pups in the prevention of *Ancylostoma caninum* infections.⁹⁹ To date, this is the only product that can potentially kill the tissue larval stages of infection. Moxidectin (1 mg/kg SC) has also been reported to effectively treat *Toxocara canis* parturition-induced activation when administered on days 40 and 50 postconception.¹²⁶ The drug is widely used in livestock and horses (Cydectin; Quest, Murray, KY) in the United States, and has been used safely in canine and feline patients outside the United States (Japan, Australia, and Canada) for years.

Moxidectin is also available on the US market as Advantage Multi (Bayer Healthcare, Shawnee Mission, KS) as a spot-on containing moxidectin plus imidacloprid for use in cats and dogs. The drug has a very long half-life and large volume of distribution compared with the other macrocyclic lactones and has been used safely as a spot-on in canines in Germany at doses of 2.5 mg/kg.¹⁴⁷ If Advantage Multi proves to be safe in further efficacy studies in pregnant animals, it may be ideal, in that it covers the majority of parasitic infections that are problematic in both feline and canine patients (Table 4).

Feline *Toxoplasma gondii* During Pregnancy

Toxoplasma gondii is a problem in cats if active infection is acquired during pregnancy. The parasite is transmitted transplacentally. Pregnant queens may present with neurological disease and subsequently abort kittens before or after birth. Prevention is preferred to treatment. Breeding cats should not be fed raw meat, particularly pork and lamb, or drink raw milk. Queens should not be allowed to hunt because insects, fish, and earthworms may be carriers. Transmission to humans can occur via oocytes in feces or contaminated soil, although transmission via handling and ingestion of raw meat and milk products is of greater concern. Human females who are infected for the first time during pregnancy are at high risk (30%-40%) of abortion or having children born with severe neurological damage (blindness, mental retardation, and so forth), depending on the gestational age. Therefore, it is suggested that pregnant females avoid changing the litter box, wear rubber gloves while gardening, wash hands after handling cats, and avoid eating or drinking any raw meat or milk products.

Antiviral Therapy Viral infections during pregnancy, including canine distemper and adenoviruses, may result in spontaneous abortions with or without fetal infection. Abortion here is often a result of the bitch's clinical disease. Near-term or newborn pups may also be lost from coronavirus or parvovirus. In nonvaccinated animals, or in those that are

Table 4. Anthelmintic Coverage in Pregnancy and Lactation

Parasite		Products						
		Advantage			Heartgard		Frontline	
Canines	Stage	Multi	Revolution	Sentinel	Plus	Interceptor	Plus	Panacur
Fleas	Adults	X	X				X	
Heartworm	L3/L4	X	X	X	X	X		
Hookworm	Adults	X		X	X	X		X
	L4	X						
Roundworms	Immature	X						
	Adults	X		X	X	X		X
	L4	X						
Whipworms		X		X		X	X	
Ticks				X				X
Ear mites				X				
Giardia								X

Felines		Advantage					Frontline	
		Multi	Revolution	Heartgard	Interceptor	Advantage	Plus	Panacur
Fleas	Adults	X	X			X	X	
Heartworm	L3/L4		X	X	X			X
Hookworm	Adults	X	X	X	X			X
	L4	X						
Roundworms	Immature	X		X				
	Adults	X	X		X			X
	L4	X						
Ticks							X	
Ear Mites		X	X					
Giardia								X

Advantage = imidacloprid, Advantage Multi = imidacloprid/moxidectin, Revolution = selamectin, Sentinel = milbemycin/lufenuron, Heartgard = ivermectin, Heartgard Plus = ivermectin/pyrantel, Interceptor = milbemycin, Frontline plus = fluralaner/methoprene, Panacur = fenbendazole.

infected with a virus for which there is no vaccine available, the infection may result in multiple harmful effects to the fetuses depending on the stage of gestation that the dam becomes infected. In large US breeding operations, in which the majority of dogs are typically vaccinated, many viral infections have largely been eliminated. However, other viruses, such as the canine herpesvirus (CHV), where vaccines are not yet readily available on the US market or those that have no vaccine to date, remain problematic.

Canine Herpesvirus

CHV prevalence in the United States is reported to be between 6% and 13% of dogs, but may be as high as 30% in some Southern states, and in Mexico and South America.¹⁴⁸ The virus is easily killed outside the body with most common disinfecting agents, but can easily be transmitted via inhalation, transplacentally, or via ingestion of contaminated products in the environment.¹⁴⁹ In large breeding operations in which exposure to contaminated biological secretions and tissues is likely, transmission may be very high. Transmission of herpes infection is critical from 3 weeks prewhelping to 3 weeks postwhelping in bitches with no natural immunity.¹⁴⁹

In the bitch, mild respiratory signs can occur, but if the virus crosses the placenta, it may cause fetal death, mummification, absorption, premature birth, weak, nonviable puppies, or neonatal death. Both normal and affected pups may be born in the same litter. Affected pups exhibit signs of viremia at 3 weeks and exhibit anorexia, hypothermia, and often death within 48 hours. On necropsy, the kidneys, liver, lungs, and intestinal mucosa can have petechiation. Inclusion bodies can also be found in affected tissues.¹⁴⁹ Virus isolation or polymerase chain reaction testing are indicated, because gross pathologic changes mimic those associated with bacterial septicemia.

Treatment of neonatal herpes in canine patients has not been well studied. Often, cases will present acutely if a littermate dies. Laboratory confirmation may take days. Supportive care (hydration, nutrition) is the mainstay of treatment; antimicrobial therapy is often presumptive until diagnostics are completed. Pups should be heated to a body core temperature of $\geq 98.6^{\circ}\text{F}$, because the virus is unable to replicate at this temperature. Heating is believed to slow progression of the virus. Hyperimmune serum may help to reduce clinical signs acutely, but it does not prevent latent infections and is

typically not readily available. Antiviral medications may be of some benefit, although much more information is needed here. Acyclovir is the drug of choice in human neonatal herpes-infected patients and has been given orally to pups (20 mg/kg orally every 6 hours \times 7 days) with some success, but remains to be further studied.¹⁵⁰ The drug is commercially available in an intravenous form, and orally as a suspension (200 mg/mL).

Canine Herpesvirus Vaccine Although not yet approved or available in the United States, a killed herpes virus vaccine (Eurican Herpes 205) has been marketed by Merial in the United Kingdom. The vaccine is a glycoprotein subunit vaccine that is aimed at inducing passive protection in pups by active immunization of the pregnant bitch. The subcutaneous vaccine is administered 1 to 2 weeks after mating and again 6 weeks later (1-2 weeks before parturition). Protective levels of antibodies decline rapidly 3 months after the last dose in the dam, so repeat administrations must be done in breeding dams. Drug company-supported trials administering the vaccine to healthy pregnant females demonstrated that pups had much higher rates of survival until 24 days of age after being challenged on day 3 with intranasal live CHV-1.¹⁵¹ However, it appeared protective in most cases; some pups died early from bacterial pneumonia, which the authors did not attribute to viral infection. However, 2 out of 4 of these pups were polymerase chain reaction glycoprotein D positive.

In the same study, a field trial was done with 89 bitches breed in 7 kennels infected with CHV-1. Sixty-one bitches were vaccinated and 28 received placebo. The rates of pregnancy, numbers of stillborn, and weaned pups were compared.¹⁵¹ There was a significant difference in mortality rates of vaccinated versus nonvaccinated pups (11.4% vs 27.7%) as well as weight of pups (123.9 g vs 85 g). However, the rates of stillbirth were similar in vaccinated versus nonvaccinated bitches (12.5.5% vs 15.1%). Although clinical trials have demonstrated efficacy in the number of live pups born, and survival until weaning, further field challenge studies are warranted before the vaccine can be recommended.

Vaccines

Limited information exists on vaccinations during pregnancy and lactation in canine and feline species. In general, vaccinations are placed in Category C in humans because of the unknown or potential concern. Although there are a few vaccines labeled for use in pregnant animals, most are not. Therefore, it is preferred to have all core vaccinations current before breeding. If breeding is planned, then the best time to vaccinate overdue animals, for optimal protection for the offspring, is several weeks before the bitch is bred. Vaccination before breeding in most cases helps assure that by the time whelping occurs, the maternal antibodies will be easily passed onto offspring. The half-life of maternally derived immunoglobulins in neonatal dogs is 9 to 12 weeks for canine distemper and hepatitis, and 10 to

14 weeks for canine parvovirus. In neonatal cats, it is only 4 to 6 weeks for feline coronavirus infection, 6 to 8 weeks for feline leukemia and rhinotracheitis, and 10 to 14 weeks for calicivirus infections.¹⁵²

Immunoglobulin G from breast milk is transported across the intestinal epithelium into the circulation of the neonate primarily over the first 24 hours, but also occurs to a limited degree throughout lactation.¹⁵² The maternal-derived antibodies help to protect the animal from infectious diseases until they begin to wean. Over time, the maternal-derived antibodies decline and the neonate can then begin to produce antibodies on its own. The exact level of circulating maternal antibodies that both protect against disease and block the neonate from producing their own antibodies is unknown, and depends on the immunogenicity of the vaccine antigen.¹⁵²

Unknown Vaccination Status Situations will arise where the vaccine status of the dam is unknown or is actually overdue. Ideally, this must be considered on a case-by-case basis, especially with the risk for potential infections. In general, certain viruses, such as parvovirus, last for years in the soil and without any protection, or low-level protection from maternal antibodies, and young pups may quickly succumb to the virus. Even with early- and high-frequency vaccinations of pups, they are still susceptible before boosters are complete. Ideally, serologic testing of such dams to establish if adequate antibodies are present can be performed. However, one must remember that serologic testing is not always a good indicator of the potential immunity for some viruses and that a low titer might not indicate the dam's ability to mount an anamnestic response once challenged. If the risk of exposure is high (such as in an animal shelter), then vaccination is indicated against potentially fatal diseases (canine and feline distemper, parvovirus). The use of recombinant vaccines is ideal in this scenario. General Vaccine Guidelines for Shelters should be followed here as outlined in the 2006 American Animal Hospital Association Canine Task Force Vaccine Guidelines (www.aahanet.org). Immediate vaccination of all dogs older than 6 weeks with core vaccines (3-4 weeks in cases of disease outbreak) is highly recommended as long as the animal is not sick or under physiologic stress.

Modified Live Vaccines In general, modified live vaccines are safe for most animals, but in the setting of pregnancy, physiologic stress, nutrient deficiencies, altered immune system response, and so forth, there is a greater chance of the "avirulent" modified live virus manifesting in disease. Therefore, vaccines that are modified live (vs killed) are not considered safe during illness in pregnancy. In a sick, pregnant dam, a modified live vaccine may result in fetal malformation, death, infertility, or abortion in the dam.¹⁵² Neonatal infection can also occur from the use of modified live vaccine, canine parvovirus vaccine, or feline parvovirus vaccine in sick puppies or kittens less than 4 to 5 weeks of age.¹⁵² Intranasal vaccines that are live attenuated and given intranasally for respiratory infections (parainfluenza, bordetella) are theoretically con-

sidered safe to administer to pregnant bitches because they replicate locally, but further studies need to confirm this.

Killed Vaccines If necessary, killed vaccines can be given during pregnancy. Typically, killed vaccines are less effective than the modified live vaccines, but remain an effective means of prophylaxis in immune-compromised or pregnant animals. A number of killed (inactivated) parvovirus vaccines that are currently recommended for use in pregnancy include: Parvocine (BioCor, Yardley, PA), Performer (Agri Labs, Central Hawkes Bay, New Zealand), Vanguard (Pfizer, New York, NY), ImunoVax (RXV, Memphis, TN) and Canlan (FD, Fort Dodge, IA). Killed vaccines do not replicate in the bitch like the modified live vaccine viruses, but often contain a large amount of reactive adjuvants. This increases the risk of allergic reactions, including anaphylaxis. Although uncommon in a pregnant animal, any sudden cardiovascular collapse or alteration of blood pressure can potentially result in death of the bitch or her fetuses.

Timing in Vaccines Because vaccines take approximately 2 to 4 weeks to produce maternal antibodies, and it is important to have antibodies pass through the mother's colostrum in the first 24 hours after whelping, vaccination must take place >2 weeks before whelping to provide protection to the neonates during lactation. Vaccination of the mother during lactation will not provide protection to pups or kittens, but will not harm them. For neonates unable to nurse, removed from the mother, or of unknown maternal background, where colostrum ingestion may have been limited, immune serum should be given (oral if within the first 48 hours of life, parenterally if > 48 hours of age); this permits vaccinations to be initiated at the routine age (6 weeks). Boosters should be continued with modified live vaccinations every 3 to 4 weeks until the animals are 15 to 16 weeks old.¹⁵²

When pregnant animals are vaccinated during late pregnancy, there will be high levels of maternal antibodies in litter mates that may persist well out to 12 to 14 weeks. This may actually place them at increased risk of infection if vaccinated on a 6- to 8- and 12-week interval, because maternal antibodies may prevent an adequate immune response of pups at such high levels. This, of course, is dependent not only on the vaccine protocol, but also on the type of vaccination used. Ideally, another booster given at 16 to 20 weeks may be required to fully vaccinate pups whelped in this setting.

Postpartum Abnormalities

Agalactia/Galactostasis Agalactia may occur in bitches or queens that do not have mammary gland development (primary), serious concurrent disease (secondary), or in which hormones or drugs have not allowed milk to let down. Galactostasis may occur in animals with inadequate nursing by neonates (small or feeble litters) Agalactia can occur post-esarean section, when elevated epinephrine from stress decreases oxytocin release. Hydration, proper nutrition, and reduction of stress with agents that promote milk let-down are beneficial. Acepromazine (0.1-0.2 mg/kg SC) or metoclo-

pramide (0.1-0.2 mg/kg SC or IM) can be used to promote prolactin release and milk let-down with an onset of action of 10 to 15 minutes. Oxytocin may also be administered starting at 0.5 to 1.0 U every 30 minutes SC, followed by suckling or gentle stripping of the glands. Intranasal oxytocin spray (Syntocinon) administered as one attenuation into one nostril every 4 to 6 hours is expensive, but produces rapid onset in milk let-down (2 minutes).¹⁵² Symptomatic relief may include soaking glands with warm water compresses, analgesics, and encouragement of the pups or kittens to nurse. Pain and anxiety control is essential to reduce maternal stress and allow adequate milk let-down. Galactostasis can proceed to mastitis.

Mastitis Mastitis typically occurs during lactation, but may also occur in late pregnancy or even pseudopregnancy. Most bacterial mastitis cases are due to *Escherichia coli*, although staphylococcal *Streptococcus* spp have also been isolated. In breeding kennels in which perinatal mortality was reported to be high, subclinical mastitis of the bitch, leading to death in newborns, was most frequently associated with *Staphylococcus aureus*, *Streptococci* (type G), and beta-hemolytic *E. coli*.¹⁵³ Single or multiple glands may be affected and can be red, hot, edematous, or firm. Mild cases may be subclinical in the bitch or queen, but can cause failure to thrive in litters. Neonates should be weighed at birth and monitored for appropriate weight gain (10% birth weight/d). Bacterial culture and sensitivity of milk are important, because unusual and resistant organisms are not uncommon.

In human medicine, methicillin-resistant *Staphylococcus aureus* (MRSA) has become more frequently seen in community-acquired mastitis infections.¹⁵⁴ MRSA has also been associated with a higher incidence of necrotizing pneumonia and cutaneous abscesses in humans compared with the methicillin-sensitive strain.¹⁵⁵ Although normally a human organism, MRSA has been isolated with increased frequency in veterinary medicine in horses, cats, and dogs, and should be considered in animals not responding to treatment. *S. aureus* infection may present as gangrenous mastitis with leukocytosis and decreased platelet counts in canines.¹⁵⁶

Staphylococcus intermedius has been shown to experimentally induce mastitis in dogs, resulting in painful, hot, enlarged, edematous glands.¹⁵⁷ However, a retrospective review of canine milk isolates and mortality in pups suggests that although *S. intermedius* has been isolated in canine milk, it does not seem to be a cause of septicemia in neonates.¹⁵⁸ From a broad spectrum of isolates from milk of healthy and diseased bitches, only *Escherichia coli*, *Klebsiella pneumoniae*, and/or B-hemolytic *Streptococcus* spp could be isolated from organs of their septicemia puppies.¹⁵⁸

For mild cases of mastitis, oral antibiotics can be administered that penetrate and concentrate into milk. Because milk is acidic, drugs that weaken bases not only distribute into milk but also get trapped into it. Cephalixin, amoxicillin-clavulanate, or macrolides may be initiated empirically until culture results return.¹⁵² Furthermore, there are many anti-

otics that should be avoided because of neonatal risks if the mother continues to nurse. Drugs including fluoroquinolones, tetracyclines, and chloramphenicol all have unwanted side effects in neonatal or growing animals. At least 2 weeks of antibiotic therapy with warm compressing and frequent milking of all glands is suggested.

In more severe cases of mastitis, fever, shock, sepsis, lethargy, vomiting, and depression may occur. For systemic infections, fluid therapy and intravenous antibiotics are recommended. In this setting, broad-spectrum antibiotics are recommended until culture and sensitivity results are back. Intravenous antibiotics that cover Gram-negative *Escherichia coli* (enrofloxacin, cefotaxime, aminoglycosides) in combination with antibiotics to cover Gram-positive organisms (ampicillin, oxacillin, ticarcillin, cefazolin, and so forth) and anaerobes (ampicillin, metronidazole, or clindamycin) should be initiated empirically. Neonates should be removed and given supplemental artificial milk or be weaned. Neonates should also be prevented from traumatizing glands in cases that develop into abscesses or open wounds. Abscessed glands should be appropriately lanced, drained, flushed, and treated as an open wound. Cabergoline (Dostinex) can be administered at 5 µg/kg daily for 5 to 7 days to suppress lactation and decrease galactostasis in other glands.

Metritis Metritis (acute uterine infection) is a postpartum disorder that can be associated with abortion, fetal infection, retained placentas/fetuses, or infection after delivery from tissue traumatization, dystocia, obstetric manipulation, or ascending infection in an unsanitary environment. Animals developing metritis are typically very ill, febrile, lethargic, and inappetent. A purulent, foul-smelling vulvar discharge that is reddish to chocolate brown occurs. A large, fluid-filled uterus is noted ultrasonographically, and typically there is leukocytosis with a left shift. Culture and sensitivity should be performed on the discharge, which is likely representative of the uterine contents. In most cases, *Escherichia coli* is the most common isolate in infected animals followed by *Staphylococcus intermedius*, beta-hemolytic *Streptococci*, and *Proteus*.^{159,160} Mixed cultures are not uncommon, so that empiric antibiotic coverage must be broad spectrum, keeping in mind nursing neonates. Mastitis and metritis can occur together, suggesting a hematogenous spread.

Intravenous fluid therapy for hydration and intravenous antibiotics can be necessary; however, some dams can be treated on an outpatient basis and remain at home to care for the neonates. Bactericidal antibiotics that cover *Escherichia coli* should be selected until culture and sensitivity results return. These include aminoglycosides, fluoroquinolones, and third-generation cephalosporins. For severely sick animals, coverage for *Staphylococcus* spp, *Streptococcus* spp, and *Proteus* should also be considered. Ampicillin, amoxicillin, cefazolin, or ticarcillin/clavulanic acid may be added to the above choices until culture results return. If the dam is nursing, the choice of antibiotics is limited to ampicillin, amoxicillin, cefazolin, or ticarcillin/clavulanic acid. Once

culture results return, antibiotics should be tailored to the sensitivity of the organism and the safety of the drug to pups if still lactating. Ovariohysterectomy can be indicated if medical management fails. Antibiotic therapy should be continued for at least 10 days if the uterus is removed, or 2 to 4 weeks if it is not.¹⁵²

In addition, oxytocin (0.25-1.0 U in bitches or 0.25-1.0 U in queens, IM) may be administered to help evacuate the uterus if given within 24 hours of parturition; after that time, the uterine receptors for oxytocin are gone. Alternatively, PGF-_{2α} (Lutalyse) at 0.1 to 0.20 mg/kg body weight SC, or synthetic prostaglandin (cloprostenol, 1-2 µg/kg SC every 12-24 hours to effect) can be administered to effect, starting at any time postpartum.⁶²

Male Infertility

Cryptorchidism

There are many factors that may contribute to the etiology of male infertility. In young dogs, bilateral cryptorchidism can occur in dogs from a sex-limited autosomal recessive trait. Unilateral cryptorchids remain fertile. Cryptorchid dogs may also have increased frequencies of other congenital defects (hernias, patellar luxation, and preputial and penile problems). There is also an increased risk of spermatic cord torsion and a much higher risk (9-14 times higher) of testicular neoplasia.¹⁶¹ Therefore, dogs with this condition should not be bred and should undergo bilateral castration. No effective medical therapy is available to induce testicular descent in dogs.

Azoospermia

Azoospermia is a common cause of canine male infertility. Azoospermia can result from pretesticular, testicular, or posttesticular abnormalities. Testicular causes of azoospermia include endocrine disturbances, elevated testicular temperature, prolonged hyperthermia, cryptorchidism, intersexes, testicular hypoplasia, injury, or neoplasia. It is important to rule out inadequate sexual stimulation; this is accomplished by repeat semen collections (1 hour apart) in the presence of an estrual bitch. Carnitine or alkaline phosphatase concentrations (epididymal origin) can be measured in completely aspermic samples to rule out bilateral tubular obstruction versus poor libido. Alkaline phosphatase concentrations in normal dog semen should be >5000 U/L and in obstruction <5000 units/L.^{161,162}

The use of PGF-_{2α} has been evaluated in dogs as a treatment for azoospermia. Kustritz and Hess evaluated the use of PGF-_{2α} (0.1 mg/kg SC) or 0.6 mL of saline solution in 8 dogs administered 15 minutes before collection of semen in the presence or absence of an estrus teaser bitch.¹⁶³ There were significantly ($P = .02$) more spermatozoa in ejaculates collected in dogs given PGF-_{2α} in the presence of a teaser bitch (852 ± 736) versus saline solution without a teaser bitch (371 ± 620), but no significant difference between remaining groups was reported. In the presence of a

teaser bitch, in dogs given saline solution only, results (600 ± 622) were not considered significantly different from the group receiving PGF_{-2 α} . PGF_{-2 α} alone, without a teaser bitch, resulted in sperm counts (556 ± 494) similar to the saline solution control with a teaser bitch. The authors suggest that this may be an additive effect and that the technique may be useful to increase spermatozoa in a single canine ejaculate.¹⁶³

Benign Prostatic Hypertrophy

Bacterial prostatitis, prostatic abscesses, and neoplasia are all significant causes of adult canine male infertility (see below).¹⁶¹ Age-related benign prostatic hypertrophy (BPH) and benign prostatic cysts do not impact fertility. BPH is extremely common in sexually intact male dogs. By the time male dogs reach 5 years of age >80% have histopathologic evidence of BPH. Dihydrotestosterone is believed to stimulate growth in both stromal and glandular prostatic compartments. Both prostatic cysts and abscesses should be ruled out via ultrasound examination, aspiration, and culture of prostatic fluid. Abscesses are a medical and surgical emergency, usually requiring antibiotics, drainage, and potentially treatment of septicemia. Clinically, dogs with prostatitis or prostatic neoplasia can have constipation, strangiuria, dysuria, and pelvic pain. Dogs with BPH can have sanguineous fluid dripping from the urethra, and may have hematuria and hemospermia, but this disease is benign otherwise. The diagnosis of specific prostatic disorders is based on physical examination, history, examination of prostatic fluids/semen, and a transabdominal prostate evaluation with possible aspirate or biopsy if indicated.¹⁶¹

Many agents have been used to treat BPH including estrogenic compounds (estradiol cypionate, diethylstilbestrol) and synthetic progestins (megestrol acetate, medroxyprogesterone). However, these agents are not approved in dogs and are not recommended to treat dogs with BPH because of potential side effects (bone marrow suppression, prostatic metaplasia).¹⁶⁴ The use of GnRH agonists (deslorelin) at doses of 0.5 to 1.0 mg/kg was also effective as long as treatment was continuous, but the drug is no longer currently available on commercial markets. Finasteride, a synthetic 5 alpha-reductase inhibitor used in human medicine, has more recently been evaluated in dogs. At a dose of 5 mg/kg orally for 8 to 53 weeks, the drug decreased serum dihydrotestosterone concentrations to baseline values and decreased prostatic size and semen volume, with no adverse effects on semen quality or testosterone concentrations.^{161,165,166} The drug is not approved in dogs in the United States but was very well tolerated with no adverse effects. A total dose of 5 mg/dog has been effective clinically.

Bacterial Prostatitis

Bacterial infections of the prostate are also common in older intact dogs. It is very rare in castrated dogs.¹⁶⁶ Dogs may have hematuria, hemospermia, or both. Large numbers of leukocytes are found in the last fraction of the ejaculate. Ejaculation can be painful. Pyuria, hematuria, and bacteri-

uria are seen on urinalysis. Cystocentesis with culture and sensitivity should be performed. Multiple bacteria may be cultured including *Escherichia coli* (most common), *Klebsiella*, *Staphylococcus*, *Streptococcus*, *Proteus*, and *Pseudomonas*. Other organisms including *Brucella canis*, *Mycotic* sp, *Mycoplasma* sp, and *Ureaplasma* sp have also been reported.¹⁶¹ Treatment is aimed at the organism recovered, with drugs that can penetrate the prostate. In acute prostatitis, inflammation alters the blood-prostate barrier, allowing most antibiotics to penetrate.

In chronic prostatitis, only highly lipophilic agents including enrofloxacin, chloramphenicol, macrolides, and trimethoprim/sulfamethoxazole (TMS) can cross into the prostate. Typically, enrofloxacin or TMS is given empirically to cover Gram-negative organisms until culture results are known. TMS is sometimes associated with severe side effects (aplastic anemia, keratoconjunctivitis sicca, polyarthritides), particularly when given long term or at high doses. Ciprofloxacin penetrates well into human prostate tissues, but its prostate:blood concentration ratios are not as high as enrofloxacin in dogs. Canine prostatic fluid tends to be more acidic than in humans, so that agents such as fluoroquinolones may be less active.⁶² If a Gram-positive organism is suspected, erythromycin, clindamycin, or trimethoprim can be given empirically. Treatment is long term for up to 4 to 6 weeks.⁶² Castration is also recommended to reduce the risks of future infections and shorten the infection duration. For some infections such as *Brucella canis*, high-dose, long-term enrofloxacin (> 30 days) or multi-drug therapy with an aminoglycoside (2 weeks) in combination with oral doxycycline or minocycline +/- rifampin for an additional 2 weeks (see antibiotic section) is recommended to successfully clear the infection.

Bacterial infections including *Brucella canis* can also present as epididymitis or orchitis. Diagnosis is based on complete blood count, urinalysis, urine culture, aspiration of the affected tissue, and brucellosis testing. If a urinary tract infection is present, the organism is assumed to be the cause of the epididymitis or orchitis and is typically *Escherichia coli*. *B. canis* is typically only seen in small numbers in urine and is more easily cultured from semen. If a urinary tract infection is not present and semen cannot be collected, aspiration of the testis or epididymis for culture and sensitivity and cytology can be performed with the patient under anesthesia.⁶² Antibiotics should be based on susceptibility testing. At least 2 to 4 weeks of antibiotic therapy are required. Empiric antibiotics may include enrofloxacin or chloramphenicol.⁶² Cool water soaks and antiinflammatories may be also be indicated. If medical management fails, bilateral orchiectomy is advised. (See previous discussion for therapy of brucellosis.)

Prostatic Neoplasias

Neoplastic disease should also be ruled out before treatment of presumed BPH. Approximately 5% to 7% of dogs with prostatic enlargement have neoplastic disease.^{167,168} The most com-

mon neoplastic disease is adenocarcinoma followed by transitional cell carcinoma. Leiomyosarcoma and hemangiosarcoma have also been reported. Dogs with prostatic neoplasia often present with tenesmus, bloody urethral discharge, hematuria, and strangiuria. Dogs may also present with weight loss, rear-limb weakness, anorexia, and lumbar or abdominal pain. Prostatic adenocarcinoma has often metastasized before diagnosis, and overall prognosis is very poor (1-2 months).¹⁶⁸ Surgery is not typically an option, and radiation results in many debilitating local side effects (colitis, urethritis, cystitis). Chemotherapy has been attempted but has not shown significant benefits.¹⁶¹ Transitional cell carcinoma has a better prognosis if treated with chemotherapy. Most protocols currently use a platinum component (cisplatin or carboplatin) or mitoxantrone along with piroxicam.

Discussion

Therapeutics in companion animal reproduction is an area of veterinary medicine that has made much progress in recent years. Substantial improvement in the diagnosis and treatment of many reproductive diseases has allowed medical management of some diseases, such as pyometras, which at one time could only be managed surgically. Although new therapeutic agents have vastly improved therapeutic outcomes in many areas, lack of product availability, manufacturer discontinuations, and cost have limited progress in other areas. Furthermore, few new drugs have been extensively studied in canine and feline patients, and most are not labeled for reproductive indications. The use of older agents (estrogens, DES, antiestrogens, and so forth) for estrus induction and pregnancy termination are associated with significant risks to the patient and should be avoided. Newer agents are expensive, but demonstrate much safer side effect profiles.

The use of many drugs during pregnancy and lactation is safe, and should not be avoided when the benefits outweigh the risks. Many antibiotics are noted to be safe when administered during pregnancy, whereas most antifungal agents are extremely teratogenic. Advances in anthelmintic treatments and prophylaxis that can be used safely in pregnant animals may improve the health of both the dam and her pups, as well as prevent further environmental contamination. Killed or recombinant vaccinations can be administered during pregnancy, but modified live vaccines should be given only when risk of infectious disease is present (eg, in a shelter). Overall, significant progress has been made in therapeutics in companion animal reproduction, and as product availability increases and costs decline, further advances are expected.

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