Case Report

Uterine prolapse in a mare leading to metritis, systemic inflammatory response syndrome, septic shock and death


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Summary

This Case Report describes severe complications associated with uterine prolapse in a mare. A 6-year-old Trakehner mare was examined for depression, moderate pain and vaginal discharge 3 days after correction of a uterine prolapse. The clinical examination and haematology revealed that the mare had an infection with systemic inflammatory response syndrome and shock. Due to the uncontrollable, persistent pain, an exploratory celiotomy was performed which revealed severe metritis. During anaesthesia, the mare developed severe cardiovascular compromise and died in recovery. In previously reported cases of uterine prolapse in the mare, the authors warn of uterine injury, broad ligament haemorrhage, metritis, endotoxaemia and laminitis but often have a successful outcome with conventional therapy. This case describes a mare that developed severe complications and death after uterine prolapse. Mares with uterine prolapse require appropriate treatment and vigilant monitoring post treatment to prevent life threatening complications.

Introduction

Uterine prolapse is an uncommon occurrence in mares after normal foaling, dystocia or retained fetal membranes (Drost et al. 2002). The previously gravid uterine horn becomes invaginated resulting in uterine eversion and protrusion from the vulva. Treatment involves cleaning and replacing the uterus into the abdomen, a retaining suture in the vulvar lips to prevent reprolapse and systemic medications including antibiotics, anti-inflammatory medications and intravenous fluids. Complications include intra-abdominal haemorrhage from injury to the broad ligaments, metritis and endotoxaemia (LeBlanc 1999). Prognosis is related to the associated damage to the uterus or broad ligaments, such as uterine tears, broad ligament haemorrhage, metritis or development of endometrial damage (Drost et al. 2002). Systemic complications including laminitis and endotoxaemia lead to a worse prognosis (LeBlanc 1999).

Case history

A 6-year-old Trakehner mare presented for evaluation of lethargy, inappetance and mild discomfort of 3 days duration post abortion and uterine prolapse. Three days prior to presentation, the mare aborted a deformed fetus and prolapsed her uterus. The placenta was passed completely. After examination by the referring veterinarian, the uterus was lavaged, lubricated and replaced. A Bühner stitch was placed into the vulva to prevent prolapse. Medical treatment with trimethoprim sulphamethoxazole and flunixin meglumine was instituted. Over the following 3 days, the mare had a decreased appetite, water intake and faecal production. Brown, malodorous urine had been noticed by the owner. After re-evaluation by the referring veterinarian, the mare was referred to the hospital for further examination and treatment.

Clinical findings and diagnosis

On presentation to the hospital, the mare was uncomfortable and febrile with pale, tarry mucous membranes, tachycardia (80 beats/min) and tachypnoea (50 breaths/min). Her gastrointestinal sounds were moderately decreased. A brown, malodorous discharge was present from the vagina and confirmed to be draining from the cervix on a brief vaginal examination. Transrectal and abdominal ultrason sound examinations revealed an enlarged uterus with a moderate amount of fluid in the...
lumen. Due to the large size of the uterus, some portions of the abdomen were difficult to examine. Rectal examination revealed an enlarged uterus without palpable gastrointestinal structures. No specific structures were painful on rectal palpation. Throughout the examination the mare appeared moderately to severely painful with pawing, shifting weight and attempts at recumbency. Due to the mare’s pain, a complete reproductive work-up with uterine lavage and culture was postponed until the mare was stable.

Complete blood count revealed a leucocytosis (31.7 × 10⁹/l [rr 6.0 × 12.0 × 10⁹/l]) from a neutrophilia (22.8 × 10⁹/l [rr 3.0 × 6.0 × 10⁹/l]) with a left shift, a normal haematocrit (39% [rr 32–48%]) and a low normal fibrinogen (1 g/l [rr 1–4 g/l]). Chemistry panel showed a moderately increased creatinine kinase (7418 u/l [rr 103–402 u/l]), elevated BUN (23.88 mmol/l [rr 3.21–8.57 mmol/l]), elevated creatinine (2.33 mmol/l [rr 2.63–3.23 mmol/l]), moderate hyperglycaemia (19.8 mmol/l [rr 6.0–12.0 mmol/l]), mildly increased aspartate aminotransferase (AST) (884 u/l [rr 144–350 u/l]), moderate hyperphosphataemia (4.17 mmol/l [rr 0.68–1.49 mmol/l]), mildly increased hyperkalaemia (4.8 mmol/l [rr 3.5–4.5 mmol/l]), moderate hypochloraemia (118 mmol/l [rr 134–150 mmol/l]), mild hyperkalaemia (4.8 mmol/l [rr 3.5–4.5 mmol/l]), moderate hyperglobulinaemia (62 mmol/l [rr 97–111 mmol/l]), moderate hyperphosphataemia (4.17 mmol/l [rr 0.68–1.49 mmol/l]), severe hyperglycaemia (19.8 mmol/l [rr 4.5–7.05 mmol/l]) and moderate low bicarbonate (9.4 mmol/l [rr 21–30 mmol/l]). There was also hypoprothrombinaemia (4.23 g/l [rr 60–86 g/l]) from hypoaalbuminaemia (16 g/l [rr 27–41 g/l]) and hypoglutathione (26 g/l [rr 28–44 g/l]).

Abdominocentesis produced orange fluid with a mildly increased cell count (13.420 × 10⁹/l) and moderately increased total protein (36 g/l). Most of the cells were moderately to severely degenerate neutrophils but no bacteria were seen. The aerobic culture had no growth and the anaerobic culture had a light growth of Bacteroides fragilis.

Prior to the haematology results during the diagnostic work-up, a 5 l bolus of Plasmalyte¹ was given i.v. to the mare. After the haematology results were available, a 6 l bolus of 0.9% sodium chloride² with 500 ml of 23% calcium gluconate³ added to the saline was administered. Potassium penicillin (Pfizerpen)⁴ (22,000 units/kg bw t.i.v.) and enrofloxacin (Baytril 100)⁵ (7.5 mg/kg bw t.i.v.) were administered. Once placed in a stall, several doses of sedatives/analgesics were administered to prevent the mare from rolling. She received a total of 12.5 mg detomidine (Dormosedan)⁶ i.v., 30 mg butorphanol (Torbugesic)⁷ i.v. and 200 mg xylazine (Anased)⁸ i.v. over a period of 35 min with no effect on her level of pain. Repeat rectal examination revealed only an enlarged uterus.

Due to the severe pain that could not be controlled with medication and no obvious cause present for the pain other than an enlarged uterus, an exploratory celiotomy was performed.

### Treatment

Anesthesia was induced with xylazine (Anased)⁸, butorphanol (Torbugesic)⁷ and ketamine (Ketaset)⁷ and maintained with isoflurane⁹ in 100% oxygen. The mare was positioned in dorsal recumbency during surgery. The pelvic flexure of the large colon was retroflexed 180° so the pelvic flexure was positioned adjacent to the liver and stomach. Moderate bruisiing and petechiation were present at the site of retroflexion, but no fluid, gas or feed distension was present in the large colon. Even with gentle manipulation, petechia developed on the serosal surface of the large colon. Further examination of the abdomen revealed a severely enlarged, thickened uterus firm in texture and mottled in colour with dark red, grey and yellow areas on the serosal surface. Thick, brown, malodorous discharge drained from the vulva during uterine palpation. Throughout surgery the mare became progressively hypotensive despite aggressive crystalloid fluid therapy, calcium administration³ and dobutamine² infusion. The mean arterial pressure was 45 mmHg and only increased to 55 mmHg with treatments. Upon manipulation of the uterus, multiple ventricular premature contractions and runs of ventricular tachycardia developed. Treatment included discontinuation of the isoflurane⁹, 10 l bolus of Plasmalyte¹, increased rate of dobutamine², 10 mg phenylephrine¹⁰ and intermittent assisted ventilation. The cardiovascular status stabilised over the next 20 min with normalisation of the ECG from resolution of the arrhythmias but the mare’s status remained life threatening.

Manipulation of the uterus was discontinued during the episodes of ventricular premature contractions and ventricular tachycardia, and the abdomen was closed due to the deteriorating condition of the mare. Heart rate and rhythm returned to normal but the mare remained hypotensive (45 mmHg). In recovery, administration of fluids, dobutamine², calcium³ and oxygen via endotracheal tube were continued. One litre of 7.2% hypertonic saline (Equi-Phar Equine 7 HSS)¹¹ was also administered i.v. Within 5 min of entering the recovery stall, the mare’s respiratory and heart rate decreased significantly. Ventilation with an oxygen demand valve, chest, compressions and 1 mg epinephrine² was given i.v. twice in an attempt to resuscitate the mare. At this time, the owner authorised euthanasia, but the mare died prior to administration of the euthanasia solution.

### Post mortem findings

Necropsy confirmed an enlarged uterus with severe metritis. The serosal surface of the uterus had multiple 5–7.5 cm haemorrhagic, yellow and slightly raised circular lesions while the uterine mucosa was diffusely grey-green and friable with a thin, brown fibronecrotic membrane. (Fig 1) The spleen was enlarged and congested. A focal area of haemorrhage was found on the mid portion of the
large colon in the same area of the retroflexion that was discovered at surgery. Histopathology on selected tissues revealed diffuse, subacute, marked, necrospurpurative metritis, mild hepatocellular vacuolarisation and mild, multifocal lymphoplasmacytic and eosinophilic enteritis and colitis. Culture of the uterus, spleen, liver and kidney grew Streptococcus equi ssp. zooepidemicus (Group C). Streptococcus bovis was also isolated from uterus and spleen while Enterococcus casseliflavius was found in the spleen and kidney.

Discussion

Uterine prolapse rarely occurs in the mare. In recently reported cases of isolated uterine prolapse without involvement of other abdominal organs, the prognosis has previously been excellent (Chisholm 1981; Schambourg et al. 2004). Uterine prolapse most commonly occurs after parturition. Causes include long mesometrial attachments, retention of the placenta at the ovarian pole of the nongravid horn, increased intra-abdominal pressure from colic, tenesmus, cribbing or dystocia with or without obstetrical manipulations (Roberts 1986; Blanchard et al. 1998). A partial prolapse has been previously reported in a yearling filly without a predisposing cause (Schambourg et al. 2004). Complications of uterine prolapse in the mare include intra-abdominal haemorrhage from injury to the broad ligaments, metritis and endotoxaemia. Treatments involve replacement of the uterus followed by a retaining suture in the vulva, broad spectrum antimicrobial therapy, anti-inflammatory therapy, intravenous fluids and possibly uterine lavage (LeBlanc 1999; Drost et al. 2002).

In our case, severe, necrotising metritis led to SIRS, systemic sepsis and septic shock. These conditions directly resulted in death of the horse, as evidenced by the same organism cultured from different organs. To understand the clinical progression of this case, systemic inflammation will be described. Although it appears that inflammation is a detrimental condition, inflammation is the body's normal response to trauma or infection to contain the infectious agent, repair tissue damage and restore homeostasis (Roy 2004). When local infection is severe, it can release the normal inflammatory mediators systemically and cause systemic illness (SIRS). Systemic inflammatory response syndrome (SIRS) is an acute syndrome that reflects widespread inflammation and is manifested by severe clinical insults manifested by 2 or more of the following conditions: 1) fever or hypothermia, 2) tachycardia, 3) tachypnoea or hypocapnia and 4) leucocytosis, leucocytosis or increased circulating immature neutrophils (Bone et al. 1992). If the systemic inflammation is induced by infection, it is defined as sepsis (Bone et al. 1992).

The main systemic inflammatory mediators involved are interleukin 1 (IL-1), tumour necrosis factor (TNF) and interleukin-6 (IL-6). Tumour necrosis factor is responsible for induction of IL-1 and these 2 molecules act synergistically to produce most of the clinical signs associated with sepsis (Roy 2004). Interleukin 1 and TNF induce the transcription of several genes involved in inflammation, such as genes for other cytokines, phospholipase A2, cyclooxygenase 2, inducible nitric oxide, endothelial adhesion molecules and chemokines. This leads to the production of several important mediators, such as platelet-activating factor, prostaglandin E2, leucotrienes and nitric oxide and to the activation and activity of neutrophils, with the final outcome being inflammation, tissue destruction and loss of function (Dinarello 1997, 2000; Roy 2004). Interleukin 6 is also elevated and is important for the hepatic acute phase response and a growth factor for B cells. It has been shown that IL-6 is elevated in colicky horses with inflammatory or strangulating lesions (Barton and Collatos 1999). It is an accurate predictor for mortality if significantly increased (Barton and Collatos 1999). Further studies on proinflammatory mediators, such as TNF IL-6, interferon γ and IL-2, were found to be significantly higher in nonsurviving septic mice than survivors (Krakauer et al. 2010). Therefore, high levels of inflammation decrease the risk of survival.

In addition to inflammatory mediators, anti-inflammatory mediators are released. These include IL-4, IL-10, IL-11, IL-13, transforming growth factor-β, soluble TNF receptors and IL-1 receptor antagonists (Roy 2004). The anti-inflammatory factors are thought to control systemic inflammation while the local inflammatory factors work to resolve the problem region. If the anti-inflammatory mediators predominate, a state of immune suppression occurs (Bone 1996). A delicate balance is important between these antagonist mediators to allow for proper healing.

The coagulation system is also affected with systemic inflammation since many inflammatory mediators have pro-coagulant properties. Interleukin-6 causes the expression of tissue factor, which causes thrombin
Gram-positive bacteria, such as lipopolysaccharide from Gram-negative bacteria, despite adequate fluid resuscitation. Although sepsis inflammatory response to it (Boller and Otyo 2009). Sepsis infection of the host with microorganisms and the host's disease process. Sepsis is the clinical syndrome caused by coagulation often leads to death. Colic (Monreal et al. 2000). Ultimately, dysregulation of coagulation often leads to death.

In addition to inflammation, infection complicates the disease process. Sepsis is the clinical syndrome caused by infection of the host with microorganisms and the host's inflammatory response to it (Boller and Otyo 2009). Sepsis can progress to septic shock when the inflammatory process causes arterial hypotension and circulatory failure despite adequate fluid resuscitation. Although sepsis and septic shock are thought to occur due to the lipopolysaccharide from Gram-negative bacteria, Gram-positive bacteria, such as Staphylococcus and Streptococcus, can cause septic shock through a toxic shock syndrome via their own toxins (Opal and Cohen 1999; Laupland et al. 2004; Boller and Otyo 2009). Septic shock has 3 phases: early, early decompensated and late decompensated. In early septic shock, neurohormonal responses contribute to release of counterregulatory hormones, such as glucagon, adrenocorticotropic hormone (ACTH) and cortisol. In early decompensated septic shock, hypotension and hypoperfusion occur (Boller and Otyo 2009). At this time, the patient is clinically depressed, shows signs of organ failure and develops coagulopathies. Our patient appeared to be in early decompensated septic shock at presentation and progressed to late decompensated septic shock during surgery. Refractory hypotension, multiple organ failure and death occur in late decompensated septic shock. Signs of decompensation include hypothermia, pale mucous membranes, slow or no capillary refill time, waning pulses and coma. As the heart and brain lose their preferential blood flow, death is imminent (Boller and Otyo 2009).

Due to the many systemic effects of inflammation and infection, SIRS and septic shock can progress to multiple organ dysfunction syndrome (MODS), where homeostasis cannot be maintained without interventions (Bone et al. 1992). Ultimately, MODS can lead to organ failure and death. The mechanism of MODS is a 2 hit theory where trauma or shock primes the inflammatory or immunomodulatory systems and a second insult, such as infection, translocation of bacteria or bacterial toxins, causes an exaggerated host response (Garrison et al. 1998; Price et al. 1999). This causes a massive release of proinflammatory cytokines, leading to haemodynamic instability and greater likelihood of developing MODS. Endothelial and subsequent epithelial damage allow for bacterial translocation causing infectious organisms to enter the bloodstream (Johnson et al. 2004). Additionally, ischaemia and reperfusion injury to tissues from hypoperfusion compounds the inflammatory response with release of reactive oxygen molecules. Due to the excessive inflammation, organs start to fail. Pulmonary, cardiovascular, renal, haematological, gastrointestinal, liver and neurological dysfunction can all occur (Johnson et al. 2004). In our case, the cardiovascular system seemed to fail due to the hypotension and ventricular arrhythmias found under general anaesthesia. Myocardial depressant factor and inhibited neuronal release of norepinephrine in the myocardium mediate the cardiac dysfunction in dogs (Kumar et al. 2000; Cheng et al. 2002). Additionally, more toxins may have entered the systemic circulation upon manipulation of the uterus, as has been seen when a large colon volvulus is corrected. The gastrointestinal tract may also have been affected in our mare since GI pain can be seen with septic equine patients. (Roy 2004)

Many abnormalities existed on the blood work of the mare in this case that support the clinical syndrome of septic shock. The leucocytosis and neutrophilia with a left shift were due to the severe metritis and subsequent peritonitis. The leucocytosis also illustrates that this inflammatory syndrome started at the time or shortly after the uterus prolapse. A leucopenia would be expected with an acute response to SIRS. Horses have a low level of white blood cells in the bone marrow and it takes a few days for the white cells to increase systemically with a severe infection. The low normal fibrinogen does not correlate with an active inflammatory process. Since fibrinogen is used as a substrate for thrombin to form fibrin in the coagulation process, its decreased level may have signified disseminated intravascular coagulation or labatory error from clotted blood (Morris and Johnston 2002). The hypoproteinaemia resulted from a combination of hypoalbuminaemia and hypoglobulinaemia. The most likely cause of hypoproteinaemia was loss into the uterus or peritoneum due to the severe inflammation. Decreased liver production or gastrointestinal loss could also explain the hypoproteinaemia but are unlikely due to the acute nature of this case and only mild gastrointestinal injury seen at surgery or pathology (Morris and Johnston 2002). An urinalysis would have been indicated if the mare had survived to determine the renal concentrating ability and confirm the azotaemia and electrolyte disturbances were at least partially due to renal compromise. The magnitude of the elevated BUN and creatinine concentrations are suggestive of significant renal injury. The electrolyte abnormalities including hypernatraemia, hypochloraemia, hyperkalaemia, hypercalcemia and hyperphosphataemia were likely from renal disease, third space fluid loss or intrastitial or intracellular sequestration. Hypoalbuminaemia can result in a low total calcium concentration, although septic patients have been previously found to be hypocalcaemic (Holowaychuk and Martin 2004). Since an ionised calcium concentration was
not determined, the concentration of the ionised metabolically active form of calcium is unknown.

Although impaired adrenal function has not been documented in the acute adult equine patient, septic neonatal foals have been documented to have relative adrenohypophsyal and adrenal insufficiency. These foals have a higher mortality rate than septic foals with a normal adrenal function (Hurcombe et al. 2008). Another poor prognostic indicator in this horse was the hyperglycaemia. The severe hyperglycaemia indicated poor glycaemic control due to the severe systemic illness and is correlated with a poor prognosis in horses presenting with colic (Hassel et al. 2009).

Treatments for this horse included analgesia, fluid therapy, broad spectrum antimicrobials and pressor agents. Due to the severe azotaemia, electrolyte abnormalities and flunixin meglumine administration prior to presentation, no additional anti-inflammatory treatment was given prior to surgery. Reported treatment for endotoxaemia/systemic inflammatory response syndrome (SIRS) in the horse includes fluid therapy, flunixin meglumine, antibiotics, dimethylsulphoxide (DMSO), lidocaine and polymyxin B (Kelmer 2009). Fluid therapy often includes crystalloid fluids for stabilisation and colloids to increase the colloidal oncotic pressure and limit protein loss (Kelmer 2009). Due to the expense of colloids, they were not given in this case prior to surgery, but may have provided better intravascular volume expansion. It was the authors’ intention to administer plasma and hetastarch post operatively. Broad spectrum antimicrobials were given to this mare prior to surgery. Penicillin and gentamicin are commonly administered, but enrofloxacin was administered in place of the gentamicin due to the severe azotaemia and its increased volume of distribution (Papich et al. 2002). Metronidazole was planned to be administered post operatively for coverage of anaerobic bacteria since it is given orally or rectally. This would have controlled the Bacteroides fragilis found on abdominocentesis, although this was thought to be a contaminant due to the light growth and inability to isolate it from cultures at necropsy. Since most cases of SIRS involve horses with acute gastrointestinal disease, DMSO and lidocaine are used to prevent further injury to the ischaemic intestinal tissue. Their anti-inflammatory effects may also help decrease the local inflammatory and systemic inflammatory responses secondary to the metritis. Polymyxin B binds the lipid A-core moiety of lipopolysaccharide, which can be present with sepsis, but this medication can be nephrotoxic at higher doses or in the face of concurrent dehydration and was not given due to the clinicipathological evidence of renal disease. Retrospectively, polymyxin would not have helped this mare since the systemic organism was Streptococcus equi ssp. zooepidemicus, which causes a toxic shock syndrome without lipopolysaccharide (Opal and Cohen 1999).

Although this mare was treated with antibiotics and anti-inflammatories prior to referral, sepsis developed. At presentation the mare was in septic shock, which progressed to decompensated septic shock. A systemic lactate and blood gas measurement would have helped determine the severity of her illness, showing the level of hypoperfusion and acid-base status. In retrospect, surgery was not indicated since the primary problem was metritis and sepsis, but the uncontrollable pain necessitated this aggressive approach. The exploratory celiotomy allowed for a complete examination of the uterus and abdomen, ruling out other possible differentials such as a strangulating gastrointestinal lesion or uterine rupture and confirmed the diagnosis of metritis. An ovariohysterectomy was considered to remove the infected uterus, but abdominal contamination was a significant concern, as was the mare’s career as a broodmare. Controlled uterine lavage under general anaesthesia was planned, but did not occur due to the declining cardiovascular status of the mare.

Upon reviewing this case further, the initial management of the mare should have been more aggressive. Although trimethoprim-sulfa is a broad spectrum antibiotic routinely effective against Streptococcus equi ssp. zooepidemicus, it did not prevent the development of SIRS, sepsis and septic shock in this mare. Since the medication is given orally, the full dose may not have been administered. The quiet demeanour of the mare and abnormal urine should have prompted daily veterinary follow-up. A complete blood count could have shown abnormalities in the white cell count and fibrinogen. Uterine lavage would have demonstrated the necrosis present in the uterus. Since fibrin thrombi were found in the uterine vessels at necropsy, ischaemia could have contributed to the severe metritis and subsequent severe pain of the mare at presentation to the hospital. Since the uterus had been prolapsed, manipulation during treatment could have also injured a portion of the uterus. Another possibility for the necrosis in the uterus and subsequent sepsis is retention of the falut membranes. This is unlikely in this case since the interior of the uterus and the placenta were examined at the time of the prolapse, but a small piece could have still been adhered to the uterine mucosa. Many cases of endotoxaemia, lamiinitis and death have been reported following retention of falut membranes. Although the placenta was thought to have been completely expelled, retention of a portion would explain the clinical syndrome. Aggressive manipulation of the placenta with subsequent tearing of a portion of the placenta or the uterine mucosa could also have commenced this scenario. With early recognition of the deteriorating condition of the uterus, intrauterine treatments, supportive care and i.v. antibiotics could have been administered. This case demonstrates the need for vigilant monitoring following a uterine prolapse to immediately identify complications. Early, aggressive treatment with broad spectrum i.v. antimicrobials, anti-inflammatory...
medications, frequent uterine lavage and supportive fluid therapy may have resolved the metritis and prevented the development of bacteraemia, sepsis, multiple organ dysfunction syndrome (MODS) and septic shock. Identification of the foetal vaginal discharge and decreased appetite should have prompted more thorough diagnostics and treatment. Although some cases of uterine prolapse have done well with conservative therapy, others may require hospitalisation and aggressive therapy.

Manufacturers’ addresses

1Baxter Healthcare Corporation, Deerfield, Illinois, USA.
2Hospira, Lake Forest, Illinois, USA.
3Vettek, Blue Springs, Missouri, USA.
4Abbott Laboratories, North Chicago, Illinois, USA.
5Fort Dodge, Fort Dodge, Iowa, USA.
6Teva, Irvine, California, USA.
7Bayer Health Care LLC, Animal Health Division, Shawnee Mission, Kansas, USA.
8AmericanChoice, Roerig Division of Pfizer Inc, New York, USA.
9Vedco, St Joseph, Missouri, USA.
10Baxter Healthcare Corporation, Deerfield, Illinois, USA.
11Bayer Health Care LLC, Animal Health Division, Shawnee Mission, Kansas, USA.

References