Thromboembolic disorder in a dog after cesarean surgery

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Abstract
A 3-year female dog (intact primiparous) overweight Labrador Retriever was presented as an emergency (fever, lethargy, and anorexia) patient. Four days earlier, this dog had a dystocia (secondary uterine inertia with stillborn fetus) that was relieved via cesarean surgery. Disseminated intravascular coagulation panel indicated marked increases in D-dimers, increases in partial prothrombin time, and decreases in antithrombin III activity. Abdominal ultrasonography revealed a severely mottled spleen with multifocal infarction. Arterial blood gas analysis indicated increases in alveolar-arterial oxygen gradient. Pulmonary thromboembolism was suspected. Based on the history (peripartum obesity and cesarean delivery) and clinical manifestation, it was hypothesized that the pregnancy-related hypercoagulable state and postpartum period led to the development of venous thromboembolism. To authors' knowledge, this is the first case report of a suspected thromboembolic disorder in a postcesarean dog.

Keywords: Overweight, peripartum, pulmonary embolism, deep vein thrombosis, spleen infarction

Background
Venous thromboembolism (VTE) is a complex disorder that can manifest as pulmonary embolism, deep vein thrombosis or cerebral venous thrombosis. Pregnancy and postpartum period in women are highly associated with increased risk of VTE. Incidence of VTE is higher (5-fold) in pregnant women compared to nonpregnant women. Although pregnancy alone is a risk factor for VTE in women, additional risk factors include age (> 35 years), cesarean delivery, hypertension, heart disease, obesity, and postpartum infection. Furthermore, hypercoagulable state of pregnancy in women is another contributing factor; characterized by increases in coagulation factors (II, VII, VIII, IX, and X), and increases in von Willebrand factor and fibrinogen. Additionally, hormones (estrogen and progesterone) are indirectly responsible for venous thrombosis. Hormonal therapy (estrogen and progesterone) may place women at increased risk for blood clots. Estrogen therapy increases synthesis of coagulation proteins (high risk for venous thrombosis). Progesterone therapy has a relaxing effect on the muscle, and apparent vasodilation leading to disorders of veins (increased capacity) and valves (insufficiency). Apparently, decreased blood vessel tone and an enlarged uterus cause obstructions in iliac vessels leading to venous stasis.

Dogs with immune-mediated hemolytic anemia, sepsis, neoplasia, protein-losing nephropathies, hyperadrenocorticism, or cardiac diseases had VTE. Clinical signs associated with pulmonary embolism included acute onset of hypoxemia and dyspnea. Although deep vein thrombosis present as sudden paralysis and pain associated with rear limbs, in a peripartum patient, exclusion of other conditions (metritis, mastitis, and eclampsia) is critical. Furthermore, diagnosis of laboratory tests (coagulation profiles, D-dimer, and thromboelastography) and diagnostic imaging (thoracic radiography, computed tomography, and abdominal ultrasonography) are necessary for a definitive diagnosis. This case (without sepsis and with no history of cancer or VTE) had cesarean surgery and developed VTE.

Case presentation
A 3-year, overweight female (intact primiparous) Labrador Retriever presented for a dystocia because of secondary uterine inertia. Prior to presentation, 1 stillborn and 3 viable fetuses were delivered. Transabdominal ultrasonography revealed a nonviable fetus (no heartbeat) and all remaining fetuses had normal heart rates (> 220 beats per minute). There was no fetal obstruction (digital examination) within the birth canal and lack of a Ferguson reflex. Emergency cesarean surgery was performed, and 5 puppies (4 viable and 1 stillborn) were delivered. Fetal membranes were removed at surgery and patient was discharged on the same day. Four days after surgery, the patient was admitted through the emergency service for fever (104.3°F), lethargy, and anorexia.

On physical examination (day 4 postpartum), the patient appeared quiet, alert, and responsive, had a heart rate of 136 beats per minute (normal: 80 - 160), a mildly increased respiratory rate of 32 breaths per minute (normal: 15 - 30), a rectal temperature of 102.6°F (normal: 100.5 - 102.5), and a body condition score of 8 out of 9 (43.50 kg). Bronchovesicular sounds were normal in the entire lung field with an increased respiratory effort. Cardiac auscultations were unremarkable. On abdominal palpation, tenderness was noted. Midline incision...
from the surgery appeared to be healing appropriately with no signs of infection (e.g. redness, swelling, or discharge). Mammary glands palpated normally and had normal milk secretion in every teat without signs of redness, discoloration, or pain. Cytology and culture of mammary secretions were not performed. Dog had moderate quantity of normal lochia without foul odor. Vaginal cytology revealed parabasal and intermediate cells with occasional cocci without inflammatory cells. Uterine horns had small quantity of anechoic fluid and mild to moderately thickened walls with normal wall layering (Figure 1) that was interpreted as normal postpartum involution. Blood gas analysis revealed metabolic acidosis (pH 7.27, reference interval (RI) 7.32 - 7.38), hyperchloremia (121 meq/l, RI 110 - 119), normoglycemia (70 mg/dl, RI 60 - 120), and anemia (25%, RI 42 - 57). After triage assessment and fluid treatment, patient remained febrile (103.2 F). Considering the clinical condition, hospitalization for further diagnostic testing was recommended. Neonatal puppies were with the dam (for nursing) and remained healthy during hospitalization.

Additional bloodwork (day 5 postpartum) revealed a normocytic, normochromic, regenerative anemia (hematocrit of 27%, absolute reticulocytes 99.6 x 10^3/μl), leukocytosis with a neutrophilia characterized by a left shift and monocytosis (WBC 43.6 x 10^9/μl, RI 5.7 - 14.2; segmented neutrophils 35.8 x 10^9/μl, RI 2.7 - 9.4; band neutrophils 0.4 x 10^9/μl, RI 0.0 - 0.1; monocytes 2.6 x 10^9/μl, RI 0.1 - 1.3), normal thrombocytes (197 x 10^9/μl, RI 186 - 545), hyperproteinemia (8.0 g/dl, RI 5.9 - 7.8) and hypoalbuminemia (1.9 g/dl, RI 3.2 - 4.1). Ionized calcium concentrations were within normal limits (1.31 meq/l, RI 1.18 - 1.37). Abdominal ultrasonography revealed a mottled spleen with well-demarcated hypoechoic regions that had a ‘lacey’ appearance (Figure 2A) and had no detectable blood flow on color Doppler examination (Figure 2B). Mild pneumoperitoneum and mild uteromegaly (interpreted as normal findings [recent laparotomy and postpartum uterus]) were noted. No other abnormalities (e.g. ischemic lesions [expected with a systemic issue]) were detected. Vascular changes noted via ultrasonography prompted a disseminated intravascular coagulation panel.

There were marked increases in D-dimers (4,965 ng/ml, RI 0 - 575), decreases in antithrombin III activity (50%, RI 65 - 145), and increases in activated prothrombin time (19.6 secs, RI 8.5 - 15.5), consistent with a consumptive coagulopathy. During the second night, patient developed increased respiratory rate and effort (36 breaths per minute) with a corresponding hemoglobin saturation oxygenation of 93% (RI > 95%). An arterial blood gas evaluation revealed an alveolar-arterial oxygen gradient of 36 mm Hg (RI 10 - 25), partial pressure of oxygen 79.3 mm Hg (RI 95 - 109), and partial pressure of carbon dioxide 29 mm Hg (RI 34 - 40). Patient was started on oxygen supplementation. Thoracic radiography revealed mild bronchial wall mineralization with no evidence of pneumonia. Increased alveolar-arterial oxygen gradient with normal thoracic radiographs and consumptive coagulopathy condition, pulmonary thromboembolism was suspected. A focused echocardiogram was performed that revealed trace regurgitation of the mitral and tricuspid valve. There was no evidence of pulmonary hypertension. However, it was apparent that Type IV pulmonary hypertension secondary to systemic inflammation and pyrexia was resolving. Absence of high velocity and tricuspid regurgitation and improving clinical signs...
were interpreted as consistent with a resolving pulmonary thromboembolic event.

**Treatment**

At hospitalization (day 4 postpartum), the patient was given intravenously a balanced electrolyte solution bolus ([5 ml/kg/hour]; Plasma-Lyte A, Baxter Healthcare, Deerfield, IL). Subsequently, intravenous fluid (60 ml/kg/day) therapy was initiated and continued. Additional treatment included intravenous ampicillin/sulbactam (Unasyn®, Pfizer, New York, NY) and maropitant citrate ([1 mg/kg every 24 hours]; Cerenia®, Zoetis, Kalamazoo, MI) for an infection of unknown origin and to prevent emesis. Anticoagulant therapy was strongly considered; however, not instituted.

**Differential diagnosis**

Thromboembolic disease (secondary to postpartum hypercoagulability), infection (following surgery) leading to sepsis, and rickettsial splenopathy with emboli were considered. Mastitis was excluded since mammary glands appeared normal (via inspection and palpation) and because teats expressed milk. Retained fetal membranes and metritis were also excluded as entire fetal membranes were removed at surgery. Furthermore, vaginal discharge and cytology were consistent with normal lochia. Additionally, ionized calcium concentrations were within normal limits throughout hospitalization.

**Outcome**

Patient was discharged on day 6 postpartum with oral amoxicillin/clavulanate ([13.75 mg/kg every 12 hours for 14 days]; Clavamox®, Zoetis) to control fever and leukocytosis. Antimicrobial therapy started during hospitalization and continued. A week later, primary veterinarian evaluated the patient and conducted bloodwork. Results revealed a normocytic, normochromic, regenerative anemia (hematocrit 23.7%, absolute reticulocytes 85.7 x 10³/µl), leukocytosis with a neutrophilia characterized by a left shift and monocytophenia ([WBC 46.53 x 10³/µl [RI 5.05 - 16.76]; segmented neutrophils 32.79 x 10³/µl [RI 2.95 - 11.64]; monocytes 2.91 x 10³/µl [RI 0.16 - 1.23], and normal thrombocyte [209 x 10³/µl [RI 186 - 545]). Patient was continued on oral amoxicillin/clavulanate ([13.75 mg/kg every 12 hours]; Clavamox®, Zoetis) for an additional month. Despite persistent leukocytosis, initial antimicrobial therapy was continued because of marked improvement in clinical signs and for the safety of nursing neonates. Patient was doing well (as per the owner) at 4 months after discharge.

**Discussion**

Cesarean surgery is performed in small animal obstetrics to prevent or to treat dystocia.13,14 Surgical intervention was necessary in ~ 60 - 80% of dystocia cases (58% occurred on an emergency basis).13,15 Cesarean surgery was needed in 48.6% (341/701) dystocia cases.17 Postcesarean problems included systemic disturbances, hemorrhage, and incisional and infectious complications.13 This case was presented 4 days after cesarian surgery for fever and lethargy. Most common postcesarean complications (e.g. peritonitis, incisional infection, metritis, mastitis, eclampsia) were excluded and the animal was suspected to have VTE.

Occurrence of VTE has not been previously reported in a postcesarean dog. Possible causes of VTE include immune-mediated hemolytic anemia, sepsis, neoplasia, protein-losing nephropathies, hyperadrenocorticism, and cardiac diseases.10 This case apparently developed VTE without underlying disease (e.g. primary cardiac or respiratory problems). Furthermore, there was no evidence of peritonitis or sepsis. Blood cultures were not performed and therefore peritonitis or sepsis should be considered as risk factors and included in differential diagnosis.

In companion animals, the correlation of antemortem diagnosis with postmortem confirmation for VTE remains poor.10,11 Alternative diagnostic tests in the investigation for patients presenting with acute onset of tachypnea, hypoxemia (determined by arterial blood gas or pulse oximeter) and absence of evidence of other causes of respiratory distress on thoracic radiographs via an echocardiogram.12 In this case, a disseminated intravascular coagulation panel suggested consumptive coagulopathy. Splenic infarction was incidental and may be unrelated to this case; however, an increase alveolar-arterial gradient with normal thoracic radiographs suggested multiple thromboembolisms that responded to oxygen supplementation. In many cases, animals were treated based on clinical signs compatible with a VTE rather than documentation of the clot.10,11 Despite advanced diagnostic techniques, diagnosis of VTE remains difficult, in human and veterinary medicine. Advanced imaging (e.g. computer tomography angiography) was not pursued in this case because of cost constraints.

Risk factors among women are age (> 35 years), pregnancy, cesarean delivery, hypertension, heart disease, obesity, and postpartum infection.1,5,6 Similarly, this case had increased risk because of cesarean surgery, obesity, and suspected postpartum infection. Possibly, VTE developed because of a pregnancy-related hypercoagulable state. Increased D-dimer concentrations and multifocal infarction in the spleen were noteworthy. Estimation of D-dimers concentrations,18 clinical signs, thoracic radiographs, and arterial blood gas analysis were helpful in reaching a tentative diagnosis. In women, D-dimer was used as an exclusion criteria biomarker for VTE disease; however, its usefulness during pregnancy had limitations because D-dimer concentrations were higher during pregnancy, preeclampsia, infection, malignancy, and in postoperative patients.18

Hypercoagulable state is considered a protective mechanism against pregnancy-related complications. In late pregnant women, marked increases in maternal blood procoagulant activity were characterized by elevation of VII, X, VII, fibrinogen, and von Willebrand factor.1,5,7 Similarly, in pregnant dogs changes in coagulation factors (e.g. increased platelets, increased activity of specific clotting factors VII, VIII, IX, and XI, and increased concentrations of fibrinogen degradation products) were observed.19,20 Additionally, pregnancy-related hypercoagulable state in women has been associated with hormonal changes that protect against premature placental separation and secure hemostasis at parturition.21,22 However, these may not be the case in dogs. For example, increased production of acute-phase reactant proteins and plasma fibrinogen was strongly considered; however, not instituted.
ogen concentrations were caused by a local reaction of the coagulation system, possibly, because of alterations in uterine epithelium and endothelium induced by placentation. In this patient, fibrinogen concentrations were within normal limits during postcesarean hospitalization. In conclusion, a case of apparent thromboembolic disorder was diagnosed in an overweight postcesarean dog. It is suggested that postcesarean dogs with potential risk factors should be closely monitored for clinical signs related to VTE.

Conflict of interest
No conflict of interest or funding sources to report.

Learning points
- Although not common, VTE following cesarean section should be considered as a differential in an overweight postpartum bitch that develops respiratory distress.
- Studies on changes in coagulation factors in dogs at various stages of pregnancy are warranted.

References