Canine Pregnancy

- Physiology & Endocrinology
- Embryonic & Fetal Events
- Diagnosis of Pregnancy
- Care of the Pregnant Bitch
- Diseases associated with Pregnancy
- Pregnancy Loss

Physiology & Endocrinology

- Maintenance of Pregnancy
  - Depends on secretion of P4 thru gestation
    - Canine placenta does not synthesize large amount of P4
    - Uterus have little effect on luteal function → Hysterectomized bitches cycle normally & normal luteal phases
  - Secretion P4 from CL is regulated by both factors
    - Pituitary luteotropic support & Luteolytic (PGF2α)
  - Conc. of PRL increase during the 2nd half diestrus
  - When conc. of P4 are declining & Higher in pregnant bitches

Physiologic & Endocrinologic Events of Pregnancy

- Gestation length varies considerably
  - Depends on the physiologic or behavioral event
  - Can be extremely variable (57-72 D) when based solely on breeding dates
- Parturition occurs approximately
  - 65 days after the LH surge
  - 63 days after ovulation
  - 57 days after the onset of cytologic diestrus

Selected Reproductive Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Days Before (-) or After (+) the LH Surge</th>
<th>Days Before (-) or After (+) Ovulation</th>
<th>Days Before (-) or After (+) the Onset of Cytologic Diestrus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovulation</td>
<td>Variable with regard to clinical signs</td>
<td>Variable with regard to clinical signs</td>
<td>Variable with regard to clinical signs</td>
</tr>
<tr>
<td>Maximal vaginal bleeding</td>
<td>-6 to 15</td>
<td>-15 to 30</td>
<td>-15 to 30</td>
</tr>
<tr>
<td>Ovary size</td>
<td>60-120 mm</td>
<td>60-120 mm</td>
<td>60-120 mm</td>
</tr>
<tr>
<td>Progesterone increases to 1.2 ng/ml</td>
<td>-1 to 0</td>
<td>-1 to 0</td>
<td>-1 to 0</td>
</tr>
<tr>
<td>LH surge</td>
<td>6 to +6</td>
<td>1 to 10</td>
<td>1 to 10</td>
</tr>
<tr>
<td>Matings that result in maximum conception rates</td>
<td>-1 to 0</td>
<td>-2 to 4</td>
<td>-2 to 4</td>
</tr>
<tr>
<td>Initial detection of vaginal masses</td>
<td>-2 to 5</td>
<td>-1 to 3</td>
<td>-1 to 3</td>
</tr>
<tr>
<td>Maximum reproducible vaginal mass</td>
<td>-2 to 5</td>
<td>-1 to 3</td>
<td>-1 to 3</td>
</tr>
<tr>
<td>Determination of gestational age</td>
<td>-2 to 5</td>
<td>-1 to 3</td>
<td>-1 to 3</td>
</tr>
<tr>
<td>Ultrasound detection of amniotic cavities</td>
<td>-16 to 24</td>
<td>+10 to 15</td>
<td>+10 to 15</td>
</tr>
<tr>
<td>Ultrasound detection of placental pole</td>
<td>+10 to 15</td>
<td>+10 to 15</td>
<td>+10 to 15</td>
</tr>
<tr>
<td>Ultrasound detection of fetal heartbeat possible</td>
<td>+10 to 15</td>
<td>+10 to 15</td>
<td>+10 to 15</td>
</tr>
<tr>
<td>Ovulation of pregnancy gonad</td>
<td>+2 to 6</td>
<td>+12 to 15</td>
<td>+12 to 15</td>
</tr>
<tr>
<td>Radiographic detection of radiopaque fetal skull and bone possible</td>
<td>+4 to 6</td>
<td>+4 to 6</td>
<td>+4 to 6</td>
</tr>
<tr>
<td>Progesterone levels in pregnant females</td>
<td>+16 to 39</td>
<td>+16 to 39</td>
<td>+16 to 39</td>
</tr>
</tbody>
</table>

*From Canine and Feline Theriogenology, Johnston SD et al., p. 67, Table 5-1*
<table>
<thead>
<tr>
<th>Days</th>
<th>Events and changes in parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>-21 to -3</td>
<td>Onset of proestrus (heat) - average Day: 9.</td>
</tr>
<tr>
<td>-3 to +6</td>
<td>Onset of estrus behavior - average Day: 1.</td>
</tr>
<tr>
<td>-3 to +8</td>
<td>First acceptance of intromission and mating - average Day 1.</td>
</tr>
<tr>
<td>-3</td>
<td>First day a single mating has significant fertility.</td>
</tr>
<tr>
<td>0</td>
<td>Pre-ovulatory LH surge - time of major increase in serum LH.</td>
</tr>
<tr>
<td>0</td>
<td>Increase in P4 from levels of 0.3 – 0.8 ng to levels of 0.9 to 3.0 ng/ml.</td>
</tr>
<tr>
<td>0</td>
<td>Onset of peak fertility for single matings by high-fertility studs.</td>
</tr>
<tr>
<td>2</td>
<td>Ovulation at 38 - 58 h after LH surge.</td>
</tr>
<tr>
<td>3</td>
<td>Primary oocyte(s) in oviduct. Potential penetration by sperm.</td>
</tr>
<tr>
<td>4</td>
<td>Oocytes presumably still without polar body or female pronucleus.</td>
</tr>
<tr>
<td>5</td>
<td>Maturation in distal oviduct. Fertilization completed if already bred.</td>
</tr>
</tbody>
</table>

### Hormone Profiles

- **Progesterone (P₄)**
- **Prolactin**
- **Estrogens**
- **Relaxin: Diagnosis kit**
Hormone Profiles: P₄

- P₄ conc. are similar in pregnant & non-pregnant
  - Differences is not great enough to provide a diagnostic test
  - Peak conc. occur during early to mid-dIE → Ends when conc. decrease to a level inadequate to support pregnancy (<1-2 ng/ml)
  - Peak conc. of P₄ are variable among bitches (10-70 ng/ml)
- Abrupt decline in P₄ conc. prior to parturition
  - Result from prepartum luteolysis
  - Decline in rectal temp. (1°C) at 8-24 hrs prior to parturition

PRL & Estrogens

- Prolactin
  - Reached peak levels at 8-52 hrs prepartum → Decreased by 36 hrs after the peak → Increasing in response to suckling
- Estrogen
  - Mid diestrus: Higher in non-pregnant bitch
  - Prepartum: Higher in pregnancy

- Cholesterol
  - Progesterone
    - 17α-Hydroxylase
      - 17α-Hydroxyprogesterone
      - Androstenedione
      - Estrogen
Relaxon

- Detected only in pregnant bitches
  - Peaking (4-6 ng/ml) 2-3 wks before parturition ➔ Persisting (0.5-2 ng/ml) for 4-9 wks after whelping
  - Measuring relaxin is suggested as a pregnancy test
  - Not detected until 3rd or 4th wk of pregnancy ➔ Pregnancy can be diagnosed by other means (abdominal palpation, U/S)
  - Might provide useful information: Whether a pregnancy had been established, fetal death & resorption occurred
  - Source of relaxin: Ovary, Mammary gland, Uterus

Implantation & Placenta

- Zonary & Endotheliochorial placentation
  - Implantation occurs 17-22 days after breeding
  - Uterine vessels lie adjacent to the fetal chorion
  - Only 5-10% Ig is transferred to the pup thru the placenta: Most of passive immunity derived thru colostrum
- Placental hematomas or extravasations
  - Blood components & play a role in the nutrition of the fetus
  - Green & brown borders or margins of the zonary placenta
  - Lochia: Observed passing from the vulva at parturition

Embryonic & Fetal Events

- Implantation & Placentation

Canine Placenta

Canine placenta (zonary)
Implantation & Placentation

- Amnion containing the fetus in the allantoic cavity
  - Attached only by the umbilical stalk
  - Pups are sometimes covered with the amnion at birth
  - Pups can suffocate if the amnion lies over the nostrils, mouth
- In the cow, sow, ewe, the amnion is attached to the allantois at several sites and is less likely to cover the fetus at birth

Canine Placenta

Canine Placenta (Zonary)

Diagnosis of Pregnancy

- Abdominal Palpation
- Radiographic Diagnosis
- Ultrasonographic Diagnosis
- Acute-Phase Protein
- Hormone Assay
  - Progesterone, Relaxin

Abdominal Palpation

- Embryos and chorioallantoic vesicles
  - Form a series of ovoid swellings in the early gravid uterus
- After ovulation
  - At 17-20 D: Identified thru abdominal wall as early as
  - At 28-30 D: Most easily & accurately palpated
  - At 35-45 D: These swellings increase in size & elongate, and diffusely enlarging > Become more difficult to identify
- After D 50: The puppies may be palpated directly
Abdominal Palpation

- Usually best to use one hand to palpate most dogs
  - Abdomen is palpated attempting to slip the uterus between the thumb & fingers
  - Smaller dogs: 1 finger can be placed in the rectum & used as a landmark
- May be difficult to determine no. of fetus & viability
  - In some larger bitches or extremely tense abdomens
  - Carrying only 1 pup or a few pups in the cranial abdomen
  - Mammary enlargement may also make palpation difficult

Radiographic Diagnosis

- Radiographic diagnosis
  - Up to 21 D: No signs of uterine enlargement
  - On 21-42 D: Enlarged, fluid-filled horns can be observed
  - On 43-46 D: Fetal calcification of the spine and skull
  - In late pregnancy: Assist in determination of litter size & Size of fetal skulls in relation to the bony maternal birth canal

### Radiographic Detection of Uterine Enlargement & Fetal Mineralization in the Bitch

<table>
<thead>
<tr>
<th>Event</th>
<th>Days after LH surge</th>
<th>Days prepar</th>
<th>Days after 1st mating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bitch 1st radiographed</td>
<td>29 (24-33)</td>
<td>36 (33-41)</td>
<td>30 (26-34)</td>
</tr>
<tr>
<td>Uterus 1st observed</td>
<td>30 (28-34)</td>
<td>35 (32-36)</td>
<td>32 (28-37)</td>
</tr>
<tr>
<td>Circular uterine swellings</td>
<td>35 (31-38)</td>
<td>37 (36-38)</td>
<td>35 (31-38)</td>
</tr>
<tr>
<td>Tubal/ovoid uterine swellings</td>
<td>41 (38-44)</td>
<td>44 (41-45)</td>
<td>43 (40-45)</td>
</tr>
<tr>
<td>Mineralized fetus 1st observed spine, skull, spine</td>
<td>45 (43-46)</td>
<td>48 (45-50)</td>
<td>46 (42-50)</td>
</tr>
<tr>
<td>Scapula, humerus, femur observed</td>
<td>48 (46-51)</td>
<td>52 (49-54)</td>
<td>50 (47-53)</td>
</tr>
<tr>
<td>Radius, ulna, tibia observed</td>
<td>52 (50-55)</td>
<td>55 (52-59)</td>
<td>53 (49-54)</td>
</tr>
<tr>
<td>Pelvis observed</td>
<td>54 (53-57)</td>
<td>57 (54-60)</td>
<td>56 (52-63)</td>
</tr>
<tr>
<td>13 pairs of tibs observed</td>
<td>54 (52-59)</td>
<td>57 (54-60)</td>
<td>56 (52-63)</td>
</tr>
<tr>
<td>Caudal vertebrae, fibula, calcaneous, paws observed</td>
<td>61 (59-64)</td>
<td>63 (60-68)</td>
<td>61 (57-70)</td>
</tr>
<tr>
<td>Teeth observed</td>
<td>61 (58-63)</td>
<td>64 (61-68)</td>
<td>63 (60-68)</td>
</tr>
<tr>
<td>Whelping</td>
<td>65 (64-66)</td>
<td>66 (63-71)</td>
<td>64 (61-72)</td>
</tr>
</tbody>
</table>

*From Canine and Feline Theriogenology, Johnston SD et al., p. 74, Table 5-6*
Ultrasonographic Diagnosis

- Valuable tool for diagnosis pregnancy & viability
- Does not always determine the no. of fetuses accurately
- Of fetal structures, head diameter was the most accurate for estimation of gestational age

<table>
<thead>
<tr>
<th>GA range at 1st U/S detection of selected features in pregnant beagles</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy feature</strong></td>
<td><strong>Days after LH surge</strong></td>
</tr>
<tr>
<td>Gestational sac</td>
<td>20</td>
</tr>
<tr>
<td>Uterine wall</td>
<td>Bipolar shape</td>
</tr>
<tr>
<td>Echogenic gestational sac</td>
<td>20-23</td>
</tr>
<tr>
<td>Placental layers</td>
<td>22-24</td>
</tr>
<tr>
<td>Zoneary placenta</td>
<td>27-30</td>
</tr>
<tr>
<td>Embryo position</td>
<td>Fetal movement</td>
</tr>
<tr>
<td>Depressed to uterine wall</td>
<td>23-25</td>
</tr>
<tr>
<td>Depressed in chorionic cavity</td>
<td>29-33</td>
</tr>
<tr>
<td>Fetal membranes</td>
<td></td>
</tr>
<tr>
<td>Yolk sac membrane</td>
<td>25-28</td>
</tr>
<tr>
<td>Allantoic membrane Tubular shape</td>
<td>27-31</td>
</tr>
<tr>
<td>Yolk sac folded cross section</td>
<td>31-35</td>
</tr>
<tr>
<td>BD Zmm &gt; HD</td>
<td>38-42</td>
</tr>
<tr>
<td>BD</td>
<td>38-42</td>
</tr>
<tr>
<td>CRL &gt; Placenta</td>
<td>40-42</td>
</tr>
<tr>
<td>BD: Outer uterine D &gt; 1:2</td>
<td>63-65</td>
</tr>
</tbody>
</table>

Signalments

- Species: Canine
- Breed: Beagle
- Age: 4 years
- Sex: Female

Normal Female Reproductive tracts

Day 23
Ovaries at Day 23

Day 25

Day 28
U/S Diagnosis: Prediction of Gestational Age

- Formula to predict gestational age (GA) in the dog
  - $< 40 \text{ D: } GA = (6 \times \text{GSD}) + 20 \text{ or } (3 \times \text{CRL}) + 27$
  - $> 40 \text{ D: } GA = (15 \times \text{HD}) + 20 \text{ or } (7 \times \text{HD}) + 29$
    - $(6 \times \text{HD}) + (3 \times \text{BD}) + 30$
  - DBP = 65 - GA

- Formula to predict gestational age (GA) in the cat
  - $> 40 \text{ D: } GA = 25 \times \text{HD} + 3 \text{ or } 11 \times \text{BD} + 21$
  - DBP = 61 - GA
**Acute-Phase Protein**

- Acute phase proteins in the dog include
  - C-reactive protein, Haptoglobin, Acid glycoprotein, Fibrinogen
  - Fibrinogen
    - Increase due to inflammation at the time the embryo is invading the endometrium
    - Rise to greater than 250 mg/dl by day 21-30 of gestation
  - C-reactive protein
    - Increasing at 20-25 D & No CRP was detected in nonmated

**Hormone Assays: P₄**

- P₄ conc. remain high in diestrus regardless of breeding status
- Maintenance of CL occurs
  - Absence of release of effective luteolysin from the uterus
  - Release of luteolysin is seen other species
  - Prolonged luteal phase preclude ability to use P₄ for diagnosis

**Hormone Assays: Relaxin**

- Produced primarily by the canine placenta
  - Nearest thing to a pregnancy-specific hormone
  - Rise significantly compared to non-pregnant dogs, beginning at 20 to 30 days of gestation
  - Peak at mid-gestation
  - ELISA detect as early as 21 days after breeding: False negative may occur when bitches are tested as early as 21 D
Pregnancy Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Optimal time for diagnosing pregnancy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal palpation</td>
<td>28-30 D after ovulation</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>31-33 D after LH surge</td>
<td></td>
</tr>
<tr>
<td>Radiographic diagnosis of calcified fetus</td>
<td>42 D after ovulation</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>&gt; 45 D after LH surge</td>
<td></td>
</tr>
<tr>
<td>U/S diagnosis</td>
<td>&gt; 22 D after ovulation</td>
<td>Can also determine fetal viability</td>
</tr>
<tr>
<td></td>
<td>&gt; 25 D after LH surge</td>
<td></td>
</tr>
<tr>
<td>Acute-phase proteins</td>
<td>&gt; 25 D after ovulation</td>
<td>Not specific</td>
</tr>
<tr>
<td></td>
<td>&gt; 28 D after LH surge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 28 D after mating</td>
<td></td>
</tr>
<tr>
<td>Serum relaxin</td>
<td>&gt; 25 D after ovulation</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>&gt; 28 D after LH surge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 21 D after mating</td>
<td></td>
</tr>
</tbody>
</table>

Care of the Pregnant Bitch

- Proper client education is essential
  - Should receive moderate exercise & good nutrition
  - Vaccines should be avoided: Properly immunized before breeding
- If a previous dystocia has occurred
  - Instruct client on obtaining the bitch’s rectal temp. 2-3 times/D, beginning 54 days after breeding
  - Temperature chart can help predict the onset of parturition

Nutritional Requirements during Pregnancy

- Fetal size rapidly increases during the last 3-4 wks
  - B.W. should increase 25 to 30% by the parturition
  - Amount of food should gradually be increased so that the bitch is receiving 25 to 30% more food by whelping
- Contains higher levels of protein, carbohydrates, & mineral
- Nutrient-dense foods (3.6 kcal/kg) may be necessary in late pregnancy (decreased stomach capacity)
- Severe & life-threatening ketoacidosis
Nutritional Requirements during Pregnancy

Table 5-8. Daily Food Consumption during the Reproductive Cycle and Pregnancy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Medium</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Large</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*From Canine and Feline Theriogenology, Johnston S. et al., p. 79, Fig. 5-8b*

Whelping Area

- Should protect the bitch & pups from injury & disease
  - Excellent sanitation, familiar environment
  - New animals with unknown vaccination or disease should not to introduced
  - Free from drafts, moisture, & excessive cold or heat
- Child’s plastic swimming pool
  - Sides should be high enough to prevent the neonate from escape
  - Bitch should be introduced about a week prior to whelping

Drug Administration

- Should be avoided if possible
  - Physiologic changes occur that affect drug availability: Change of albumin ➔ Drug distribution that is highly protein bound
- Doses may need to be altered
  - Also must be selected with the developing pup
  - Embryos & fetuses becomes an inadvertent recipient
  - Embryotoxic, teratogenic ➔ Abortion, congenital malformation
  - 6-20 D after the LH surge: Critical time for embryotoxicity

Physiologic Alterations in the Pregnant Bitch

- Increased
  - Heart rates, Cardiac output, Blood & Plasma volume, O₂ consumption
  - Gastric emptying time, Intragastic pressure
  - Gastric Cl⁻ & enzyme concentration
  - SGOT (serum glutamic-oxaloacetic transaminase)
  - LDH (lactate dehydrogenase)
  - Sulfobromophthalein (BSP) retention time
  - Renal plasma flow, Glomerular filtration rate (GFR)

Physiologic Alterations in the Pregnant Bitch

- Decreased
  - Packed cell volume (PCV), Hemoglobin conc.
  - Plasma protein conc., Gastric motility, BUN, Creatinine
  - pH of gastric secretions, Plasma cholinesterase conc.
- Unchanged
  - Arterial blood & Central venous pressure, Total lung & vital capacity
  - Functional residual capacity, Na⁺ & water balance

Drug Administration

- Once the placenta has formed
  - Nutrients & drugs must cross the placenta to reach the fetus
  - Numerous factors that govern the transfer of drugs
- Should produce no teratogenic effects
  - Administered for a short time at relatively moderate doses
  - Advice to clients of the potential danger & select drugs
**Drug Administration**

- Factors that influence the transfer of drugs across the placenta
  - Placental blood supply, Age of gestation
  - Placental drug-metabolizing capabilities, Drug size
  - Drug’s lipid solubility, Drug dose, Species of animal
  - Duration of drug exposure, Maternal/fetal pH differential
  - Maternal/fetal drug protein-binding differences,

**Antimicrobial**

- Class A
  - Ampicillin, Amoxicillin, Carbenicillin, Cephalosporins, Clavulanic acid-amoxicillin, Clindamycin, Dicloxacillin, Hetacillin, Oxacillin, Penicillin G (benzyl penicillin), Ticarcillin: Crosses the placenta but has not been shown to be harmful to fetus
  - Erythromycin, Neomycin: Not absorbed sufficiently to cause systemic effects after oral administration

**Drug Administration**

- Papich reported numerous drug used in treating pregnant & classified them on the basis of drug safety
  - Class A: Probably safe for use, although specific studies may not have proved the safety in dogs & cats
  - Class B: Safe if used cautiously; studies in some laboratory animals may have revealed some risk
  - Class C: Have potential risk; should be used cautiously & only as a last resort when the benefit of therapy clearly outweighs
  - Class D: Contraindicated during pregnancy; have been shown to cause congenital malformations or embryotoxicity

**Antimicrobial**

- Class B
  - Sulfonamides: Cross the placenta and have produced congenital malformations in rats & mice, but problem have not been reported in dogs & cats; avoid long-acting sulfonamides
  - Trimethoprim: Teratogenic in rats but probably safe in other species. Folate antagonism & bone marrow depression are possible with prolonged use
  - Trimethoprim-sulfadiazine (T/S), Tylosin

**Antimicrobial**

- Class C
  - Amikacin, Gentamicin, Tobramycin: Aminoglycoside antibiotics easily cross the placenta & may cause 8th nerve toxicity or nephrotoxicity
  - Chloramphenicol: May decrease protein synthesis in fetus, particularly in bone marrow
  - Metronidazole: Teratogenic in laboratory animals, but there is no information for dogs & cats. Avoided during first 3 wks

**Antimicrobial**

- Class D
  - Ciprofloxacin, Enrofloxacin: Quinolones are associated with articular cartilage defects
  - Doxycycline, Tetracycline: Can cause bone & teeth malformations in fetus, toxicity in mother
  - Oxytetracycline: Toxic to fetus & may increase risk of hepatitis in mother
  - Streptomycin: Higher incidence of 8th nerve toxicity than other aminoglycosides
**Antifungal**

- Class A: Miconazole
  - Apparently safe if applied topically
- Class B: Ketoconazole
- Class C: Amphotericin-B
  - No known teratogenic effects, but amphotericin is extremely toxic
- Class D: Griseofulvin
  - Teratogenic in rats: Causes multiple skeletal & brain malformation

**Antiparasitic**

- Class A
  - Diethylcarbamazine: May be given to dogs throughout gestation
- Class B
  - Febendazole, празiquantel, Bunamidine: Safe. no adverse effects in pregnant bitches
  - Ivermectin: Safe. Reproduction studies in dogs, cattle, horses, pigs have not shown adverse effects
- Class C
  - Piperazine, Thenium: Safe. No known contraindications

**Anticancer**

- Class C
  - Doxorubicin hydrochloride, Chlorambucil, Cisplatin*, Cyclophosphamide, Methotrexate, Vinca alkaloids: May malformations in newborn or embryo toxicity *nephrotoxicity
  - Azathioprine: May produce congenital malformation but has been used in pregnant women safely

**Analgesic**

- Class C
  - Acetaminophen, Ibuprofen, Phenylbutazone*: Safety in pregnancy has not been determined (*depress bone marrow)
  - Indomethacin: Can be toxic in adult dog; premature closure of ductus arteriosus if administered near term
  - Aspirin, Salicylates: Embryotoxicity has been seen in lab. animals. Late in pregnancy, pulmonary hypertension and bleeding disorders

**Anesthetic & Preanesthetic**

- Class A
  - Lidocaine: All local anesthetics appear to be safe
  - Nalbuphine: Has been shown to be safe
- Class B
  - Acepromazine: Avoided near term ➔ Neonatal CNS depression
  - Atropine: Cross the placenta ➔ May cause fetal tachycardia
  - Butorphanol, Codeine: Safe for short-term. Neonatal depression
  - Isoflurane, Ketamine: Probably safe. Depression may be seen in neonates after C-section
  - Morphine, Oxy morphine: Neonatal sedation & depression
### Anesthetic & Preanesthetic

- **Class C**
  - Diazepam: Congenital defects in mice, rats, & people
  - Halothane, Methoxyflurane: Depression in neonates after C-sec., Excessive uterine bleeding may be seen when C-sec.
  - Thiamyl, Thioptal: Easily crosses the placenta; all barbiturates produce respiratory depression in fetus; however, thiobarbiturates are not as toxic as pentobarbital
- **Class D**
  - Pentobarbital: High incidence of neonatal mortality

### Gastrointestinal

- **Class A**
  - Antacids
- **Class B**
  - Antiemetics, Cimetidine, Dimethyldihydrate, Diphenoxylate, Laxatives, Metoclopramide, Prochlorperazine, Ranitidine, Sulfasalazine
- **Class C**
  - Diphenoxylate, Loperamide, Methscopolamine

### Cardiovascular

- **Class B**
  - Atropine, Furosemide, Dopamine, Heparin, Hydralazine, Lidocaine, Propranolol, Quinidine, Theophylline
- **Class C**
  - Captopril, Isoproterenol, Nitroglycerin, Nitroprusside, Propanolol, Thiazide diuretics
- **Class D**
  - Warfarin

### Anticonvulsant, Muscle Relaxants

- **Anticonvulsant**
  - Class B: Phenobarbital
  - Class C: Diazepam, Phenytoin, Primidone, Valproic acid
- **Muscle relaxants**
  - Class B: Dimethyltubocurarine, Gallamine, Pancuronium, Succinylcholine
  - Class C: Dantrolene, Methocarbamol

### Endocrine

- **Class B**
  - Thyroxine
- **Class C**
  - Betamethasone, Cortisone, Dexamethasone, Flumethasone, Prednisolone
- **Class D**
  - Diethylstilbestrol (DES), Estradiol cypionate (ECP), Mitotane, Stanozolol, Testosterone

### Diseases Associated w/ or Exacerbated by Pregnancy
Pregnant Toxemia

- Lack of carbohydrates or alteration of its metabolism
  - Inadequate nutrition or not enough carbohydrates
  - Carrying large no. of pups
- Anorexia
  - Temporary anorexia during mid-gestation & labor
  - Anorexia the last 2 wks associated with pregnancy toxemia
- Diagnosis: Urine ketone (↑), no urine glucose, glucose(↓)

Diabetes Mellitus

- Risk for alterations in glucose homeostasis
  - P₄ conc. (↑) → Secretion of GH (↑) → Insulin antagonist → Glucose conc. (↑) → Size of fetus (↑)
  - Exogenous glucose was necessary to maintain euglycemia
- Macrosomia in diabetes bitches
  - Increase of insulin from fetal pancreas by excessive availability of glucose & other metabolic fuels from the diabetic dam
  - Difficulty in maintain the pregnancy by insulin antagonism of P₄

Pyelonephritis

- Result from alterations of the urinary system
  - Hormonal stimulation, urine stasis from increased pressure by distended uterus → Dilation of ureters & collecting tubules
- Clinical signs
  - PU/PD, vomiting, anorexia, unusual gait
  - Some of these signs are also observed in normal pregnant dog
  - Urinalysis should be performed as a screening test

Pregnancy Loss

- May occur at any stage of gestation
  - Embryonic death or resorption
  - Abortion of a live or dead fetus, Stillborn
  - Fetal death, mummification, & retention in the dam’s uterus or peritoneal cavity beyond the normal time of parturition
- Embryonic death & fetus
  - Difficult to determine the pregnancy loss
  - In the 1st ½ of pregnancy, resorption or observed abortion

Definition
**Definition**

- Abortion
  - Occurs in the 2nd 1/2 of pregnancy, clinical signs may be absent
  - Expulsion of a dead conceptus or a living one incapable of independent life
  - If dies in late gestation, fetal emphysema & maceration
  - Macerated fetus ➔ Foul, fetid discharge ➔ Systemically ill

- Stillbirth
  - Reported as 2.2-4.6%, Increase with dystocia
  - Similar incidence in male & female puppy
  - 22.3% (mortality) in bitches who were experiencing dystocia

- Maceration
  - Followed by fetal mummification: Autolytic changes by absorption of placental & fetal fluids
  - Involution of the maternal placenta occurs

**Causes in the Dog**

- Infectious causes
  - Bacteria, Virus, Parasites
- Noninfectious causes
  - Maternal endocrine abnormalities, Exogenous Drugs
- Immunologic, Genetic, Nutritional factors
- Sampling for diagnosis
  - Aborted fetus should be chilled (4°C), but not frozen
  - More than 3 fetuses if several fetuses are aborted
  - Histologic, microbiologic, toxicologic, & chromosomal analysis
  - Serum from dam for serologic testing
- Abortion
  - Occurs in the 2nd 1/2 of pregnancy, clinical signs may be absent
  - Expulsion of a dead conceptus or a living one incapable of independent life
  - If dies in late gestation, fetal emphysema & maceration
  - Macerated fetus ➔ Foul, fetid discharge ➔ Systemically ill

**Samples to submit for diagnosis of fetal loss in dog**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole fetus</td>
<td>Chilled to 4°C and submitted with 24 h of abortion or death</td>
</tr>
<tr>
<td>Fetal tissues</td>
<td>Chilled to 4°C and submitted with 24 h of abortion or death</td>
</tr>
<tr>
<td>Heart, Lung, Liver</td>
<td></td>
</tr>
<tr>
<td>Stomach &amp; contents</td>
<td></td>
</tr>
<tr>
<td>Gut, Kidney, Brain</td>
<td></td>
</tr>
<tr>
<td>Bitch's serum</td>
<td>5 ml for various serologic tests, pending necropsy results of fetus</td>
</tr>
<tr>
<td>Vaginal &amp; uterine discharge</td>
<td>Transport medium will vary depending on suspected pathogen.</td>
</tr>
<tr>
<td>or swab</td>
<td>Contact laboratory for collection and shipping instructions</td>
</tr>
<tr>
<td>Placenta</td>
<td>Chilled to 4°C and submitted with 24 h of abortion or death</td>
</tr>
</tbody>
</table>

**Bacteria**

- *Brucella canis*
- *Campylobacter species*
- *Salmonella species*
- *Escherichia coli*
- *Streptococci*

**Bacteria: Brucella canis**

- Embryonic death, abortions, testicular atrophy
  - Epididymitis, scrotal dermatitis, infertility
  - At 7-9 wks of gestation, prolonged vaginal discharge following abortion, are characteristic of canine brucellosis
  - Abort 2 wks before term or stillborn or weak pup

- Transmission
  - Ingestion of aborted placental tissues & vaginal discharge
  - Mammary secretions, urine, saliva, nasal secretions, semen
  - Via mucosal surfaces: Oral cavity, vagina, conjunctiva
  - Oral infectious dose ➔ Conjunctival (10-100 times)
  - Venereal (Mating; male ➔ female or female ➔ male)
**Brucella canis**

- **Treatments**
  - Expensive, difficult: Not recommended in breeding kennels
  - Antibiotic therapy: Has not been proven to result in cure \(\rightarrow\) Unsuccessful because of the intracellular location of B. canis
  - Eradication of infected animals is suggested
  - Tetracycline hydrochloride (30 mg/kg 2 daily for 28 d) + IM streptomycin (20 mg/kg 1 daily for 14 d): Apparent cure of 94%
  - May relapse after cessation of therapy in next estrus, pregnancy

- **Neutering is recommended**
  - Reproductive tract is reservoir of organisms
  - Remission but not cure
  - Less likely to discharge the large no. of organisms in human infections
  - Follow-up serology for 3 months
  - Euthanasia is considered: Cost, infection to human

**Infectious Causes: Bacteria**

- **Campylobacter species**
  - Majority in sheep & cow, also isolated from aborted pups
  - **Campylobacter jejuni**
  - Abortion approximately 45 D, weak pups (pneumonic lesions)
  - Oral erythromycin (10-15 mg/kg every 8 hrs) or oral neomycin (2.5-5 mg/kg every 12 hrs)
  - Other antibiotics: Tetracycline, chloramphenicol

- **Salmonella species**
  - Mobile, non-spore-forming, G (-), Entrobacteriaceae
  - Transmission: GI route (food, water, fomites)
  - **Salmonella panama**
  - Abortion at 45 days
  - Treatments: Chloramphenicol, T/S, Amoxicillin
  - Prevention: Sanitization

**Infectious Causes: Bacteria**

- **Escherichia coli**
  - Most common bacterium isolated from the vagina
  - Majority in metritis & pyometra
  - Abortion in late gestation with hemorrhagic discharge
  - Produce an endotoxin
  - Medical or surgical treatment are recommended: PGF₂α + Antibiotics or OHE

- **Streptococci**
  - β-Hemolytic S. is common isolate from normal vagina
  - Infertility, uterine disease, abortion, neonatal septicemia
  - Abortions mainly observed during the last 10 d of pregnancy
  - Difficulty in differentiation of normal flora
Viruses

- Canine Herpesvirus (CHV)
- Canine Parvovirus Type 2 (CPV-2)
- Minute Virus of Canines (MVC)
- Canine Distemper Virus (CDV)

Canine Herpesvirus

- Focal necrosis & hemorrhage
  - First reported in 1965 by fatal viral disease in newborn pups
  - Mild or inapparent in adult dog
  - Generally restricted in respiratory & genital tracts in adult
- Transmission
  - Mainly licking (saliva, nasal mucus) + coughing (aerosol)
  - Pregnant bitch is infected ➔ Spread to fetus ➔ Fetal death, mummification, abortion, premature birth, stillbirth

Canine Parvovirus Type 2

- Transplacental infections
- Rarer in dogs than in other species
- Decrease in reproduction efficiency

Minute Virus of Canines (MVC)

- Canine parvovirus type 1
- Transplacental infections
- Embryonic/fetal death approximately 2 wks after exposure
- Dead or drying pups
  - Anasarca, lung consolidation, pneumonitis, myocarditis

Canine Distemper Virus (CDV)

- Transplacental infections
- Abortion, congenital infections
- Abortion can result from
  - Severe systemic effects on bitch or direct infection of placenta or fetuses
  - Viral antigens were not identified in fetus because of maternal systemic effects
Parasites

- Toxoplasma gondii
- Neospora caninum

Toxoplasma gondii

- Transmission thru congenital, ingestion of infected tissues or contaminated food or water
- Less common than other species
- In pregnant bitch:
  - Systemic illness 3-5 D after inoculation with depression, anorexia, diarrhea, nasal discharge
  - Aborted at 4-6 D after inoculation

Neospora caninum

- Recently recognized
  - Have been confused with toxoplasmosis
- Mid-gestation
- Myocarditis was detected in the pup

Maternal Endocrine Abnormalities

- Hypoluteoidism (Inadequate luteal phase)
- Hypothyroidism

Hypoluteoidism

- $P_4 > 1-2$ ng/ml for maintenance of pregnancy
- Resorption, abortion, premature deliveries may be result of inadequate production of $P_4$
- Treatments
  - $P_4$ in oil, 2-3 mg/kg IM every 1-2 D & discontinue injections prior to anticipated whelping
  - Exogenous $P_4$ → Masculinize female
  - Ally-trenbolone (0.088 mg/kg/day Oral) as a $P_4$ agent

Hypothyroidism

- Hypothyroidism
  - In human: stillbirth rate twice
  - Causes: lymphocytic thyroiditis and idiopathic thyroid atrophy
  - Lymphocytic thyroiditis → Lymphocytic orchitis in male
  - Abnormal behavioral estrus & unreceptive to breeding
  - Abortion at midgestation & stillbirths
Genetic Factors

- Mosaicism
  - 177, XXY/156, XYY
  - 78,XY/156,XXYY
  - 78,XX/78,XY
- Monosomy X: 77,XO
- Triploidy: 117, XXX
- Resorption and abortion may occur in early pregnancy

Other Factors

- Exogenous Drugs
- Immunologic Factors
  - Systemic lupus erythematosus (SLE) in human
- Environmental Factors
  - Heavy metal: Mercury, Lead, Zinc & Copper
  - Rubber, Plastics & Solvents
- Nutritional Factors