

REVIEW ARTICLE

Management of envenomations during pregnancy

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Context. Envenomations during pregnancy pose all the problems of envenomation in the nonpregnant state with additional complexity related to maternal physiologic changes, medication use during pregnancy, and the well-being of the fetus. **Objective.** We review the obstetric literature and management options available to prevent maternal morbidity and mortality while limiting adverse obstetric outcomes after envenomation in pregnancy. **Methods.** In January 2012, we searched the U.S. National Library of Medicine Medline/PubMed, Toxline, Reprotox, Google Scholar and Micromedex databases, core surgery and internal medicine textbooks, and references of retrieved articles for the years 1966 through 2011. Search terms included “envenomation in pregnancy,” “stings in pregnancy,” “antivenom use in pregnancy,” “anaphylaxis in pregnancy,” and variants of these with known venomous animals. Reference lists generated further case reports and articles. We included English language articles and abstracts. Levels of Evidence (LOE) for the reports cited and Grades of Recommendations (GOR) based on LOE for our recommendations use the National Guidelines Clearinghouse metric of the US DHHS. **Results.** Recommendations for the management of envenomation in pregnancy are guided primarily by studies on nonpregnant persons and case reports of pregnancy. Clinically significant envenomations in pregnancy are reported for snakes, spiders, scorpions, jellyfish, and hymenoptera (bees, wasps, hornets, and ants). Adverse obstetric outcomes including miscarriage, preterm birth, placental abruption, and stillbirth are associated with envenomation in pregnancy. The limited available literature suggests that adverse outcomes are primarily related to venom effects on the mother. Optimization of maternal health such as management of anaphylaxis and antivenom administration is likely the best approach to improve fetal outcomes despite potential risks to the fetus of medication administration during pregnancy. Obstetric evaluation and fetal monitoring are imperative in cases of severe envenomation. **Conclusion.** The medical literature regarding envenomation in pregnancy includes primarily retrospective reviews and case series. The limited available evidence suggests that optimal management includes a venom-specific approach, including supportive care, antivenom administration in appropriate cases, treatment of anaphylaxis if present, and fetal assessment. The current available evidence suggests that antivenom use is safe in pregnancy and that *what is good for the mother is good for the fetus*. Further research is needed to clarify the optimal management schema for envenomation in pregnancy.

Keywords Pregnancy; Snakes; Scorpions; Spiders; Hymenoptera; Jellyfish

Introduction to envenomations in pregnancy

The incidence and prevalence of envenomation during pregnancy have been notoriously difficult to estimate. These difficulties emanate from the rarity of exposures in industrialized nations, reporting bias related to the underreporting of minor envenomations, and limited reporting capabilities of the countries where the bulk of envenomations occur.

Envenomations during pregnancy pose all the problems of envenomation in the nonpregnant state with additional complexity related to maternal physiologic changes, concerns related to medication use during pregnancy, and the well-being of the fetus. Possible adverse obstetric outcomes

after envenomation include placental abruption, preterm labor, and fetal loss. Clinicians faced with an envenomation during pregnancy should be familiar with the principles of envenomation treatment during pregnancy, the nuances related to the type of envenomation, management of possible complications of envenomation, and reasonable measures to assure fetal well-being.

However, evaluation and management of envenomation in pregnancy are hampered by the paucity of evidence on this topic. Case series, retrospective reviews, and poison center database analyses make up the bulk of available literature. Level I evidence is conspicuously absent, as is true for many topics which are both rare and concerning obstetric issues. In addition, publication bias and changes in publication practices over time may confound interpretation of the reported rates of adverse envenomation effects in pregnancy. Although there are a few prospective studies and some large retrospective cohort studies in envenomation research, there are virtually none with regard to envenomations in pregnancy. Most scientific

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evidence is either extrapolated from nonpregnant patients or based on case series and reports and thus the Level of Evidence (LOE) is III or less. With only Level III scientific evidence, the basis for Grade of Recommendations (GOR) becomes “C” at best (see Table 1). In our review, all LOE is “III” and all GOR is “C” unless otherwise indicated.

We report the evaluation and management of clinically significant envenomations in pregnancy for snakes, spiders, scorpions, jellyfish, and hymenoptera (bees, wasps, hornets, and ants).

Methods

In January 2012, we searched the U.S. National Library of Medicine Medline/PubMed, Toxline, Reprotox, and Micromedex databases, core surgery and internal medicine textbooks, and references of retrieved articles for the years 1966 through 2011. Search terms included “envenomation in pregnancy,” “stings in pregnancy,” “antivenom use in pregnancy,” “anaphylaxis in pregnancy,” and variants of these with known venomous animals. Reference lists generated further case reports and articles. We included English language articles and abstracts.

Snake bites

There are an estimated 1.2 million to 5.5 million snake-bites per year, with up to 1.8 million envenomations and up to 94,000 deaths.¹ There are five families of medically important snakes: Atractaspididae, Colubridae, Elapidae, Hydrophiidae, and Viperidae. In the United States, Viperids are represented by three genera and over 30 species of the Family Crotalinae (rattlesnakes, copperheads, and cottonmouths) and two genera and three species of one Elapid, the coral snake. Crotalinae generally produce a syndrome characterized by local tissue injury, which may

include necrosis, and hematologic toxicity, including thrombocytopenia, hypofibrinogenemia, and other coagulation abnormalities. There may be systemic effects, such as nausea and diaphoresis or hypotension and, rarely, neurotoxicity such as muscle fasciculation or weakness that usually does not result in respiratory compromise. The coral snake, typical of elapids, generally does not produce significant local tissue effects and primarily produces neurotoxicity, which can include respiratory arrest. In other parts of the world, elapids, such as the spitting cobra (*Naja mossambique*) in Africa and the spotted black snake (*Pseudechis guttatus*) in Australia, may produce significant local tissue injury, and other elapid venoms may cause rhabdomyolysis, renal injury or other effects.²⁻⁴ Knowledge of envenomation syndromes in a geographic area often informs evaluation and management decisions.

Snake envenomation during pregnancy

Case reports with adverse outcomes. Adverse pregnancy effects may be due to the direct effects of venom on the mother or fetus or secondary to primary maternal illness.⁵ In a report on an envenomation in a pregnant woman bitten by a brown snake (genus *Pseudonaja*), death of the mother was believed to be associated with supine hypotension from aortocaval compression rather than entirely from the venom itself.⁶ A woman bitten by a pit viper in Japan at 10 weeks gestation developed systemic effects, including paralysis of the right oculomotor nerve and rhabdomyolysis and was administered intravenous cepharanthine, ulinastatin, hydrocortisone sodium succinate, gabexate mesylate, and antibiotics. Although she recovered, fetal demise was confirmed one week later on ultrasound examination.⁷ A 2010 report from Nepal described a 33-week pregnant woman who was bitten by a green tree viper (*Trimeresurus albolabris*) 6 days prior to presentation. She developed vaginal bleeding, anemia, and severe abnormalities in her coagulation profile. Her fetus was dead when she presented for care. After correction of the coagulation profile, labor was induced and she subsequently recovered.⁸ There are also a number of case reports of placental abruptions associated with altered maternal coagulation following snake bite, primarily from the Viperidae family.⁸⁻¹¹

Case series with adverse outcomes. In a letter to the editor in 1985, which included very abbreviated case reports regarding unknown snake envenomations in Sri Lanka, indirect evidence of placental transfer was described with adverse fetal effects in the absence of maternal symptoms. In that letter, four cases of maternal snake bites were reported in which fetal movements were perceived as being less or became absent before or in the absence of maternal illness. In three of those cases, where bites occurred at 32 to 36 weeks gestation, the fetuses survived and were delivered alive at term. In the fourth case, of unspecified gestational age, fatal maternal illness developed, although not until after fetal movement had slowed. The fetus was

Table 1. Levels of evidence and Grades of Recommendations.*

Levels of evidence:	
IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Grades of recommendations:	
A	Directly based on Level I evidence
B	Directly based on Level II evidence or extrapolated recommendations from Level I evidence
C	Directly based on Level III evidence or extrapolated recommendations from Level I or II evidence
D	Directly based on Level IV evidence or extrapolated recommendations from Level I, II, or III evidence

*From Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Developing clinical guidelines. West J Med. 170(6):348-51, 1999 June.

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stillborn the day before the mother's death, after the onset of maternal signs and symptoms of illness.¹² A 2002 series of 39 snake-envenomated pregnant women in Sri Lanka had a fetal loss rate of 30%. Fourteen patients were hump-nosed vipers (*Hypnale hypnale*); nine were Russell's vipers (*Daboia russelii russelii*); two were by the Sri Lankan krait (*Bungarus ceylonicus*); and 14 were by unknown species. Patients were followed up in hospital for at least 10 days post-bite and for pregnancy outcome. Loss of pregnancy, when it occurred, happened within 7 days of the bite in all cases and only in pregnancies of 18 weeks or less. Maternal outcomes were good in all cases, but fetal loss occurred in four of the Russell's viper, one of the Sri Lankan krait and five of the unknown envenomations; and there were fetal malformations (hydrocephalus and polydactyly) in one of Russell's viper envenomations that occurred at 16 weeks gestation. Seventeen patients received antivenom and, of these, ten had fetal loss and one had malformations. As with retrospective reports, causality is impossible to attribute, but the patients who exhibited systemic effects were more likely to receive antivenom.¹³ A 1992 review of 50 cases of Crotalidae (rattlesnake, copperheads, and cottonmouths) snake bites during pregnancy in the United States, which occurred during the pre-FabAV era, reported a 10% maternal mortality rate and a 43% fetal demise rate. Aside from differences in basic medical care compared to today, increased antivenom-related morbidity and mortality from the higher rates of anaphylaxis secondary to an unpurified IgG antivenom, and the greater reluctance to use a potentially fatal treatment might also have contributed to the rates of maternal and fetal morbidity and mortality.¹⁴

Finally, a review summarized the worldwide snake-bite experience in pregnancy from 1966 to 2009. With modern cases taken into account, maternal mortality was 4% and fetal loss 20% among 213 envenomations during pregnancy. In this series, 96 pregnant women received antivenom. Among women treated with antivenom, maternal death was less frequently recorded (2.1% vs. 6.6% untreated), but fetal loss was more common (30.2% vs. 11.3% untreated). Without being able to control for venom source, severity of envenomation, gestational age, access to care, or antivenom type, it is impossible to draw conclusions regarding the benefit of antivenom. It should be noted, however, that only one reported case of serum sickness in a pregnant patient envenomated by a *Vipera palaestinae* snake followed administration of an unknown amount of antivenom.¹⁵

Case series with more favorable outcomes. In contrast to the relatively high rates of fetal loss in the above reports, our report in 2010, a retrospective case series of rattlesnake bites between 2001 and 2007 using the American Association of Poison Control Centers (AAPCC) database, suggested a lower short-term risk in pregnancy. Sixty-one poison control centers reported a total of 8,413 rattlesnake bites, with 767 (9.1%) involving reproductive age women. Of these, 11 (1.4%) were pregnant. It is difficult to compare the severity of envenomation between the earlier U.S.

study and our report, since differences can be a function of healthcare access, quality of supportive measures, and perhaps most importantly, frequency and timing of antivenom treatment, particularly in light of FabAV's improved safety profile. Six of eleven cases were coded as having moderate or major envenomation effects, which was not different from nonpregnant matched controls. There were no significant differences between pregnant and nonpregnant victims with regard to rates of hospital admission, antivenom administration, or overall outcome codes. Eight of the 11 pregnant patients received antivenom, which was higher than that for nonpregnant patients. There were no adverse reactions to antivenom in pregnant women and no maternal deaths or fetal losses while in the hospital or during the period of poison control center follow-up.¹⁶

Case reports and series with good outcomes. A number of reports and series of snake bites during pregnancy from a variety of species and from varied geographic locations around the world have revealed normal outcomes, even when antivenom was thought necessary.^{17–22} Although limitations of snake identification, inconsistent medical evaluation of envenomation, incomplete follow-up data and other methodological difficulties exist in these reports, it is reasonable to conclude from both these and the prior series that snake envenomation is not inevitably associated with adverse outcomes on the fetus.

Management of snake envenomation during pregnancy. Initial first aid is directed at reducing spread of the venom and expediting transfer to an appropriate medical center.²³ The patient should be removed from the snake's territory, kept warm and at rest, and be reassured. Although there are few data regarding positioning of the bitten body part and outcomes, as a default option, the injured part of the body should be immobilized in a functional position at or slightly below the level of the heart. If the pregnant patient is in a supine position, standard obstetric practice would favor a left lateral decubitus position.

In elapid envenomations in which local tissue injury is likely to be minimal, the use of a pressure bandage with immobilization (PBI) will retard venom entry into central circulation and may allow for initiation of antivenom before neurotoxic effects occur. Training and retention of skills of lay and pre-hospital providers have proven problematic and may result in either ineffectual or overly constricting bandaging.²⁴

A recent position statement of six toxicology societies, reflecting the consensus of toxicologists on four continents, reviewed the scientific evidence for PBI in *Crotalinae* envenomations. While animal studies demonstrated delayed systemic absorption of venom and delayed mortality, the local effects of sequestering cytotoxic venom in the extremity included elevated tissue pressures to levels that could impair vascular supply.²⁵ The routine use of pressure bandaging in such envenomations is not recommended.²⁶ The risk-to-benefit determination in such cases when severe early systemic effects are seen should be made with the assistance of an experienced clinician.

Investigations into venom suctioning or removal devices do not show additional benefit, may cause additional local tissue injury and/or delay transport, and are therefore not recommended.^{24,27,28}

Knowledge about the toxicity profiles of local snake species is vital, and expert advice should be sought when managing a snake envenomation in a pregnant patient, when the clinician is unfamiliar with envenomation, or if severe or unusual effects occur. During pregnancy, antivenom should be considered in snake envenomations for which it is usually required as definitive management or in envenomations which are refractory to initial supportive care.

Snake envenomations, particularly with Crotaline and other viperid snakes, may be accompanied by hematologic abnormalities, such as thrombocytopenia, hypofibrinogenemia and prolongation of INR or aPTT. Laboratory testing should evaluate for these potential abnormalities. Additional antivenom is the mainstay in treating hematologic abnormalities. Blood products are reserved for significant bleeding and when there is the possibility of persistent or recurrent venom, antigenemia should be given with additional antivenom.²⁹ Although there are no cases or series relating to pregnancy and the use of blood products in envenomation, based on nonpregnancy management recommendations, we believe that blood products may be used in this context with the same indications and recommendations.^{29–31}

In the pregnant patient, prolonged monitoring in the hospital is indicated.^{7,14,16} We recommend a minimum of 8 h of fetal heart rate (FHR) monitoring if the pregnancy is at a viable stage (usually beginning at 24 weeks).⁶ Although the evidence is weak and may vary by snake species and geographic location, an extended period of observation, perhaps a week or more (although not necessarily as an inpatient), of envenomated pregnant patients appears warranted. Reports of decreased fetal movements and fetal death a few days after clinically significant envenomations suggest that ongoing outpatient surveillance with daily FHR monitoring for up to 1 week may be helpful in identifying pregnancies at risk for adverse outcome.^{7,16} Patients may be counseled that prognosis for the fetus is especially guarded in the first trimester.

Spider bites

Reports of spider envenomation during pregnancy

Black widow spider (*Latrodectus spp.*) envenomation is a rare occurrence in pregnant women, and short-term outcomes appear to be favorable.³² There are four published case reports of widow spider bites in pregnant women, whose gestational ages ranged from 16 weeks to 38 weeks.^{33–35}

In addition, we previously reported a large observational study based on a review of the AAPCC database from 2003 to 2007.³⁶ Of the 12,640 human black widow spider envenomations, 3,194 (25.3%) involved women of reproductive age and 97 (3%) of these were pregnant. When pregnant women were compared with nonpregnant women, no significant differences were found in recommended or administered treatments.

A significantly higher percentage of pregnant patients were treated at a healthcare facility and admitted for care (13.4% v. 4.0%, $p < 0.001$) than nonpregnant patients.³⁶ There were no documented immediate pregnancy losses in that series, though the period of follow-up was not specified.³⁶

There have been six reported cases of *Loxosceles* bites in pregnant women. Although the victims were apparently in considerable discomfort, they were generally managed with supportive care, including analgesics, antihistamines, and short courses of low-dose steroids, and pregnancy outcomes were favorable in all instances.^{37,38} Although a *Loxosceles* antivenom is available in South America, we have been unable to locate any reference about the use of the antivenom during pregnancy.³⁹

Management of spider bites in pregnancy

Most patients who sustain a spider bite require only topical therapy (clean with mild soap and water; apply cold, not frozen, packs; and elevate affected body part).

Latrodectus envenomations

Patients with moderate to severe envenomations from *Latrodectus* spiders, as characterized by severe local pain and/or muscle spasm or the presence of regional or systemic symptoms, require supportive care and monitoring for complications. Parenteral or oral opioid analgesia and parenteral or oral benzodiazepines as needed, and tetanus toxoid may be used safely during pregnancy.^{40,41} Hypertension persisting beyond pain and muscle spasm control may rarely require management. Hydralazine or labetalol may be safely used in pregnancy in an acute or subacute care setting. Oral antihypertensives considered safe in pregnancy include methyldopa, labetalol, and nifedipine.^{42–44}

Because opioids and benzodiazepines provide only transient relief of symptoms, and may be required at high doses and for prolonged durations, *Latrodectus* antivenom (*Latrodectus mactans*, Wyeth; US FDA Pregnancy Category C) should be considered early in the course of an envenomation in a pregnant patient. Local, regional, or systemic effects that are not readily responding to moderate doses of opioids and/or benzodiazepines should prompt consideration of the use of *Latrodectus* antivenom. Antivenom may still be effective if administration is delayed and has been reported to be effective up to 90 h post-envenomation.¹⁰⁶ The dose of antivenom is one vial, which may be repeated once and rarely twice. The antivenom usually results in complete resolution of the envenomation syndrome within a few hours and may prevent the need for hospitalization, and adverse effects of the antivenom in pregnancy have not been described. Mortality due to widow bites is low.⁴⁵ There are a number of *Latrodectus* antivenoms worldwide and these appear to have cross-efficacy.⁴⁶

Loxosceles envenomations

There are no treatments that have been shown to alter outcomes in *Loxosceles* envenomations. If the wound appears

infected, antibiotics are indicated. Necrotic ulcers that are large and slow-healing may require surgical management.

Dapsone, an anti-inflammatory agent, has been shown to provide some improvement when given to experimental animals prior to envenomation, but it has not been shown to be of value in human envenomations and is not indicated.⁴⁷ Conflicting animal studies have led some clinicians to continue using dapsone. Dapsone may induce hemolysis and/or methemoglobinemia, particularly in patients with G6PD deficiency. Although there are reports of approximately 1000 pregnant women who have been treated with dapsone without adverse effect, those reviews and case reports were not specifically designed to study possible reproductive effects of dapsone, and dosage and timing of dapsone use were not always clear.^{47,48} Some cases of hemolytic anemia have occurred in mothers and their offspring after exposure to dapsone, both during gestation and while breastfeeding. As such, we do not recommend dapsone use for spider bite in pregnancy.

There is no obstetric literature pertaining to the Funnel-web spider (*Atrax* spp) and the Brazilian wandering spider (*Phoneutria* spp) and, in general, standard management of these envenomations, including the use of available and specific antivenoms, should be employed.

Scorpion stings

Scorpion stings result in a variety of presentations from mild symptoms to death. Differences in scorpion venoms and healthcare systems may affect outcomes. Envenomations by scorpions in North Africa, South America, and the Indian subcontinent cause significantly greater morbidity and mortality than in North America, but reports in pregnancy are rare.^{49–51} In the US, one species of scorpion is of particular clinical significance, *Centruroides sculpturatus*, for which there is now an FDA-approved antivenom.

Animal studies of scorpion envenomation during pregnancy

Evidence regarding the natural history and treatment of scorpion envenomations in pregnancy is derived from animal data, and extrapolation to humans is limited by differences in study design and interspecies differences and response to envenomation. The gestation period in rats, for example, is 21–23 days. Although days 1–7, 8–14, and 15–23 represent the first, second, and third trimesters, respectively, direct comparison to human development is imperfect. Investigations in gravid rodents have revealed mixed results. Turkish investigators reported that pregnant rats treated with venom from the fat-tailed scorpion (*Androctonus amoreuxi*) had an elevated incidence of fetal resorption, ossification defects, and reduced weight. Use of radio-labeled venom indicated that only a small fraction (0.08–0.331%) was detected in fetuses or placenta.⁵²

A single subcutaneous injection in pregnant rats with venom from the Brazilian scorpion *Tityus serrulatus* at 0.3 or 1 mg/Kg on gestation day 5 or 10 did not produce

adverse effects on the offspring.⁵³ Pregnant rats exposed to the venom of the Brazilian scorpion (*Tityus bahiensis*) at doses not toxic to the dam bore offspring with alterations in the time to achieve developmental milestones.⁵⁴

The presence of 5-hydroxytryptamine in some scorpion venoms (found in scorpions native to North Africa, the Middle East, the Arabian Peninsula, India, Pakistan, and Nepal) may act as a uterine stimulant and induce abortion.^{55–57}

Management of scorpion envenomation in pregnancy. Regardless of location, in the instance of mild symptoms, initial management is the same during pregnancy: cleansing of the sting site, using oral or parenteral sedative and pain medications (e.g. midazolam and morphine sulfate), and administering tetanus prophylaxis. Nonsteroidal anti-inflammatory drugs should be avoided in pregnancy; some, though not all, epidemiology studies have suggested that use of nonsteroidal anti-inflammatory drugs, including ibuprofen, during pregnancy may increase the risk of cardiac defects and gastroschisis.⁵⁸

Use during late pregnancy should be avoided due to concerns about premature closure of the fetal ductus arteriosus.^{59,60}

Pregnant patients should be observed for at least 4 h to ensure that there is no further progression of pain or other symptoms. Those with rare but significant systemic symptoms, including restlessness, muscular fasciculation, hypersalivation, and cranial nerve palsies, require immediate supportive interventions.^{61,62} Airway management, including frequent suctioning of oral secretions or endotracheal intubation, may be indicated in patients with pulmonary edema accompanied by hypoxemia or significant difficulties in maintaining airway patency. Maintaining adequate maternal oxygenation is of utmost importance to the fetus. Close monitoring for and treatment of myocardial ischemia is also warranted in patients with severe symptoms. Short-term treatments during pregnancy may include intravenous fentanyl for pain, and intravenous benzodiazepines (lorazepam or continuous midazolam infusion) may be given for sedation and to treat muscle spasticity.

Scorpion antivenom (Anascorp[®], Bioclon, Mexico) was approved for use in the United States in August, 2011.⁶³ Because the neurotoxic syndrome is seen almost exclusively in children < 10 years of age, antivenom use is most likely to be considered in that population. However, severe pain in adults not responding to reasonable doses of opioids or other systemic effects that may pose a danger to the patient or a fetus should be considered for antivenom therapy. There are anecdotal reports about pregnant women treated with *Androctonus* antivenom without adverse fetal effects.⁵⁷ No immediate hypersensitivity reactions, serum sickness, or deaths have been reported in studies of adults and children receiving the *Centruroides* antivenom.⁶⁴ We have been unable to locate any additional references on possible adverse reproductive or lactation effects from these agents.

Hymenoptera

Hymenoptera of clinical relevance include membrane-winged insects such as bees, wasps, and hornets, and wingless insects such as fire ants. Stings from these hymenoptera involve the injection of venom, which is almost always acutely painful and noticed by the patient. Although most stings require only symptomatic relief for acute pain, anaphylactic hypersensitivity occurs in 0.3–3% of patients with an insect venom allergy.⁶⁵

Reports of hymenoptera envenomation during pregnancy

A few case reports of hymenoptera envenomation were located in the obstetric literature, and predictably focused on clinically significant events such as anaphylaxis. It is unknown if systemic reactions to hymenoptera venom are more or less likely during pregnancy. Unfavorable perinatal outcomes are most likely to be reported, and fetal effects of envenomations are speculative.

A case report from Croatia described a multigravida who presented at 27 weeks gestation with anaphylaxis after a wasp sting. The authors noted that delivery occurred at 35 weeks despite tocolysis and a cerclage, and attribute the delivery to a “post-anaphylactic reaction.” The child developed normally after the delivery.⁶⁶

Another adverse outcome was reported in association with anaphylaxis after a bee sting. A 31-year-old was stung at 30 weeks gestation and developed severe anaphylaxis. Details of treatment were scant but included IV hydrocortisone acetate. Subsequently, the fetus was noted to have an increased biparietal diameter and decreased movement. Spontaneous preterm labor occurred at 35 weeks, and the infant was found to be cyanotic and hypotonic. The infant died at 64 days, and autopsy demonstrated cystic cavitation of the white matter consistent with hypoxic injury. It was speculated that infantile encephalomalacia resulted from maternal anaphylaxis after bee envenomation.⁶⁷

A case from the United Arab Emirates linked placental abruption and intrauterine death with an ant sting. A 21-year-old woman at 40 weeks gestation presented with dyspnea and swelling after a Samsun ant (*Pachycondyla sennaarensis*) sting. She was treated for anaphylaxis, the details of which are unclear, then developed vaginal bleeding 16 h later. On ultrasound, a placental separation and fetal demise were diagnosed. A retroplacental clot was confirmed at delivery.⁶⁸ Of course, retrospectively identifying causation is a perilous process; in animal studies, medications used in treatment of anaphylaxis such as epinephrine also carry a risk of placental abruption.⁶⁹

Management of hymenoptera envenomations during pregnancy

Desensitization to venom proteins for venom allergy to prevent future reactions in previously stung patients who developed large local or systemic reactions has been available for over 30 years and is highly effective.⁷⁰ Initiation of venom immunotherapy in pregnancy is generally avoided

by allergists due to a lack of safety data, although limited reports of use in pregnancy do not suggest an increased risk of adverse outcomes. As such, pregnant women should be considered for continuation of venom immunotherapy if initiated prior to pregnancy. Care should be taken to monitor for signs of preterm labor in this group, because uterine contractions have been reported during or after venom immunotherapy in several case reports.⁷¹ Victims of hymenoptera envenomation who develop systemic reactions or severe local reactions should be referred upon discharge to an immunologist for evaluation and possible treatment with immunotherapy.⁷²

During pregnancy, management of hymenoptera envenomation consists of standard first aid as well as evaluation for anaphylaxis. The very limited evidence regarding fetal effects suggests that management of maternal anaphylaxis is the most important and perhaps only relevant intervention.

Jellyfish

Although there are over one hundred species of jellyfish known to cause human envenomations, the most clinically relevant species include *Chironex fleckeri* (box jellyfish), *Carukia barnesi*, and *Physalia physalis* (Portuguese Man-of-War).⁷³ The subsequent local and potentially systemic reactions range from minor nuisance to myocardial injury or Irukandji Syndrome (*C. barnesi*), a life-threatening cascade of multisystem organ failure due to systemic hypersensitivity.⁷⁴

Reports of jellyfish envenomation during pregnancy

Only one case report of serious jellyfish envenomation was found in the obstetric literature. This case involved a 20-year-old woman at 34 weeks gestation in Australia. She was stung extensively by the box jellyfish *Chironex fleckeri*, began screaming in pain, and then experienced pallor and altered mental status. A park official reported that she developed apnea and cyanosis. He doused the tentacles and stings with methylated spirits and began cardiopulmonary resuscitation (CPR) with expired air. A nurse, who also happened to be pregnant at 37 weeks, was summoned. She also observed cyanosis and performed CPR, which led to spontaneous ventilation. In doing so, the gravid nurse suffered stings from adherent tentacles. The original victim was transported by ambulance to a hospital and antivenom was administered within 30 min of the envenomation. She recovered, was discharged from hospital on day 4, and delivered a healthy term infant. No further information is available regarding the treatment or outcome of the gravid nurse.⁷⁵

The above case is too limited to draw conclusions. There were, however, no documented adverse fetal outcomes associated with the two known jellyfish stings during pregnancy.

We recommend steps to limit jellyfish exposure during pregnancy. Protective mesh clothing and commercially available Safe Sea lotion (Nideria Technology Ltd, Israel; concentrations of ingredients not specified by the

manufacturer) have been shown to reduce sting frequency, though there are no data regarding safety in pregnancy for the latter.⁷⁶ If a jellyfish sting is suspected or confirmed, symptom relief and observation is usually the only necessary treatment. Tentacles and nematocysts should be removed with a plastic object such as a credit card and washed with seawater.⁷⁷ Vigorous rubbing and immersion in cold freshwater should be avoided due to the potential to trigger nematocyst discharge. A randomized control trial with nonpregnant volunteers (Level II evidence) suggests that immersion in water heated to 110–113°F (43.3–45°C) and treatment of affected areas with acetic acid (household vinegar) are beneficial.⁷⁸ Pregnant women with a small-area sting and mild, strictly local symptoms do not require medical attention other than tentacle removal and sea water and vinegar application. Immersion in hot water should be restricted to extremities only.

Severe jellyfish stings with systemic effects require immediate medical care and possibly antivenom administration.⁷⁹ In Australia, box jellyfish (*Chironex fleckeri*) stings have caused more than 70 known deaths. Large tentacle exposure can produce cardiotoxic, neurotoxic, dermonecrotic, and hemolytic effects.⁸⁰ *Carukia barnesi*, found in Australia, Hawaii, and Florida, can cause a hypersensitivity reaction marked by myocardial injury and pulmonary edema known as Irukandji Syndrome.⁷³ *Chironex fleckeri* antivenom and magnesium sulfate may play a role in patients with cardiogenic shock, pulmonary edema, or deteriorating critical condition.⁸¹

A delayed hypersensitivity reaction can occur 7–14 days after jellyfish envenomation. Symptoms can include papules, urticaria, and an erythematous welt in the shape of the jellyfish tentacles.⁸² Antihistamines and topical corticosteroids are recommended. Resolution is expected within 10 days, although some reactions can be refractory.

Any sign of systemic reaction should be taken seriously and would include inpatient evaluation or prolonged observation. If cardiopulmonary compromise is present or suspected, supportive intervention should be initiated as with a nonpregnant patient. Sheep serum antivenom may be considered in severe cases of box jellyfish envenomation with life-threatening processes such as airway compromise and cardiovascular collapse if maternal benefit would be expected. Magnesium sulfate therapy, which is considered to be safe in pregnancy and is commonly used for other obstetric conditions, has been suggested as a beneficial adjuvant therapy in patients receiving antivenom.⁸¹

General principles of envenomation in pregnancy

Pregnancy testing should be considered in all reproductive aged women after clinically significant envenomation. Depending on the venomous animal involved, clinical evaluation of envenomation may be the same as in the nonpregnant patient, or may be complicated by obstetric concerns. For instance, black widow envenomation may produce hypertension, abdominal pain, headache,

and proteinuria in both the pregnant and nonpregnant patients.⁴⁵ The pregnant patient, however, requires a workup for pre-eclampsia in addition to Latroductism. This includes complete blood count, liver function tests, serum creatinine, lactate dehydrogenase, uric acid, and evaluation for proteinuria. Persistent hypertension and proteinuria, particularly in the setting of an elevated uric acid or hemolysis, suggest pre-eclampsia.⁸³

During pregnancy, symptomatic and supportive drugs are used sparingly and at the lowest doses in order to avoid confounding clinical assessment and to minimize fetal risk. In general, for nearly all envenomations, prophylactic use of antibiotics (e.g. dicloxacillin, cefazolin, and metronidazole) after envenomation is not indicated unless signs suggestive of infection are present, which is unlikely to be seen prior to 24–48 h after an envenomation. With snake envenomations that include tissue necrosis, prophylactic antibiotics are sometimes recommended, although their efficacy in preventing infection is not known.² Any short-term course of broad-spectrum antibiotics is presumed to be safe during pregnancy, with the exception of tetracyclines, fluoroquinolones, and chloramphenicol.⁸⁴ Metronidazole in the first trimester and trimethoprim–sulfamethoxazole in the third trimester are relatively contraindicated in pregnancy.^{85,86} The need for tetanus toxoid should be assessed and administered to people at risk of tetanus regardless of pregnancy status.^{40,87} A CDC Immunization Safety Review Committee assigned with studying tetanus prophylaxis in pregnancy did not find an increase in adverse outcome after tetanus toxoid maternal inoculation.⁸⁸

Consultation with a poison center and its medical toxicologist (1-800-222-1222, in the U.S. and served territories) or other clinician with expertise in managing envenomations is recommended when treating an envenomated pregnant patient. The poison center can also be helpful in locating and obtaining antivenom for unusual or non-native (exotic) envenomations, which may not be stocked at the hospital pharmacy.

Laboratory studies are guided by the usual assessment of any particular envenomation. Additional serum testing (electrolytes, coagulation tests, liver enzymes, etc.) may be needed depending upon the scenario and clinical course.

Concerns about pregnancy, or obvious pregnancy-related risks or effects, may prompt providers to observe envenomated patients longer in an emergency department, or to admit them to the hospital for monitoring or additional treatment. There are few data on pregnancy outcomes in most envenomations. There are variable rates of fetal loss throughout the world. Higher rates in some areas may be secondary to venomous animals with higher degrees of maternal or fetal toxicity or may be secondary to a lack of appropriate medical care in their native environments.^{89,90} In the U.S. there are few reports of significant, adverse pregnancy outcomes with envenomations, other than when there is significant maternal toxicity. More comprehensive studies are needed to better characterize the long-term results of specific envenomations in pregnancy and to determine any additional strategies other than standard therapies.

Management of envenomation-related anaphylaxis in pregnancy

In the pregnant patient, standard treatment for signs of anaphylaxis (widespread hives, wheezing, airway compromise, and altered mental status) should be administered. This includes antihistamines and early administration of intramuscular epinephrine. If the individual has a history of hypersensitivity, and an anaphylaxis kit with antihistamines and an autoinjector of epinephrine is available, it may be used following a sting. Pre-hospital providers may also administer antihistamines and intramuscular epinephrine as indicated and provided in their policies and procedures. Injection of epinephrine in experimental animals interferes with embryo development, possibly through hemodynamic effects and decreased uterine perfusion.⁹¹ In the setting of anaphylaxis, however, the benefit of epinephrine almost always outweighs the theoretical risk. In pregnancy, we recommend Trendelenburg/left lateral recumbent positioning, which may be especially important as poor cardiac return has been suggested as the final step in anaphylactic deaths.⁹²

Particularly in the acute care setting, maternal resuscitation is the fastest and safest way to assure fetal well-being. However, antepartum anaphylaxis following antibiotic administration has been associated with severe fetal neurologic injury after initial efforts to resolve hypoxia and hypotension failed.⁹³ In the event that initial efforts to restore maternal oxygenation and circulation are unsuccessful, emergent cesarean section provides the only way of restoring fetal oxygenation (See Fig. 1).

Corticosteroids are often used with significant Type 1 and Type 3 (antibody–antigen immune complexes) allergic reactions. The effects of corticosteroids will not begin for many hours after administration and they should not be used for mild to moderate reactions that have resolved or are resolving. In pregnancy, prolonged corticosteroid use is

associated with fetal growth impairment, though short-term use is unlikely to have an effect.⁹⁴ In early pregnancy, corticosteroids increase oral clefting in experimental animals, yet are less likely to do so in humans.⁹⁵ If bronchoconstriction is a concern, inhaled beta-sympathomimetics may be considered. Human studies on inhaled beta-sympathomimetics during pregnancy have not suggested an increased risk of birth defects.⁹⁶

Antivenom use during pregnancy

Any decision to use a specific antidotal therapy—antivenom—must take into account the potential for allergic reactions, either Type 1 (anaphylactic or anaphylactoid) or Type 3 (antibody–antigen immune complexes), the risk of complement activation, and the specific risk-to-benefit assessment in pregnancy, which includes the potential for adverse effects on the fetus. Antivenoms are generally indicated in any of the following situations: 1) evidence of systemic envenomation (e.g. neurotoxicity, coagulopathy, rhabdomyolysis, persistent hypotension, or renal failure), 2) severe local envenomation effects such as the extensive local tissue injury following snakebite, and 3) as prophylaxis against envenomations with high potential for effects.^{97,98}

A systematic review of antidote use during pregnancy was published in 2003. Few cases of antivenom are included, though the authors concluded that no antivenom was clearly associated with negative fetal effects and recommended treatment to improve maternal morbidity and mortality.⁹⁷ Specific reviews of antivenom use in pregnancy are lacking. However, a summary of modern case series of envenomation in pregnancy reveals that antivenom use is frequent and fetal loss is the exception (see Table 2).

Most antivenoms have little or no reproductive safety data. Reproduction studies regarding the *Crotalinae*

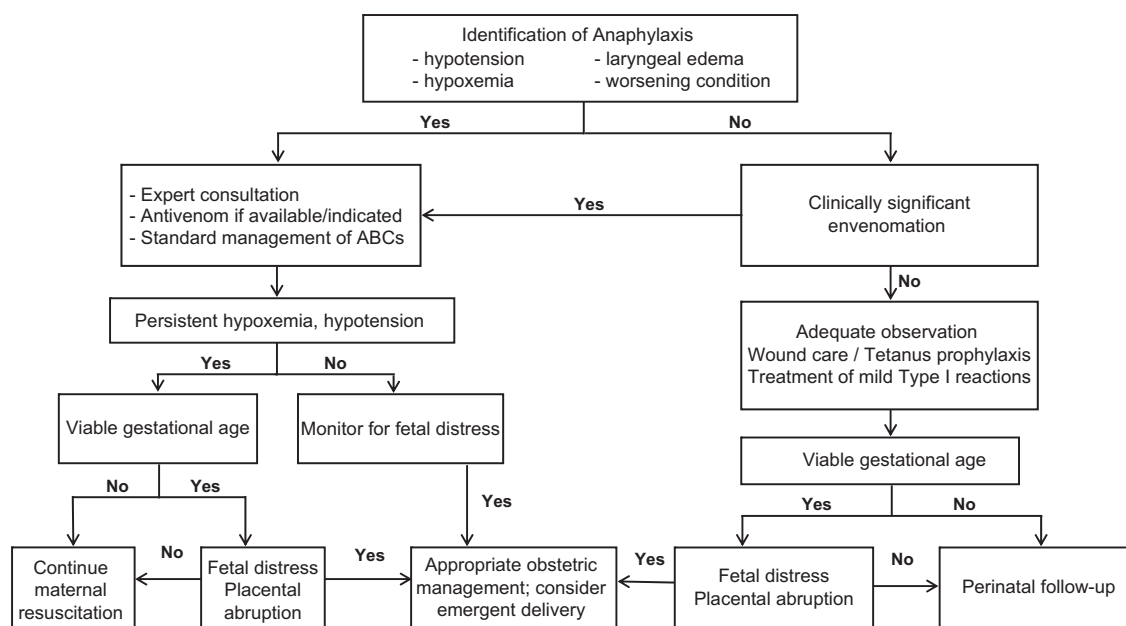


Fig. 1. Acute care of envenomation in pregnancy.

Table 2. Studies and case series of envenomation in pregnancy.*

Envenomation	No. of cases	No. receiving antivenom	Maternal mortality	Fetal loss	Study (first author)
Snakes					
<i>Agkistrodon contortrix</i>	19	0	0	0 ^a	Seifert ¹⁰⁵
<i>Agkistrodon piscivorus</i>	5	1	0	0 ^a	Seifert ¹⁰⁵
<i>Duboisia russelii russelii</i>	9	7 (78%)	0	4 (44%)	Seneviratne ¹⁶
<i>Echis ocellatus</i>	10	10 (100%)	0	1 (10%)	Habib ⁶
<i>Hypnale hypnale</i>	14	0	0	1 (7%)	Seneviratne ¹⁶
Rattlesnake (NOS)	7	4 (57%)	0 ^a	0 ^a	LaMonica ²¹
Rattlesnake (NOS)	4	4 (100%)	0	0	Seifert ¹⁰⁵
<i>Trimeresurus stejnegeri</i>	3	2 (66%)	0	0	Chen ⁹
Viper (NOS)	11	11 (100%)	0	1 (9%)	Sarkar ¹⁵
Viper (NOS)	3	3 (100%)	0	0	Sebe ¹⁰
Spiders					
<i>Latrodectus spp</i>	97	4 (4.1%)	0 ^a	0 ^a	Wolfe ³⁶
<i>Loxosceles</i>	5	0	0	0	Anderson ³⁷
Scorpions					
Scorpion (unidentified)	12	12 (100%)	0	0 ^a	Dittrich ⁶²

NOS indicates that specific species were either mixed or not otherwise specified.

^aLimited follow-up.

*Case reports and series where the LOE is at least IIB or higher.

antivenom, CroFab® (BTG), have not been reported in animals or humans. There are no animal or human data regarding the safety of *Centruroides* (scorpion) Immune F(ab')₂, an equine-derived antivenom indicated for the treatment of patients with clinical signs of scorpion envenomation. An Australian antivenom specific for *Chironex fleckeri*, Box Jellyfish Antivenom® (CSL, Australia), is made from hyperimmunized sheep. The previously mentioned report is the only published data regarding its reproductive safety.⁷⁵

Black widow spider antivenom is not associated with additional adverse fetal effects.³² While there are only limited long-term evaluations of children whose mothers were administered black widow spider antivenom, it appears to be a reasonable therapy if indicated after clinical evaluation.

It is unlikely that F(ab')₂ and IgG antivenoms cross the placenta in large amounts. Drugs larger than 1000 Da cross the placenta very poorly. Low molecular weight heparins (3,000–15,000 Da), for instance, are known not to cross the placenta.⁹⁹ And studies in rats have shown that negligible amounts of IgG administered to the mother are found in the fetus.¹⁰⁷ Although no human studies have been performed and direct extrapolation from animal studies is not possible, F(ab')₂ and IgG antivenoms are unlikely to freely cross into fetal circulation. Fab antivenoms have a molecular weight of approximately 50,000 Da and presumably do not cross, although studies are lacking. There have been no studies evaluating the risk of antivenoms during pregnancy, nor have there been reports of adverse effects of antivenom administration in pregnancy.⁹⁷

One potential teratogenic component of antivenom is mercury, present in some antivenoms as Thimerosal (merthiolate and thiomersal). The amount of mercury in a typical dose of antivenom is not expected to cause any harm to the fetus. This component is anti-infective and preservative and has been used as an additive in many biologics, vaccines, and antivenom.¹⁰⁰ There are insufficient data to make a causal connection between thimerosal and any increased risk for

birth defects in exposed offspring. In addition, epidemiologic studies have not demonstrated a causal relationship between thimerosal and autism or autism spectrum disorders.⁸⁸

Another concern regarding antivenom use in pregnancy is anaphylaxis. Most modern, highly purified Fab, F(ab)₂, and IgG antivenoms have relatively low rates of Type 1 (anaphylaxis or anaphylactoid) hypersensitivity reactions. Before administering any antivenom, medications and equipment for the treatment of anaphylaxis should be immediately available, including intravenous fluids, epinephrine, and intubation equipment. For antivenoms with a high incidence of Type 1 reactions, in atopic individuals, those with a history of serum allergy or those already demonstrating an allergic response to envenomation, the use of histamine 1 (H1) and histamine 2 (H2) receptor blockers may be considered prior to the administration of antivenom and/or as part of the management of the reaction. The anti-histamines as a class are considered safe in pregnancy.¹⁰¹ Pretreatment with epinephrine for antivenom administration is usually not indicated, but it may be required to manage a severe Type 1 reaction.

Frequencies of Type 1 and Type 3 hypersensitivity reactions from antivenoms are presumed to be similar regardless of pregnancy. Allergic reactions should be managed by immediately stopping intravenous infusion of the antivenom (if applicable) and treating symptoms appropriately. Delayed serum sickness-like reactions are unlikely. However, any patient receiving antivenom should be informed about possible symptoms suggestive of a Type 3 hypersensitivity reaction (rashes, pruritus, arthralgia, and fever) and advised to seek medical care if such symptoms develop.

In the envenomated pregnant patient, consultation with a medical toxicologist or other physician with experience in managing various envenomations is recommended before any antivenom administration. For some envenomations, several antivenoms may be commercially available, and toxicologists or other knowledgeable providers can be helpful

in ordering the antivenom which may not be at the hospital pharmacy. Although no antivenoms have been specifically evaluated in pregnant patients, long experience has not demonstrated any particular risks and, in general, the management which is most beneficial to the mother will provide the best outcome for the pregnancy.

Principles of fetal surveillance after envenomation

Assessment of fetal well-being in the immediate aftermath of an envenomation begins with history-taking. The pregnant patient who reports of decreased fetal movement, loss of fluid, or contractions requires a full obstetric evaluation. Patients with a gestational age less than twenty-three to twenty-four weeks are considered to have pre-viable pregnancies and are appropriate for obstetric follow-up rather than urgent consultation. After this gestational age, however, initial assessment should include fetal heart rate monitoring. If maternal hemodynamic instability is identified, initial efforts should focus on correction of hypotension and hypoxemia. In the hemodynamically stable pregnant patient, fetal distress after envenomation may require emergent delivery.

If vaginal bleeding or abdominal pain creates concern for placental abruption, ultrasound evaluation of the placenta may also be performed, though up to 40% of acute abruptions are not visualized on ultrasound exam.¹⁰² In this setting, full laboratory evaluation for coagulopathy and continuous fetal monitoring of the viable fetus should also be performed. Although Kleihauer–Betke testing for materno-fetal hemorrhage has not been evaluated in the envenomated pregnant patient, in other instances of placental abruption, this test can be helpful in confirming the clinical suspicion.¹⁰³ Diagnosis of progressive placental abruption requires emergent delivery, usually by cesarean section, though mild abruptions in the premature fetus may be managed expectantly.¹⁰⁴

After stabilization and discharge, follow-up obstetric care is indicated. The evidence for transplacental passage of venom is mostly from limited studies in animals. The transplacental transfer of venom in humans may be different and also may depend on numerous factors such as characteristics of the venom and of the exposure. Because of the potential for such transfer, we recommend fetal surveillance including ultrasound evaluation of fetal growth on an ongoing basis. This is best accomplished through maternal-fetal medicine consultation.

Conclusions

In the evaluation and management of an envenomated, pregnant patient, the following questions must be considered:

1. Is the evaluation different from that of the nonpregnant patient?
2. What are or might be specific obstetrical and/or non-obstetrical complications of the envenomation? and
3. Is the management of the envenomation different in the pregnant patient and what is the role of antivenom?

Envenomations from snakes, spiders, scorpions, hymenoptera, and jellyfish likely occur with similar frequencies among reproductive aged women regardless of pregnancy. Adverse outcomes may result directly from the venom in the fetal circulation or indirectly from maternal illness or placental compromise. Prolonged or more frequent monitoring of both the patient and her fetus is justified. The same fundamental principles of symptomatic and supportive care apply to the pregnant patient. Limited experience with antivenom therapy suggests that it is safe and effective during pregnancy and may improve fetal outcome. The preponderance of available data on antivenom in pregnancy suggests that clinically indicated administration should be the standard approach to severe envenomations, regardless of gestational age. Prospective evaluations of specific envenomations and antivenoms in pregnant women would permit a clearer understanding of both short- and long-term pregnancy outcomes, though the rarity of these cases and potential for harm will likely preclude future prospective or randomized studies. With the current limited body of knowledge regarding envenomation in pregnancy, we are essentially left with the old obstetric dogma: *what is good for the mother is good for the fetus*. Despite these limitations, the limited available evidence suggests that optimal management includes a venom-specific approach, including supportive care, antivenom administration in appropriate cases, treatment of anaphylaxis if present, and fetal assessment.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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