Noninfectious Spontaneous Pregnancy Loss in Bitches

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ABSTRACT: Spontaneous pregnancy loss in bitches is manifested by resorption during the first half of gestation and usually followed by abortion or stillbirth during the second half. General categories of noninfectious causes of pregnancy loss include chromosomal and developmental abnormalities of fetuses, maternal systemic or endocrine diseases (e.g., hypothyroidism, hypoluteoidism, cystic endometrial hyperplasia), occlusions of the uterus, chemicals, toxins, exogenous drugs, and trauma. This article briefly reviews the most relevant causes of canine noninfectious spontaneous pregnancy loss and provides a systematic approach to this challenging reproductive problem.

Spontaneous pregnancy loss can be caused by an implantation or maintenance failure in an otherwise normal pregnancy. Therefore, pregnancy loss can occur during the embryonal or fetal periods of gestation and may be clinically manifested by resorption, abortion, stillbirth, mummification, or maceration of fetuses. Spontaneous pregnancy loss during the first half of gestation is followed by resorption, whereas interruption during the second half is usually followed by abortion or stillbirth of fetuses. Resorption has minimal clinical signs; conversely, abortion is frequently associated with vaginal discharge.

The incidence of canine resorption or abortion is difficult to assess. Unfortunately, there is no available method for early (i.e., less than 21 days after the luteinizing hormone surge) pregnancy detection in dogs. Therefore, resorption is usually mistaken for infertility. Although abortion is characterized by the expulsion of nonviable or dead fetuses of recognizable size, it is not always accompanied by significant prodromal signs. Moreover, bitches may consume aborted fetuses, making it difficult to determine that an abortion has occurred.

Any agent that adversely affects the conceptus (i.e., fetus and placenta) may cause pregnancy loss. Pathologic etiologies are usually divided into infectious and noninfectious. Noninfectious causes of spontaneous pregnancy loss include genetic abnormalities of fetuses; metabolic or endocrine diseases of bitches; trauma; occlusions of the uterus; exposure to drugs, chemicals, or toxins; and nutritional deficiencies. This article reviews the most relevant causes of canine noninfectious resorption and abortion.

CLINICAL APPROACH
Pregnancy should always be detected by palpation, a relaxin test (Witness
Relaxin, Synbiotics), or ultrasonography as soon as possible after mating. Complete resorption or abortion in bitches should be confirmed by ultrasonography. Signs of resorption include death of all embryos, decreased volume of the embryonal sac, cardiac arrest of fetuses, and homogenization of embryos, whereas abortion is confirmed by expulsion of all fetuses and uterine vacuity determined by ultrasonography.

Once pregnancy loss has been confirmed, the bitch should be evaluated for underlying illness. Any infectious, metabolic, or endocrine disorder can prevent completion of normal pregnancy. Therefore, a thorough physical examination and routine laboratory tests, including a CBC, urinalysis, and serum chemistry profile, should always be conducted. Bitches that have aborted should be hospitalized to permit close observation; complete, specific diagnostic test results should be obtained; and supportive care should be provided, if necessary (Figure 1).

**NONSEXUAL ENDOCRINE DISORDERS**

Although a clear correlation between reproductive problems and hypothyroidism has been found in women, very little about such a correlation has been described in dogs. In women, hypothyroidism has been associated with an increased incidence of abortion, stillbirth, premature delivery, and fetal anomalies. In bitches, hypothyroidism reportedly causes infertility and prolonged anestrus. Abortion at midgestation, stillbirth at term, and mummified fetuses were also described in a colony of hypothyroid borzois.

If, as in women, reproductive disorders represent a unique, initial sign of hypothyroidism in dogs, hypothyroidism should always be considered in the differential diagnosis of canine pregnancy loss, even if typical signs are absent. To avoid a false-positive test result, complete recovery of the dam following an abortion is necessary before assessing thyroid function. Hypothyroidism should be suspected with low total and free serum thyroxine (T₄) concentrations and confirmed by low levels of thyrotropin-stimulating hormone (TSH) and a non-responsive TSH stimulation test. If hypothyroidism is confirmed, treatment with levothyroxine (22 µg/kg PO bid) should be initiated and a cause and effect relationship established during the next estrous cycle.

Through progesterone, pregnancy may induce insulin resistance and carbohydrate intolerance in bitches as well as predispose them to diabetes and abortion. Hypo- and hyperadrenocorticism may also affect fetal and embryonic development in dogs but are usually diseases of older bitches not used for reproduction.

**PROGESTERONE DEFICIENCY**

Because progesterone is essential for maintaining pregnancy, hypoluteoidism is a probable cause of pregnancy loss in bitches. Hypoluteoidism in a pregnant bitch is defined as abnormally low serum progesterone concentrations (<5 ng/ml) with healthy fetuses in the uterus. Care should be taken to distinguish primary luteal insufficiency from secondary corpus luteum lysis due to inflammatory uterine conditions. In the latter case, progesterone supplementation is contraindicated because it would prevent termination of an abnormal pregnancy. Serial fetal ultrasonographic monitoring should be conducted.
Cystic endometrial hyperplasia

Combined lifetime effects of ovarian estrogen and progesterone in bitches frequently result in hyperplasia of the endometrium. Furthermore, the hyperplastic endometrium often becomes cystic, thereby preventing implantation. The only clinical sign of cystic endometrial hyperplasia may be infertility. The ability to depict cystic glandular hyperplasia on an ultrasonogram depends on the size of the endometrial cysts and volume of accumulated fluid. Detecting this condition is successful only in cases of severe endometrial degeneration that leads to the presence of large cysts. Definitive diagnosis is usually based on histopathologic examination. It has been suggested that mibolerone (Cheque Drops, Upjohn) for 6 months may help the uterus rest and improve this disease, but it is no longer available in many countries. Antiprogesterins, such as aglepristone (Alizine, Virbac, France), may also be used to manage endometrial abnormalities, but further clinical and histologic studies are necessary to confirm this.

Bilateral occlusions of the uterus

Congenital, bilateral, segmental aplasia, or any other acquired disease (i.e., infectious, postcesarean, whelping trauma) of the uterine horns can result in occlusion of the tubular female tract, thereby causing a failure in implantation. Diagnosis is difficult and usually requires laparotomy in which the patency can be assessed by injecting saline into the uterus, occluding the body, and observing liquid leak out of the oviducts. Although not easy to perform, hysterography (a radiographic contrast technique in which a radiopaque contrast medium is infused through the cervix into the uterine body) may also be helpful in diagnosing uterine abnormalities. Opening an occluded horn has not been described, and bitches with this condition are usually considered infertile.

Drugs

The developing embryo or fetus becomes an inadvertent recipient of drugs administered to a pregnant animal. Adverse drug effects may be either teratogenic, causing congenital malformation, or embryotoxic, causing abortion or resorption. The conceptus is extremely sensitive to chemical insult early in gestation (i.e., 6 to 20 days after the luteinizing hormone surge) when bathed in uterine fluid. Uterine fluidattains drug concentrations reflective of maternal extracellular fluid, resulting in spontaneous pregnancy loss. Although...
Drugs must cross the placenta once it is formed, the placenta does not represent a real barrier. All drugs administered to the mother can enter fetal circulation. Therefore, administering drugs to pregnant bitches should be avoided, if possible. If a drug must be administered during the critical period, or even during the remainder of the pregnancy, the drug’s safety should be evaluated.

Drugs have been classified according to their safety (see box on this page). There is little information about the safety of drugs in pregnant bitches, however; most of the data have been taken from other species.

### GENETICS

Early abortion in women has been associated with chromosomal abnormalities (i.e., polyploidy, autosomal monosomy, sex chromosome abnormality). Fetal chromosomal abnormalities associated with resorption, abortion, stillbirth, or mummification in bitches include triploidy (XXX) and mosaicism (XXY, XXY). When genetic etiology of pregnancy loss is suspected, aborted fetal tissue should be submitted for karyotyping. Karyotyping of fetuses does not, however, reveal single-gene enzyme defects that may also contribute to fetal loss.

Inbreeding has also been shown to decrease conception rates and the number of puppies born alive. Therefore, evaluation of pedigrees for the inbreeding coefficient may help determine the cause of early abortion. Quantification of inbreeding from mating of closely related individuals can be estimated through the F. Wright coefficient, which expresses the probability of an individual to carry identical genes from a common ancestor and ranges from 0 to 1. Inbreeding is known to reduce reproduction efficiency in many species, including dogs. Breeding programs that include dogs with a coefficient of 0.12 to 0.56 can experience reduced reproductive performance. Breeders should be instructed that inbreeding increases the chances of genetic abnormalities. If repeated unexplained abortion or resorption occurs in a breeding pair, a different bitch or male should be used in future matings.

### NUTRITION

Nutritional causes of pregnancy loss in bitches are rare. Vitamin and mineral deficiencies, such as vitamin A and iodine, do not frequently result in infertility. Manganese deficiency reportedly causes early embryonic death. Nutritional deficits can be ruled out as a cause of pregnancy loss when a bitch has been fed a good-quality, balanced, commercial dog food. Conversely, mineral and vitamin supplementation during pregnancy and, more recently, antioxidants (e.g., butylated hydroxytoluene, butylated hydroxyanisole) in pet food have been suspected of causing reproductive dysfunction.

### MISCELLANEOUS CAUSES

Miscellaneous etiologies, including immunologic and environmental factors (e.g., maternal illness, including heart or renal disease, hypertension, anemia; environmental substances including pollutants, anesthetic gases, heavy metals) have reportedly caused spontaneous abortion in women and need to be studied in dogs. Toxins, such as lead, mercury, pesticides, and nicotine, may also adversely affect fetuses.

Fetuses with congenital malformations severe enough to interfere with their viability or physical well-being are
often spontaneously eliminated. Multiple fetuses would have to be affected for an abortion to occur. Also, hypocalcemia, hypoglycemia, or significant trauma to the abdomen could lead to fetal death and/or abortion.136

CONCLUSION

Canine spontaneous pregnancy loss is one of the most puzzling aspects of small animal reproduction and a diagnostic challenge for practitioners. When infectious causes have been ruled out, definitive diagnosis appears even more difficult. Noninfectious causes of pregnancy loss have been poorly described in the literature (Table 1). Male or female infertility can be distinguished from pregnancy loss by detecting pregnancy early and subsequently detecting failures of implantation or maintenance of gestation. However, the lack of early pregnancy markers in dogs is an important limiting factor. A systematic approach to spontaneous pregnancy loss in bitches is necessary to determine its cause and establish preventive strategies for subsequent pregnancies.

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**ARTICLE #2 CE TEST**

The article you have read qualifies for 1.5 contact hours of Continuing Education Credit from the Auburn University College of Veterinary Medicine. Choose the best answer to each of the following questions; then mark your answers on the postage-paid envelope inserted in *Compendium.*

1. Spontaneous pregnancy termination during the first half of gestation is usually followed by
   a. resorption.
   b. abortion.
   c. cystic endometrial hyperplasia.
   d. mummification of dead fetuses.

2. Abortion is characterized by
   a. retention of macerated fetuses.
   b. expulsion of dead fetuses.
   c. expulsion of fetal membranes.
   d. expulsion of embryos.

3. Complete resorption or abortion is best confirmed by
   a. abdominal palpation.
   b. radiography.
   c. vaginal palpation.
   d. ultrasonography.

4. Pregnancy loss can be distinguished from infertility by
   a. clinical signs.
   b. early pregnancy detection.
   c. ovulation tests.
   d. changes in the duration of the interestrous interval.

5. Hypoluteoidism in a pregnant bitch is characterized by progesterone serum concentrations __________ ng/ml.
   a. greater than 10
   b. less than 5
   c. greater than 5
   d. less than 10

6. When treating hypoluteoidism, progesterone supplementation should be withdrawn
   a. at the moment of parturition.
   b. 2 to 3 days before whelping.
   c. 1 week before whelping.
   d. 2 to 3 days after whelping.

7. The conceptus is extremely sensitive to chemical insults during ________ gestation.
   a. early
   b. mid
   c. late
   d. all of the above

8. Severe cystic endometrial hyperplasia can prevent
   a. fertilization.
   b. implantation.
   c. ovulation.
   d. postimplantation maintenance of pregnancy.

9. Mild cystic endometrial hyperplasia can always be confirmed by
   a. contrast radiography.
   b. histopathology.
   c. typical clinical signs.
   d. ultrasonography.

10. Chromosomal abnormalities in pregnancy loss can be diagnosed by
    a. karyotyping the aborted fetus(es).
    b. histopathologic examination of the aborted fetus(es).
    c. calculating the inbreeding coefficient.
    d. gross gonadal examination of the aborted fetus(es).