

Köpek ve Kedilerde Prenatal Dönemdeki Yavru Kayıpları

Ayşe Merve KÖSE¹

Tevfik TEKELİ¹

¹Selçuk Üniversitesi, Veteriner Fakültesi, Doğum ve Jinekoloji Anabilim Dalı, Konya, Türkiye.

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Özet

Köpek ve kedilerde prenatal gelişim blastogenezisi, embriyonal periyod ve fetal periyodu kapsamaktadır. Yavru kayıpları; embriyonik ölüm, fetal ölüm ya da ölü doğum şeklinde gebeliğin herhangi bir periyodunda oluşabilir. Embriyonik ya da fetal ölümler; yavrunun rezorbsiyonu, mumifikasyonu, maserasyonu ya da abort ile sonuçlanabilir. Bu yavru kayıplarının nedenlerini infeksiyöz veya non-infeksiyöz faktörler oluşturur. İnfeksiyöz nedenler; bakteriler, virüsler ve protozoalar iken non-infeksiyöz faktörler ise hipolüteodizim, travma, ilaçlar ve kromosom bozuklukları gibi nedenlerdir. Kedi ve köpeklerde infertilitenin büyük bir bölümünü bu yavru kayıpları oluşturmaktadır. Bu derleme; köpek ve kedilerde prenatal dönemde şekillenen yavru kayıpları hakkında bilgiler içermektedir.

Anahtar Kelimeler: Kedi, Köpek, Prenatal Dönem, Yavru Kaybı

Loss of Juveniles During Prenatal Period in Dogs and Cats

Abstract

Prenatal growth in dogs and cats consist of blastogenesis, embryonal period and fetal period. Juvenile losses may occur in any period of pregnancy as embryonic death, fetal death or stillbirth. Embryonic or fetal deaths may result in resorption, mummification, maceration or abort. Those juvenile losses are caused by infectious and non-infectious factors. Infectious agents include bacteria, viruses and protozoa or non-infectious causes such as hypoluteoidism, trauma, drugs and chromosome errors. Those losses of juveniles consist of major part of infertility in dogs and cats. Information about juvenile losses during prenatal period in dogs and cats is presented in this compilation.

Key Words: Cat, Dog, Juvenile Loss, Prenatal Period

INTRODUCTION

Prenatal growth in dogs consists of three parts as ovum, embryonal and fetal period. Ovumperiod (2nd - 17th days) is characterized by a blastocyte which is free in uterus horns and moving towards uterus following fertilization. Embryonal period (19th - 35th days) begins with implantation

of blastocyte into uterus and ends with completion of organogenesis. Fetal period (35th day - birth) is the period with fast growth in which the characteristic traits of fetus can be identified (34). Prenatal growth in cats consist of blastogenesis (11st - 17th days), embryonal period (18th - 22nd days) and fetal period (22nd day - birth) (25). Juvenile losses may occur in any period of pregnancy as embryonic

İletişim/Correspondence

Ayşe Merve KÖSE: Selçuk Üniversitesi, Veteriner Fakültesi, Doğum ve Jinekoloji Anabilim Dalı, 42003, Konya-Türkiye, Tel: +905365790702, Fax: +903322416300, E-posta: evrem_85@hotmail.com

death, fetal death or stillbirth (47). Embryonic or fetal deaths may result in resorption, mummification, maceration or abort (18,40). There are infectious or non-infectious reasons among etiology of juvenile losses in dogs and cats (8,42,46,47).

Reasons of Juvenile Losses During Prenatal Period in Dogs

Infectious Reasons

***Brucella canis*:** *Brucella canis* is a small, Gram-negative, intracellular coccobacillus. That infection may cause infertility, early embryonic deaths, fetal resorption and abortions in late period of pregnancy in bitches (18,31,41). The most important clinical signs are abort in late pregnancy (after 45th day) in bitches, epididymitis in male dogs and besides diffuse lymphadenitis, discospondylitis and uveitis in both male dogs and bitches (28,33,48). Although there was no clinical signs prior to abortion, a serosanguinous discharge may be observed for 1-6 weeks following abort (18,28). As the characteristic lesions of generalized bacterial infections, aborted juveniles usually have partial autolysis, subcutaneous edema, and degenerative disorders in liver, spleen, kidney and intestines (33). Definitive diagnosis of *B. Canis* infections are made by microbiological cultures and some serological tests (slide agglutination, tube agglutination, ELISA, agar-gel immunodiffusion) performed on blood, lymph node aspirate, infected tissue or discharge (3,30,41). *B. Canis* is an intracellular microorganism thus the effects of antibiotics are limited and successful treatment cannot be achieved by a single antibiotic. Recommended antibiotics for *B.canis* treatment are minocycline (25 mg/kg SID, 21 days) and dihydrostreptomycin (5mg/kg IM, 7 days) combined, tetracycline (30 mg/kg BID, 21 days) and streptomycin (20 mg/kg IM, 14 days) combined and per os enrofloxacin for 4 weeks (1,33,49).

***Campylobacter*:** It is a Gram-negative bacillus. Its most common species is *Campylobacter jejuni*. *Campylobacter* related abort cases are too rare in dogs (33). *C.jejuni* is a zoonotic pathogen thus it is very important in regard of public health (18,33). Definitive diagnosis can be made by microbiological cultures of fetal or neonatal tissues, contents of stomach and intestines, placenta and vaginal discharges. Culture dependent antibiotic selection is available for the treatment. Per os erythromycin and neomycin may be used in *Campylobacter* treatment. Other antibiotics that reported to be effective are tetracycline and chloramphenicol (24,33).

***Salmonella*:** *Salmonella* is a Gram-negative bacillus. It causes abort, stillbirth and weak neonatals in dogs (18). *Salmonella duesseldorf* is the most frequently isolated type. Besides, *S. enteriditis* and *S. typhimurium* were also encountered during screening studies. Some other researchers report that *S. typhimurium* and *S. anatumun* are most common serotypes. It was reported that *S. panama* was also isolated from abort cases. *Salmonella* is a zoonotic bacteria that causes mild gastrointestinal diseases in human. Definitive diagnosis can be made depending on results of microbiological cultures of fetal tissues and membranes. Recommended antibiotics for Salmonellosis treatment are chloramphenicol, trimethoprim-sulfonamides and amoxicillin (24,33).

***Streptococci*:** It is a Gram-positive micrococcus. Although it does not cause any reproductive problems solely itself, may cause abort, infertility and neonatal septicemia (17,18,24,33). *β -hemolytic streptococci* causing infertility, abort, some uterine diseases and neonatal septicemia (8,43) can be isolated from bitch vagina commonly. *Streptococcus canis* causes abortions and genital tract infections in dog and it is a zoonotic pathogen (33,39).

Escherichia Coli: *Escherichia coli* is the most common bacteria isolated from normal genital tract of bitches and uterus with metritis and pyometra (17,18,43). Endotoxins produced by *E.coli* may cause abort and loss of pregnancy in bitches. Definitive diagnosis is made by bacterial culture (33,39).

Mycoplasma and Ureaplasma: *Mycoplasma* is a Gram-negative bacteria. Mycoplasmas and ureaplasmas cause urea-genital system infections and reproductive disorders such as decreased pregnancy rate, early embryonic death, fetal resorption, abort, stillbirth, weak neonatals and neonatal death in bitches. Its intrauterine inoculations cause purulent endometritis (8,17,18,33).

Canine Herpesvirus: *Canine herpesvirus* (CHV) causes subclinical infections in adult dogs limited with respiratory and genital system (24). Fetal death, mummification, abort, premature birth and stillbirth may occur if pregnant bitches are infected (9,29,39,44). It is reported that latent infections may be present in bitches and male dogs (26,47). Many reproductive disorders such as uterus infections during pregnancy or estrus cycle or reactivation of present latent infection are reported to be related to *Canine herpesvirus* (47).

Canine Distemper Virus: *Canine distemper virus* (CDV) is a morbillivirus. Intrauterine infections are too rare (9). CDV passes placenta and causes abort, stillbirth and congenital infections in neonatals. Abort cases occur due to systemic effect (4,14,18,24).

Canine Parvovirus Type 1 [Minute Virus of Canine (MVC)]: Parenteral introduction of MVC to bitches at first half of the pregnancy causes transplacental infections and resorption of fetus (4,5,24). Besides, pathogenicity of MVC is high in direct inoculation and in case of transplacental

infection between 25th – 35th days of pregnancy (5,8,38). Embryonic / fetal deaths occur approximately after two weeks of amniotic infection. It causes abort or stillbirth in bitch which has infection in last period of the pregnancy (24,38).

Canine Parvovirus Type 2 (CPV-2): Adverse effects of CPV-2 on reproductive performance of bitches are less as compared to those of other viral infections. It was found in a retrospective study on birth records that reproductive efficiency was decreased at first infection with. However, there was no change in reproductive parameters (pregnancy rate, stillbirth rate, number of puppies in a batch) of animals with chronic CPV-2 infection (8,24).

Toxoplasma gondii: *Toxoplasma gondii* is a protozoan (33). It causes congenital juvenile infections and aborts following experimental infections of bitches (14,18). In a trial of experimental infection, systemic symptoms such as depression, anorexia, diarrhea, ocular and nasal discharge were observed in 3-5 days following inoculation of tachyzoites, the infected puppies were rescued after 4-6 following inoculation but died immediately after birth (24,33). Definitive diagnosis of *Toxoplasmosis* is made by histological observation of *T. Gondii* cysts in fetal tissues (33).

Neospora caninum: *Neospora caninum* is a protozoan (24) of which its final host is dog (33). *Neosporosis* causes early fetal death, mummification, fetal resorption and weak neonatals in pregnant bitches (6,8,11,12). However, it is not definite yet if *N. Caninum* is the primary reason of natural aborts of bitches or not (18,24,33). Diagnosis of *N.caninum* is made by histology, immunohistochemistry and molecular techniques, biopsy or post mortem examinations. It is reported that clindamycine and sulphonamides are efficient (33).

Non-Infectious Reasons

Spontaneous pregnancy losses in bitches are fetal resorption at first half and abort or stillbirth in second half of the pregnancy. Usually there are no clinical signs in fetal resorption cases but generally vaginal discharge is present in abort cases (19). Every factor with adverse effects on fetus or placenta may cause pregnancy losses. Non-infectious reasons causing spontaneous pregnancy losses are genetic abnormalities of fetus, metabolic or endocrine diseases of bitches, trauma, uterine problems, drugs, chemicals, toxins or insufficient nutrition (19,26).

Genetic Factors: It was reported that the reason of conceptus deaths with monosomy and trisomy is linked to karyotype abnormalities of bitches. On the other hand, it is also reported that chromosomal abnormalities does not or too rare cause embryonic and fetal deaths (4,36).

Hypoluteodism: Hypoluteodism is due to insufficiency of plasma progesterone concentration (23,33,36). Hypoluteodism is accepted as one of the possible reasons of pregnancy losses because progesterone provides continuousness of pregnancy (7,23,47). Experimental studies show that plasma concentration of progesterone should be 2-3 ng/ml and lower levels for 24-48 hours will cause loss of pregnancy (20,33). The best option accepted in hypoluteodism treatment is daily administration of 0,1 mg/kg *Megestrol acetate* up to 62nd day of pregnancy which is a synthetic progestin (36).

Hypothyroidism: Hypothyroidism is a common disease of dogs causing infertility or fetal losses in bitches however, there is not adequate information available to show its relation with those problems (16,24,36,47).

Other Endocrine Irregularities: Endocrine irregularities such as diabetes mellitus, hypoactivity

or hyperactivity of adrenal glands effects embryos or fetuses during pregnancy (24).

Trauma: Direct uterine trauma in an abdominal operation or indirect trauma of bitch may cause conceptus death due to placental separation (4,36).

Uterine Pathology: The most important and common uterine pathology is cystic endometrial hyperplasia/pyometra complex (17,31,46,47). Disease occurs due to open cervix uteri during estrus, proliferation of vaginal originated bacteria in uterus and inability to eliminate those bacterial contamination during diestrus. The common predisposing factors in bitches are age, progesterone administrations for estrus suppression or estrogen administration for terminating unwanted pregnancies. It is highly common in old bitches and cause infertility (2,14,17,20). Congenital bilateral segmental aplasia or acquired infections of uterine horns or trauma linked obstructions of tubular channels prevent implantation and may cause losses of pregnancy (19).

Drugs: Adverse effects of drugs in pregnant cause congenital malformation of embryo or fetus due to teratogenic effect or cause fetal resorption or abort because of embriyotoxic effect (10,19). The most sensitive period of pregnant bitches against drug administrations is the first month in which organogenesis in progress. Every substance reaches in maternal blood circulation in this period also reaches in endometrium (19,35,37,50). If any drug administration is necessary in early or late pregnancy, the safety of that drug must be assessed (Table 1) (19). Drugs such as aspirin, dexamethasone, bromocriptine, carbaryl, estradiol

Table 1. Classification of drugs according to their safety during pregnancy (19).

Safe	Careful Operational Safety	Risky	Contraindicated	
Amoxicillin	Antiemetics	Amikacin	Prednisolone	Ciprofloxacin
Ampicillin	Atropine	Amphotericin	Primidone	Diethylstilbestrol
Antacids	Cimetidine	Aspirin	Propranolol	Estradiolcypionate
Cephalosporins	Diazepam	Amitraz	Salicylates	Griseofulvin
Clavulanic acid	Diphenhydramine	Betamethasone	Thiacetarsamide	Oxytetracycline
Diethylcarbamazine	Dopamine	Captopril	Tobramycin	Stanozolol
Digitalis	Furosemide	Chloramphenicol	Valproic acid	Streptomycin
Erythromycin	Ketoconazole	Cortisone	Phenylbutazone	Testosterone
Fenbendazole	Metoclopramide	Dexamethasone	Phenytoin	Tetracycline
Ivermectin	Ranitidine	Flumethasone		
Lincomycin	Sulfasalazine	Flunixinmeoglumine		
Mebendazole	Sulfonamides	Gentamicin		
Miconazole	Theophylline	Ibuprofen		
Neomycin	Thyroxine	Indomethacin		
Piperazine	Trimethoprim	Levamisole		
Praziquantel		Metronidazole		
Pyrantel				
Sucralfate				

benzoate, prostaglandin F_{2α} and antiestrogens are defined as most important reasons of embryonic/fetal deaths (35,37).

Nutrition: Nutrition related pregnancy losses in bitches are rare. However, it is reported that insufficiency of vitamin A and iodine results in infertility in most of the cases and lack of manganese causes embryonic deaths. It is also reported that added vitamins and minerals and especially recently added antioxidants cause reproductive dysfunctions (19,23).

Reasons of Prenatal Juvenile Losses in Cats

Infectious Reasons

It is reported that possibility of bacterial infections related pregnancy or juvenile losses are rare in queens kept under appropriate hygienic conditions (27). Although the incidence is not high, if the bacteria commonly present in vaginal flora (*E.coli*, *Staphylococcus sp.*, *Streptococcus sp.*) spread through uterus and cause fetal infection may end in abort (18,24).

Feline Herpes Virus: *Feline herpesvirus* (FHV) is similar to canine herpesvirus (22,47). *Feline herpes*

virus is an alpha virus rhinotracheitis in cats (18,44). It causes aborts in queens as a complication of upper respiratory tract infection (4,9,22,44). Juveniles are also infected during neonatal period in cases without abort (47). The control of the disease is possible by vaccination of queens prior to coitus (27).

Feline Immunodeficiency Virus: *Feline immunodeficiency virus* (FIV) is a lymphovirus similar to Human immunodeficiency virus (HIV) and it is not clear yet if it causes reproductive problems or not. But FIV infected pregnant queens also passes virus to their kittens as reported in some recent researches (47). It is reported that FIV is transmitted both directly (coitus) and indirectly (excretes such as milk, semen) (4,27). Intrauterine infection causes ceased fetal development, abort, stillbirth and live but infected neonatals in pregnant queens (18,21,27).

Feline Infectious Peritonitis Virus: *Feline infectious peritonitis virus* (FIPV) is mutated from *feline enteric corona virus* (FECV) (27,32,47). Reproductive problems, aborts and stillbirths were reported in cats with high FECV titration (27). FIP causes fetal resorption, abort, stillbirth and

endometritis in queens with late pregnancy (14,18). Thus FIP is assumed as main reason of pregnancy losses and kitten deaths in cat shelters. ELISA and Polymerase Chain Reaction (PCR) tests are used in detection of the virus (47). All cats must go through test in every 3-6 months and seropositive ones must be separated from seronegative ones for proper protection (27).

Feline Leukemia Virus: *Feline leukemia virus (FeLV)* is a retrovirus which is common in cat shelters and is transmitted horizontally (27). FeLV causes pregnancy losses by fetal resorption and abortions in pregnant queens (if ELISA or Immunofluorescent Assay (IFA) positive). Although those pregnancy losses seem as happened due to direct infection of fetus, they may also occur because of impaired placental-endometrial integrity by FeLV. For appropriate management of FeLV, all cats must be checked by ELISA, positives must be separated from the rest and negatives must be re-checked by ELISA after 90 days (14,21,47).

Feline Panleukopenia: Panleukopenia or *Feline panleukopenia virus (FPLV)* which is the pathogen of feline distemper is a parvovirus (27). FPLV causes uterine infection, early embryonic death, fetal resorption in early periods and abort, mummified or macerated fetus in later periods of pregnancy. It causes cerebellar hypoplasia or ataxia in kittens in later periods of the pregnancy (4,14). Diagnosis is made by necropsy of fetus/neonatal or virus isolation from uterus or neonatal kittens with ataxia and characteristic symptoms. It is recommended to vaccinate the cats with FPLV prior to parturition (47).

Toxoplasma gondii: *Toxoplasma gondii* is a protozoan of which its final host is cat. Cats are infected by eating animal tissues with cyst. Toxoplasmosis caused reproductive problems are highly common in pregnant queens with

neurological disease, abort or carrying infected kittens via placenta. Protection is important in controlling spread of the disease. Domestic cats must not be allowed to go outside and must not feed by raw meat (13,27).

Non-Infectious Reasons

Cystic Endometrial Hyperplasia / Pyometra Complex: This problem is less common in cats as compared to dogs. Usually no accompanying important hematological or biochemical change is observed together with clinical signs of the disease in queens. Its relation with progesterone is not certain. Because natural progesterone effect is only revoked following ovulation in queens due to provoked ovulation. Bacterial proliferation or cystic endometrial hyperplasia/pyometra complex is developed as a result. Definitive diagnosis is made by uterus biopsy and culture (15,47).

Nutritional Deficiency: The possibility of insufficient nutrition related pregnancy and juvenile losses in cats are low because they are fed by commercial diets. However, vitamin A and taurine insufficiencies must receive attention in pregnant queens (45,47). Lack of vitamin A causes reproductive problems such as anestrus, lower pregnancy rates, early embryonic death, abort and congenital disorders. Queen does not show any clinical symptom in case of taurin insufficiency but still may have some reproductive problems (27,47).

Hypoluteodism: There is no certain evidence about progesterone insufficiency (hypoluteodism) related pregnancy losses in cats which is the hormone provides continuousness of pregnancy. However it is thought that abort cases in queens between 50th – 58th days may be due to hypoluteodism. Natural progesterone administrations are recommended for treatment of hypoluteodism (20,23,47).

Fetotoxic Drugs: Some drugs administered throughout pregnancy and have toxic effects on fetus may cause fetal deaths or damages. Almost all of the drugs pass placental barrier, reach high fetal concentrations and have teratogenic or lethal effects. Major drugs known to make fetal damages and should be avoided during pregnancy are antibiotics (trimethoprim-sulfonamides, quinolones, tetracyclines, gentamicin), antifungal drugs (griseofulvin), antiinflatuars, anesthetics, gastrointestinal drugs (misoprostol), anticonvulsants (phenytoin), steroids (testosterone and estrogen analogues) and vitamin A analogues (isotretinoin). Administration of organophosphorus insecticides, antineoplastic drugs, corticosteroids and modified live vaccines should be avoided in pregnant animals (35,47,49,50).

Genetic Disorders: Chromosomal abnormalities may cause fetal losses. Genetical abnormalities are responsible for 15% of pregnancy losses in all animals including cats. Predisposition for the genetic abnormalities is higher in pregnancies acquired by coitus of individuals from same line (47).

As a conclusion, many factors during pregnancy in dogs and cats can cause pregnancy loss. Pregnancy loss can be due either to infectious or noninfectious causes. The etiology of infectious causes should be investigated. Then, in order to prevent the loss of offspring during pregnancy preventive treatment methods can be used.

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