CASE REPORT

Presumed Copperhead Snakebite and Antivenom Administration in the Third Trimester

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Snake envenomation during pregnancy is an uncommon emergency with several potential complications associated with the poisoning and its treatment. This case discusses a 27-y-old gravida 3, para 1102 (3 total pregnancies, 1 term birth, 1 premature birth, 0 abortions, 2 living births, twins) at 36 wk gestation who was bitten by a presumed *Agkistrodon contortrix* (copperhead snake). She had worsening pain and swelling in the right lower limb. Crotalidae polyvalent immune Fab was administered. The patient felt significantly better with improvement in swelling. She had a reactive nonstress test and reassuring coagulation studies. She gave birth to a healthy female infant 12 d later. This case supports the use of Crotalidae polyvalent immune Fab for venomous snakebites in pregnant patients to prevent possible maternal and fetal morbidity and mortality.

Keywords: antivenom, complications, *Agkistrodon contortrix*, crotalid, pit viper, pregnancy

Introduction

The North American copperhead snake, *Agkistrodon contortrix*, is a pit viper responsible for many envenomations in the United States annually. In the 2017 American Association of Poison Control Centers annual report, 2008 verified copperhead envenomations were reported. There were also 998 “unknown crotalid envenomations,” some of which could have been from *A. contortrix*. Copperhead venom contains proteins, which primarily cause local tissue damage and destruction. These tissue effects can produce pain, swelling, lymphatic damage, tissue necrosis, and limb dysfunction.¹ More severe venom effects include hypotension and coagulopathy caused by depletion of fibrinogen and platelets. These systemic effects, although much rarer in copperhead envenomation than in envenomation by other North American pit vipers, are of increased concern in pregnant patients. Death from copperhead envenomation is extremely rare.² Fewer than 3 fatalities have been reported in association with *A. contortrix* envenomation.¹

Snake envenomation in pregnant women is uncommon. In the United States, there were 65 cases of venomous

snakebites in pregnant women compared to 23,611 cases in the nonpregnant population between 2001 and 2005.² Due to the low incidence, there are no evidence-based guidelines on management and antivenom use during pregnancy. Crotalidae polyvalent immune Fab (CroFab) was approved by the Food and Drug Administration in 2000 and is pregnancy category C; therefore, its use requires a risk benefit analysis. Data regarding adverse effects during pregnancy are limited. A literature review reveals only 1 case report of CroFab use in a pregnant patient following a copperhead envenomation in the third trimester.³ In the majority of cases regarding CroFab use in pregnant patients, infant outcomes are often missing or lacking longitudinal follow-up beyond Apgar scores, a method that summarizes the initial health of newborns, and initial screening examination.^{3,4}

In the nonpregnant population, CroFab has reduced the incidence of adverse events compared to previously approved antivenom.⁵ It is derived from affinity-purified bovine Fab immunoglobulin fragments produced in sheep immunized with *Crotalus atrox* (western diamondback rattlesnake), *Crotalus adamanteus* (eastern diamondback rattlesnake), *Crotalus scutulatus* (Mojave rattlesnake), and *Agkistrodon piscivorus* (cottonmouth or water moccasin).⁵ By eliminating the Fc portion of the immunoglobulin, the risk of severe adverse reactions (anaphylaxis) has been significantly reduced.

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Risks of CroFab include immediate and delayed hypersensitivity reactions. Immediate reactions are primarily cutaneous: itching, redness, and urticaria. Anaphylactoid reactions with airway compromise, hypotension, and other severe symptoms are very rare.⁵ Delayed hypersensitivity reactions (serum sickness) are characterized by malaise, myalgia, arthralgia, low-grade fever, and rash. A literature review of 9 publications on CroFab containing postmarketing patient exposure data revealed the incidences of immediate and delayed hypersensitivity reactions to be 8 and 13%, respectively.⁶

A review of data from the North American Snakebite Registry revealed that out of 373 patients receiving CroFab, 10 patients experienced adverse effects. Rash was the most common. Severe adverse events such as hypotension, bronchospasm, and angioedema occurred in 4 patients. Fortunately, no deaths were reported.⁵

A review of the American Association of Poison Control Centers database reported that from 2001 to 2005, 65 venomous snakebites in the United States occurred during pregnancy. Of those, 32% occurred in the third trimester. Antivenom was administered to 17% of victims. There were no deaths or adverse reactions reported.²

This case presents a patient at 36 wk gestation who was bitten by a presumed copperhead snake. The snake was presumed to be a copperhead snake by the emergency department physician because copperheads are the only native venomous snakes in the immediate region where the bite occurred. After initial observation demonstrated progression of the swelling in her right lower extremity, she was treated with CroFab without any known adverse drug effects and delivered at 37 wk, 5 d. The authors obtained patient approval for this report by written and verbal consent.

Case report

A 27-y-old gravida 3, para 1102 (3 total pregnancies, 1 term birth, 1 premature birth, 0 abortions, 2 living births, twins) at 36 wk gestation was bitten by a presumed copperhead snake at approximately 1000 while walking near her home. She presented to the emergency department at 1030 with right lower extremity pain and swelling, and the snake was presumed to be a copperhead snake by the emergency department physician. Her obstetrical history was complicated by preterm delivery at 21 wk gestation and a planned cerclage placement for the current pregnancy. This planned cerclage was scheduled by her obstetrician owing to her history of incompetent cervix leading to preterm labor and fetal loss. She also had a cesarean section planned at 37 wk 5 d due to a previous cesarean at term, desiring a repeat of the procedure.

The patient had 2 puncture wounds near the fourth metatarsal of the right foot. She reported pain, swelling, and erythema from the right ankle to the midcalf (*Figure 1*). The patient denied systemic symptoms, chest pain, or dyspnea. She had no vaginal bleeding, leakage of fluid, or contractions. There was no clinical evidence of ecchymosis, compartment syndrome, or rhabdomyolysis. Vital signs in the emergency department were temperature 36.8°C, blood pressure 136/86 mm Hg, pulse 103 beats·min⁻¹, respiration rate 18 breaths·min⁻¹, and SpO₂ 96%. Laboratory studies showed normal coagulation and renal function tests. Complete blood count was unremarkable with normal platelets. The initial nonstress test (NST) was reactive.

The patient was admitted to the obstetrics service at 1500 for further monitoring of her symptoms and for fetal monitoring. She began experiencing worsening pain and extension of swelling. After discussion with a toxicologist at the regional poison center, the patient was administered 6 vials of CroFab by intravenous infusion starting at 1540 and lasting 1 h. No additional antivenom was recommended by the poison center, based upon their protocol. Fetal monitoring was performed during infusion and over 18 h afterward, with a consistent category I fetal heart rate tracing. Her pain was controlled with acetaminophen-oxy-codone. Thirteen hours after admission, the patient reported feeling significantly better with minimal pain and ability to

Figure 1. Right lower extremity swelling. Lines drawn to monitor progression.

ambulate without assistance. Her right lower limb swelling stabilized (Table 1). She was discharged the following day as her symptoms continued to abate. She had reassuring fetal monitoring including a reactive NST and coagulation studies on day of discharge. The patient had a planned cesarean section (for factors unrelated to the snakebite) 12 d later and gave birth to a healthy female weighing 2778 g. Apgar scores were 7 and 9 at 1 and 5 min. No other complications were reported. In follow-up discussions, the patient reports that her infant is doing well at 12 mo of age, meeting all developmental milestones and without any known complications.

Discussion

Although rare, venomous snakebites during pregnancy are medical emergencies with risks to both the mother and fetus. As with other medical emergencies in pregnant patients, treatment and stabilization of the mother is of paramount importance. This case illustrates a presumed copperhead snake envenomation with signs of active progression of local tissue injury. The patient met criteria for antivenom therapy, and CroFab was used with apparent efficiency and no apparent complications. The evaluation of a pit viper envenomation in a pregnant patient starts with assessing the airway, breathing, and circulation, while addressing vital sign abnormalities and rendering supportive care. Intravenous access should be obtained, and volume expansion with isotonic solution should be started. The removal of any constricting items (tourniquets, tight clothing, jewelry) is important. The bitten area should be elevated above the level of the heart and monitored for progression of tissue injury. Our regional poison center's protocol was used. Measurements of the foot, ankle, calf, and thigh were performed every 4 h (Table 1). Alternatively, the leading edge of pain or tenderness, swelling, or redness can be marked, timed, and updated periodically to assess for progression.¹

Important laboratory studies include complete blood count, basic metabolic panel, prothrombin time, international normalized ratio, fibrinogen, and urinalysis. In a pregnant patient with a copperhead envenomation, we

recommend checking initial laboratory studies and then repeating the tests in 6 to 8 h because coagulopathy, although rare, may be delayed. For rattlesnake envenomations, repeat labs are essential and should be performed in the hospital within 5 to 7 d after hospital discharge (or immediately if signs of bleeding occur) because delayed or recurrent coagulopathy can occur.

The first line treatment for tissue injury, coagulopathy, and systemic signs of envenomation is antivenom, which binds and neutralizes the venom proteins and facilitates their elimination. Blood products are not recommended as first line agents for coagulopathy and should not be routinely considered unless aggressive antivenom therapy has failed and the decision is made in consultation with a toxicologist or envenomation specialist.

The amount of antivenom required is variable and depends upon the patient's signs and symptoms, laboratory values, and response to initial antivenom doses. Consultation with a poison center or envenomation specialist to assist with dosing is recommended.

Fetal monitoring is also critical. Fetal monitoring with NST and fetal movement assessment (kick counts), maternal perception of 10 distinct movements in a period of up to 2 h, is recommended for a minimum of every 8 h.⁷ There have been reports of decreased fetal movement and fetal death occurring within days of envenomation, which suggests observation and ongoing outpatient surveillance may be helpful for up to 1 wk.⁷

The adverse effects of CroFab antivenom in pregnancy have not been extensively studied. Severe obstetric outcomes are possible after snake envenomation, including placental abruption, preterm labor, and fetal loss.⁸ A careful risk versus benefit analysis should be done and thorough informed consent obtained before administration. Limited data regarding antivenom use in pregnancy do suggest that it is safe and may improve fetal and maternal outcomes.⁷

In this case, antivenom was used and the patient had a successful delivery at 37 wk 5 d. To date, no infant abnormalities have been identified; however, we only have 12 mo of longitudinal follow-up, so we cannot conclude that CroFab had no harmful long-term effects. Furthermore,

Table 1. Right lower extremity measurements

Extremity	Day and time					
	Day 1 1930	Day 1 2330	Day 2 0330	Day 2 0730	Day 2 1130	Day 2 1542
Foot (cm)	23.0	23.0	23.5	23.0	23.6	23.4
Ankle (cm)	24.0	24.0	24.0	23.8	23.9	23.6
Calf (cm)	42.0	41.3	41.0	41.9	42.8	42.9
Thigh (cm)	58.5	58.0	55.5	57.0	56.0	56.5

because delivery occurred only 12 d after antivenom administration, it is possible that earlier fetal exposure could be harmful. Unfortunately, there is no literature that studies the long-term effects of in utero CroFab exposure on infant outcomes.

Management for venomous snakebites during pregnancy has not been extensively studied owing to low incidence. As more cases of venomous snakebites occur in pregnant patients, guidelines for management would be a useful resource to optimize the benefits of antivenom for pregnant patients and their fetuses. Prior to this case report, the literature had reported only 1 case in which CroFab was given in the third trimester but without longitudinal data on the infant.³ Based on our experience, the use of CroFab for a progressive envenomation during the third trimester resulted in improvement in maternal health and no known impacts on the fetus or subsequent infant outcomes. As with other conditions that threaten the health of the mother and fetus, snake envenomation warrants a careful risk versus benefit analysis of antivenom administration. A discussion with the patient and obtaining informed consent prior to treatment is recommended.

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