Clinical management of postpartum hemorrhage following failure of cervical dilation in an alpaca

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Summary

A 9 year old female Huacaya alpaca was maintained on exogenous progesterone (hydroxyprogesterone caproate) during pregnancy due to previous pregnancy loss. Dystocia due to partial failure of cervical dilation at 345 days of gestation was complicated by rupture of the vaginal artery. Severe hemorrhage was treated with application of pressure to the vaginal artery by use of a vaginal tampon, and administration of aminocaproic acid, supplemental oxygen, and fluid therapy. After stabilization, the female was treated for retained placenta and anemia. Unique features of this case include treatment of postpartum hemorrhage with aminocaproic acid, documentation of luteal insufficiency, and failure of cervical dilation after use of exogenous progesterone during pregnancy.

Keywords: Camelid, aminocaproic acid, dystocia, endoscopy, hydroxyprogesterone caproate, progesterone

Background

This case of periparturient hemorrhage in an alpaca is unique in several aspects. First, we documented the use of aminocaproic acid as a component of treatment of postpartum hemorrhage in an alpaca. We also documented luteal insufficiency during pregnancy, a condition long-suspected in many females but rarely documented in alpacas. Lastly, this female experienced partial failure of cervical dilation subsequent to exogenous progesterone administration, a complication which has been anecdotally reported in alpacas. This case provides data to the field of camelid theriogenology regarding these conditions.

Case presentation

The breeding management of a 9 year old Huacaya alpaca had been overseen by the Theriogenology service at Washington State University (WSU) for several years. Two years previously the alpaca had experienced dystocia at 325 days of gestation due to bilateral carpal flexure of the fetus which the owner resolved. The fetus was non-viable. The female was presented to WSU after the dystocia and hysteroscopy demonstrated no cervical tears. Subsequently, the female had been bred several times without establishment of a pregnancy. Reproductive evaluation at that time included serial ultrasonography, endometrial cytology, endometrial culture, endometrial biopsy, and hysteroscopy. In summary, she had normal follicular waves and ovulation. The uterus developed edema with small amounts of fluid during estrus, and cytology showed few neutrophils. Culture was negative for pathogenic bacteria. The biopsy was classified as category 1a, with few histologic changes. Hysteroscopy demonstrated normal uterine appearance and cervical function. A pregnancy was finally established after use of a modified minimum-contamination breeding technique. This entailed the use of systemic antibiotics for one day prior to and two days after breeding (Excenel®, 2.2 mg/kg SQ, Zoetis Animal Health, Florham Park, NJ), as well as induction of ovulation of a dominant follicle using a gonadotropin releasing hormone (GnRH) analogue (Cystorelin®, 50 mcg IM, Merial, Duluth, GA) and use of a systemic anti-inflammatory (flunixin meglumine, 1.1 mg/kg SQ). The pregnancy was maintained with exogenous progesterone (hydroxyprogesterone caproate, 250 mg IM, Unique Pharmaceuticals, Temple, TX) which was administered every three weeks after ultrasonographic determination of a viable fetus. The exogenous progesterone was administered from 7 to 300 days of gestation.

Due to the value of the pregnancy and history of infertility, empiric progestagen therapy was elected. However, to retrospectively analyze the alpaca's endogenous progesterone production during pregnancy, serum was collected and frozen at -20°C throughout pregnancy and analyzed postpartum

(Table 1) using a commercial radioimmunoassay (Siemens Healthcare Diagnostics, Los Angeles, CA). All samples were analyzed in one assay; the intra-assay CV was 5.8%.

The female was hospitalized at 324 days of gestation to monitor for parturition. She received oral domperidone therapy (Equidone®, 220 mg PO, Dechra Veterinary Products, Overland Park, KS) from days 326 to 332 of gestation due to insufficient mammary development. Serial transabdominal ultrasonography using a curvilinear 3.5 MHz transducer (Aloka 500, Hitachi Aloka, Tokyo, Japan) demonstrated normal fetal heart rate (80 to 96 beats/minute) and movement during hospitalization.

At 345 days of gestation, rupture of the chorioallantois occurred and fetal limbs were observed protruding from the vulva despite the lack of obvious abdominal contractions. Reproductive examination demonstrated partial failure of cervical dilation, at 6 to 8 cm diameter, which allowed protrusion of the fetal limbs but not the head. Cesarean section was considered; however, given the extent of partial cervical dilation, manual dilation and prompt fetal delivery was the treatment option selected. The cervix was manually dilated over 10-15 minutes and a viable male cria was born via assisted vaginal delivery. The cria weighed 7.73 kg, a moderate size for the breed. Subsequent to delivery of the cria, profuse arterial hemorrhage from the vulva was evident.

Treatment

At the onset of vaginal hemorrhage, an intravenous jugular catheter was placed and initial blood values obtained. The packed cell volume (PCV) was 31% and serum total protein (TP) was 6.0 g/dL. Aminocaproic acid (Hospira Inc., Lake Forest, IL) was administered at a loading dose of 5 g in 500 mL of lactated Ringer's solution (LRS) IV over 15 minutes. Several large blood clots were passed from the vulva. The female collapsed in the stocks and began open-mouthed breathing. Supplemental oxygen therapy was initiated. A vaginal tampon was fashioned from brown gauze over roll cotton, covered with sterile lubricant, and inserted into the vagina to apply pressure to the site of hemorrhage. Visual inspection ensured the tampon remained in place. Fluid therapy was initiated and 3L of LRS were administered over 1 hour, after which PCV was 23% and TP was 4.1 g/dL. The animal's heart rate increased to 120-152 beats per minute with irregular rate and rhythm due to hypovolemic shock.

The vaginal tampon was removed after 1 hour and vaginal palpation demonstrated a tear of several centimeters involving, and just cranial to, the cervix at the 4 o'clock position, and a firmly attached placenta. At that time, the animal had stabilized and was able to walk to a stall. The female was administered oxytocin at a dose of 20 IU IM every 4 hours; flunixin meglumine 1.1 mg/kg SQ once for pain; ceftiofur (Excenel®) 2.2 mg/kg SQ every 12 hours for 7 days; and aminocaproic acid 2.5 g in 500 mL LRS IV every 6 hours for a total of 3 doses. Packed cell volume and TP were monitored every 4 hours (Table 2). Routine neonatal cria care was implemented including umbilical treatment and monitoring of adequate nursing.

Twelve hours after the hemorrhage event, transabdominal unltrasonography did not demonstrate any free fluid in the abdomen, suggesting that the uterine and cervicovaginal tears were not full-thickness. The detached portion of the retained placenta was manually removed. Ultrasonographic examination after placental removal demonstrated normal uterine contractions and initiation of involution.

Twenty hours after the hemorrhage event, endoscopic examination of the reproductive tract was performed. Two tears were identified: one in the cranial vagina, involving the first cervical ring, and one in the uterine body, unassociated with placental retention. Both tears appeared less than 2 cm in size. No active hemorrhage was noted. By that time cardiac auscultation demonstrated normal rhythm although tachycardia persisted (100 beats per minute).

Thirty-four hours after the hemorrhage event, the remainder of the placenta was passed and oxytocin therapy was discontinued. The alpaca was administered a B-complex vitamin injection of 5 mL SQ and started on Red Cell® iron and mineral supplementation (Farnam Companies, Phoenix, AZ) at a dose of 20 mL PO, once daily, for 3 weeks to treat anemia.

Complete blood count (CBC) and serum biochemistry analysis were performed at 10, 82, and 154 hours after the hemorrhage event, as well as at 21 days (Table 3). The alpaca displayed leukocytosis due to neutrophilia at 2 of the 4 sampling times with minor derangements in electrolytes and glucose. At both

82 hours and twenty-one days postpartum, the CBC demonstrated a large number of eosinophils $(1.2 \times 10^3 \text{ and } 2.4 \times 10^3, \text{ respectively})$. A fecal analysis was performed 32 days postpartum and was negative for parasites. The inciting cause of the eosinophilia was not identified.

Twenty-one days after the hemorrhage event, transrectal ultrasonography, using a 7.5 MHz linear transducer mounted on an extension rod, did not demonstrate free fluid in the uterus and involution was proceeding normally. Endoscopic examination of the vagina demonstrated that the vaginal tear was granulating normally with no evidence of recent hemorrhage. The developing scar tissue appeared to extend to the first cervical ring although the extent of cervical involvement or function could not be ascertained at that time. Endoscopy of the uterus was not attempted.

Outcome

In a follow-up discussion with the owner nine months later, it was noted that the female was comfortable at the farm and had raised the cria to weaning. She had not shown any ill effects although the extent of cervical competency and functionality of the reproductive tract was unknown. The owner did not desire to breed her again. After two years the owner reported that the animal was still in good health.

Discussion

Postpartum hemorrhage in alpacas is rare and most often is subsequent to obstetrical manipulations or fetotomy (Table 4). This is one major reason why the authors do not advocate fetotomy in alpacas and are more likely to recommend cesarean section in cases of severe dystocia than to spend excessive time attempting vaginal delivery. In the authors' practice, all obstetrical manipulations are limited to 20 minutes, after which cesarean section is performed. In contrast to mares, the affected artery is typically the vaginal artery, a large vessel easily palpated in the wall of the vagina during obstetrical manipulations.^{1,2} Due to this anatomical location, the site of hemorrhage is typically the uterus or vagina, whereas in mares, hemorrhage into the broad ligament or abdomen is commonly identified. Observed clinical signs of acute volume depletion may include cardiovascular shock, tachycardia, pale mucous membranes, muscle fasciculation, sweating, recumbency, and death.³ In alpacas, if the hemorrhage is not noted externally (i.e., expulsion of blood from the vulva), the female is often found dead several hours after parturition.²

If the veterinarian is presented with an alpaca with clinical signs of cardiovascular shock after parturition or is presented with hemorrhage after obstetrical manipulations, the application of pressure to the site of hemorrhage is paramount. This treatment approach is unique to camelids, as the site of arterial rupture is typically the vaginal artery. A large vaginal tampon is easily constructed from common medical supplies and is lubricated with sterile lubricant or antibiotic-impregnated lanolin. One of the authors (AT) has treated a postpartum arterial rupture by placing a ligature around the vessel. This was achieved under epidural anesthesia and after caudal retraction of the cervix using long-handled forceps.

Intravenous catheter placement is recommended for fluid replacement therapy; camelids in general are very susceptible to fluid overload and pulmonary edema, and the use of hypertonic saline and large volumes of crystalline fluids are contraindicated.⁴ In this case, the female was administered 3L of LRS over one hour after aminocaproic acid in LRS administration (500mL volume over 15 minutes). Additional doses of aminocaproic acid (2.5 g in 500mL LRS) were given at 6 hours interval. The maintenance dose of fluids for adult alpacas is 4 to 6mL/kg/hour.⁵ For this particular 86 kg female, the dose of IV fluids at the time of hemorrhage was approximately 40mL/kg which provided cardiovascular stabilization without the onset of pulmonary edema. This dose is twice that of recommended dosing for volume-depleted alpacas,⁶ but is reflective of the volume of blood loss during the hemorrhage event. Whole blood transfusion has also been described when PCV < 10%.² There are no studies of aminocaproic acid use in alpacas to determine the optimal dosing and volume of fluid administration, and the treatment options selected in this animal were clinically based.

Retained fetal membranes are often a component of dystocia and hemorrhage events. The vaginal tampon will need to be removed for passage of fetal membranes. The practitioner may elect to

treat the female with oxytocin intramuscularly after cessation of hemorrhage to assist with placental passage. As opposed to mares, fetal membranes are considered retained in alpacas after six hours and often do not result in systemic illness. Presence of retained fetal membranes may act to place pressure on a uterine or vaginal site of hemorrhage; passage of retained fetal membranes may release this pressure or disrupt clot formation, and animals should be monitored for resumption of hemorrhage.³ The vaginal tampon should not be left in place for long periods of time due to the risk of vaginal mucosal irritation and likelihood of straining by the female. Uterine lavage as a treatment for retained fetal membranes is often contraindicated, especially in cases of hemorrhage. Additional risks of uterine lavage in postpartum females include delay of uterine involution and, in the presence of full-thickness uterine tears, peritonitis.

As hemorrhage events in postpartum alpacas are rare, extrapolation of treatment protocols in mares were used by the authors, including the use of aminocaproic acid. Aminocaproic acid is a synthetic derivative of the amino acid lysine which has been commonly used in human medicine. Although the mechanism of action is unknown, aminocaproic acid acts by inhibiting plasminogen activation which alters the dynamics of clot breakdown, resulting in stabilization and prolongation of a clot without disrupting its formation.⁷ The pharmacokinetics and pharmacodynamics of this drug have been examined in horses which demonstrated no detrimental effects on healthy horses.⁷ Several dosing protocols have been suggested, including a loading dose followed by intravenous continuous rate infusion to achieve therapeutic plasma concentrations.⁷ More commonly in horses, a loading dose is followed by a lesser dose at 4 to 6 hour intervals.⁸⁻¹⁰ In humans, thrombotic complications have been reported, as well as an increase in plasma levels of the drug in patients with renal disease.⁷ The drug is contradicted for use in patients with disseminated intravascular coagulation. To the authors' knowledge, this is the first reported use of aminocaproic acid in an alpaca although we have referred to this case previously.^{3,11} The dosage was extrapolated from the dosing for the equine which is recommended as a loading dose of 20 g per horse in IV fluids, with subsequent doses of 10g per horse in IV fluids every 4 to 6 hours.^{9,10} As the alpaca in this report was approximately one-fourth the size of an average horse, the dose was administered at that ratio (5g loading dose with subsequent doses of 2.5g).

As postpartum hemorrhage events in alpacas are rare, and most of what is known about the disease pertains to broodmares, a review of the literature was performed to compare the disease in the two species (Table 4). Periparturient hemorrhage events represent a significant cause of death in the broodmare.^{9,12} In a study of mares which presented to a referral hospital postpartum, not only did mares with postpartum hemorrhage present significantly sooner after foaling, but represented significantly older mares (average age 13 years, range 8 to 21) compared to other postpartum complications such as metritis or large colon volvulus.¹³ Likely this is due to the rapid onset of clinical signs, and represents the degenerative changes within the intima of the affected vessel. The average time from foaling to presentation in that study was 96 hours (range 3 to 720h).¹³ The wide range reflects the fact that mares tend to hemorrhage into the broad ligament, a self-limiting space which applies pressure to the affected vessel. In contrast, alpacas tend to hemorrhage into the uterus or vagina, which in an infinite space, and which is why most affected animals are found dead within several hours of parturition.

Data regarding postpartum hemorrhage in alpacas are lacking. The incidence is not known and almost certainly under-reported. Complicating diagnosis and characterization of this disease is the lack of standardized anatomical description of the vasculature of the camelid reproductive tract.^{16,17} The cases which have been described or treated by the authors involved rupture of the vaginal artery. Recent studies on the pathology of periparturient hemorrhage in mares have demonstrated that the most common affected vessel is the middle uterine artery. In one study of 31 hemorrhage events, the uterine artery ruptured in 24 cases (77.4%), with most occurring on the left side.¹⁴ The majority of these (n=18) ruptured proximally within 15 cm of branching from the external iliac artery. Other rupture sites included the internal pudendal artery (n=5) and the internal iliac artery (n=1). Similarly, another study demonstrated that 54 of 71 mares which died had rupture of the uterine artery; 33 of these were on the left side.¹⁵ This site is hypothesized to be most often affected because the sharp curve which the artery takes at this location may predispose it to rupture when under the high blood pressures associated with

parturition, with increased risk in mares with atrophy of the tunica media smooth muscle and fibrosis, common in older mares.

In addition to the treatments described above in reference to the alpaca of this report, other treatments used in horses for acute events of hemorrhage include: formalin, naloxone, the Chinese herb Yunnan baiyao, conjugated estrogens, hetastarch, morphine caudal epidural administration, and corticosteroids.^{8-10,12} To the authors' knowledge, none of these treatments have been used in alpacas with hemorrhage events. Controversy exists regarding the use of acepromazine as a tranquilizer in mares due to its hypotensive effects, but this drug is not a routine part of camelid practice and butorphanol tartrate remains the drug of choice in camelid species for sedation and analgesia.

During the examination of mares, there are often concerns about performing transrectal palpation and the types of physical restraint implemented. In alpacas, the goals are to keep the female calm by use of a chute system or small pen. Physical restraint may be required but is not as likely to elevate blood pressure as the restraint of an uncomfortable horse (i.e., lip twitch or chain) which may disrupt clot formation. In one study of hemorrhage events in broodmares, only tachycardia was associated with clinical outcome.⁹ There are not enough cases of hemorrhage events in alpacas to make epidemiological inferences. Other major concerns in mares which survive periparturient hemorrhage events are not common features in alpacas and include endotoxemia and laminitis.

The female alpace of this report sustained partial failure of cervical dilation after treatment with exogenous progesterone every three weeks up to 300 days of gestation. Previous reports of failure of cervical dilation have been made in alpaces.^{1,3,18} However, not all females which maintain pregnancy due to exogenous progesterone administration have experienced failure of cervical dilation, and not all females which experience failure of cervical dilation have been treated with exogenous progesterone. Furthermore, the number of animals which are administered exogenous progesterone which actually have luteal insufficiency is not known.

Owners of animals receiving progestagen supplementation should be educated to monitor for signs of labor and dystocia. In the case of the animal of this report, the risk of complication is what led the owner to hospitalize the animal at 324 days of gestation. Other causes of failure of cervical dilation include fetal maldisposition (does not engage the cervix) and uterine inertia. In this case, the female alpaca was not demonstrating strong abdominal contractions despite appropriate presentation of the cria. Serum calcium levels ten hours postpartum were slightly below reference ranges (7.5 mg/dL; reference range 8.4-10.4 mg/dL) but were not low enough to be considered deficient (< 7.0 mg/dL).¹⁹

Retrospective analysis of serum progesterone concentrations from day seven of gestation to the day of parturition in the animal of this report supports a diagnosis of luteal insufficiency, considered at progesterone concentrations < 1.0 ng/mL (Table 1).² Luteal insufficiency has been commonly suspected in females with unexplained pregnancy loss and no abnormalities as identified by breeding soundness examination and advanced reproductive evaluation such as uterine biopsy and hysteroscopy. As mentioned previously, complete reproductive evaluation did not demonstrate a cause for infertility in this animal. Furthermore, the body weight at breeding was high (96 kg). She was placed on dietary modifications throughout pregnancy and after parturition weighed 86 kg. Serum progesterone levels were > 2.5 ng/mL until 71 days of gestation. At 95 days of gestation, progesterone was 1.28 ng/mL. The lowest measured serum levels were 0.6 ng/mL at 179 days of gestation, although levels increased slightly in late gestation. Fluctuations in progesterone concentrations may be reflective of body weight, hydration status, liver metabolism, and lactation as seen in dairy cattle, but remain to be examined in alpacas. Differences in laboratory protocols may also account for some variation, although in our case all samples were run in the same assay.²⁰ This case demonstrates that animals with luteal insufficiency can be successfully maintained to parturition with exogenous progesterone and produce a viable cria. However, as mentioned previously, there are risks associated with this treatment and the owner and practitioner should be prepared for dystocia.

Last, the alpaca of this report was treated with an iron-mineral supplement which has been demonstrated to increase the risk of copper toxicity in alpacas. Its use must be carefully monitored to ensure that toxicity does not occur.

In conclusion, management of high risk pregnancies in alpacas can be challenging. Maintenance of proper body condition, use of a minimum contamination breeding technique, and exogenous progesterone use all resulted in a live cria from this female. However, the end result was not without life-threatening complications. Further studies are needed of these types of cases to improve welfare of pregnant animals during gestation, parturition, and the postpartum period.

Learning points

- Aminocaproic acid was administered, in conjunction with other therapies, to an alpaca experiencing postpartum hemorrhage, with a successful outcome.
- Luteal insufficiency was documented and treated by administration of exogenous progesterone up to 300 days of gestation.
- Failure of cervical dilation occurred subsequent to exogenous progesterone administration and resulted in dystocia and postpartum hemorrhage.
- Treatment of hypovolemic shock in alpacas should be performed carefully as to not result in fluid overload and pulmonary edema in affected animals.

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Days of gestation	Progesterone (ng/mL)
7	3.64
28	2.66
71	2.50
95	1.28
116	1.20
179	0.60
326	1.60
344	0.09
345	parturition

Table 1. Endogenous serum progesterone levels of an alpaca with luteal insufficiency which was maintained on exogenous progesterone from days 7 to 300 of gestation.

Table 2. Packed cell volume (PCV) and total protein (TP) of an alpaca during and after an event of postpartum hemorrhage.

Hours	0	4	8	10	18	24	82	154	21 days
postpartum									
PCV (%)	31	23	22	18	14	13	15	14	21
TP (g/dL)	6.0	4.1	4.6	4.5	4.4	4.4	5.5	5.7	6.3

Table 3. Complete blood count and serum biochemistry analysis of an alpaca after an event of postpartum hemorrhage, select values. Abnormalities are highlighted in bold.

Hours postpartum	10	82	154	21 days
Total white blood cells	17.0	9.7	19.5	10.1
$(x10^{3}/\mu l)$				
Neutrophils $(x10^3/\mu l)$ (%)	15.0 (88%)	5.0 (52%)	18.3 (94%)	6.8 (67%)
Eosinophils $(x10^3/\mu l)$ (%)	0.3 (2%)	1.2 (12%)	0.6 (3%)	2.4 (24%)
BUN (mg/dL)	19	20	20	18
Creatinine (mg/dL)	1.7	1.4	1.1	1.4
Glucose (mg/dL)	326	125	97	122
Calcium (mg/dL)	7.5	8.0	8.3	9.0
Phosphorus (mg/dL)	7.1	2.8	3.7	7.8
Sodium (mEq/L)	154	156	156	161
Chloride (mEq/L)	116	120	117	117
Potassium (mEq/L)	4.6	4.7	4.8	4.4

Table 4. Common features of periparturient hemorrhage in mares versus alpacas.

	Mares	Alpacas	
Incidence	Most common emergency in	Rare	
	postpartum mares ¹²		
Site of hemorrhage	Uterine artery	Vaginal artery	
Pathogenesis	Degeneration of intima of arteries in	Usually secondary to obstetrical	
	older or multiparous mares; site of	manipulations	
	vascular curving or bending with		
	high hemostatic pressures		
Location of hemorrhage	Broad ligament, abdomen	Uterus, vagina	
Clinical signs	Colic, cardiovascular shock	Acute death	
Survival	84-88% ^{8,12}	Unknown	
Future fertility	50% ⁸	Unknown	