

Anaphylaxis during pregnancy

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Anaphylaxis during pregnancy, labor, and delivery can be catastrophic for the mother and, especially, the infant. Symptoms and signs can include intense vulvar and vaginal itching, low back pain, uterine cramps, fetal distress, and preterm labor. During the first 3 trimesters, etiologies are similar to those in nonpregnant women. During labor and delivery, common etiologies are β -lactam antibiotics, natural rubber latex, and other agents used in medical and perioperative settings. Important caveats in management include injecting epinephrine (adrenaline) promptly, providing high-flow supplemental oxygen, positioning the mother on her left side to improve venous return to the heart, maintaining a minimum maternal systolic blood pressure of 90 mm Hg to ensure adequate placental perfusion, and continuous electronic monitoring. Cardiopulmonary resuscitation and emergency cesarean delivery should be performed when indicated. In all women of child-bearing age, allergy/immunology specialists can help to prevent anaphylaxis in pregnancy through prepregnancy risk assessment and risk reduction strategies, such as confirming the etiology of systemic allergic reactions, providing written instructions for allergen avoidance, and initiating relevant immune modulation. In pregnant women the benefits versus risks of skin tests, challenge tests, desensitization, and initiation of immunotherapy with allergens should be carefully weighed; if possible, these procedures should be deferred until after parturition. Prospective interdisciplinary studies of anaphylaxis during pregnancy are needed. (J Allergy Clin Immunol 2012;130:597-606.)

Key words: Anaphylaxis, pregnancy, labor, delivery, penicillin allergy, neuromuscular blocker allergy, latex allergy, neonatal group B streptococcal infection, amniotic fluid embolism, resuscitation

During pregnancy, anaphylaxis can be catastrophic and can lead to hypoxic-ischemic encephalopathy and permanent central nervous system damage or death in the mother and, more commonly, in the fetus or neonate.¹

The allergy/immunology literature includes few publications about anaphylaxis during pregnancy,²⁻⁹ and only a few allergy/immunology guidelines or practice parameters mention

Abbreviations used

AFE: Amniotic fluid embolism
GBS: Group B streptococcal
NRL: Natural rubber latex

pregnancy.^{10,11} The true incidence of anaphylaxis during pregnancy is unknown. Although it is considered uncommon, as ascertained from a gradual crescendo of relevant publications in indexed peer-reviewed journals,²⁻²⁹ it might be increasing in parallel with the increased incidence of anaphylaxis in the general population.

Here we discuss the evidence base for the assessment and management of anaphylaxis during pregnancy, labor, and delivery, consisting mostly of epidemiologic studies and case reports. We focus on the role of the allergy/immunology specialist on risk assessment and risk management in anaphylaxis in all women of child-bearing age.

ETIOLOGY

In the first 3 trimesters, before labor and delivery, the etiologies of anaphylaxis in pregnancy are similar to the etiologies of anaphylaxis in the general population. It typically occurs through an IgE-mediated mechanism leading to mast cell activation. Etiologies include allergens such as foods (shellfish, peanut, tree nuts, and others), stinging insect venoms, medications, and natural rubber latex (NRL; Table I).¹⁰

In a review of 23 patients with anaphylaxis in pregnancy reported from different countries, the etiology was a β -lactam antibiotic in 8 of 23 patients, NRL in 6 of 23 patients, and other antigens, such as suxamethonium, propanidid, ranitidine, chlorhexidine, snake antivenom, and a bee sting, in the remainder. There were no maternal deaths; however, 1 infant died and 7 infants, including 3 who were delivered at less than 32 weeks gestation, had severe neurologic anomalies.¹

In an epidemiologic study of approximately 700,000 postpartum women discharged from Texas hospitals in 2004-2005 with a diagnosis of anaphylaxis, 19 cases of anaphylaxis during labor and delivery were reported (2.7 cases per 100,000 deliveries). The etiology was a β -lactam antibiotic in 11 of 19 parturients, other antibiotics in 2 of 19 parturients, oxytocic agents in 2 of 19 parturients, and an antiemetic, antihypertensive, antirheumatic agent, or radiocontrast media in the remainder. Most (74%) of the mothers had a cesarean delivery. Information about the infants' gestational ages and outcomes was not available.²

During labor and delivery, the most common etiology of anaphylaxis is prophylactic injection of a penicillin or cephalosporin to prevent neonatal group B streptococcal (GBS) infection or to prevent maternal infection after cesarean delivery (Table I).^{1,2,4-6,14-18} Other antibiotics, oxytocin, and agents used

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TABLE I. Etiology of anaphylaxis during pregnancy

First 3 trimesters, before labor and delivery
Foods
Stinging insect venoms
Medications*
Biologic agents, including allergen immunotherapy
NRL
Other†
Labor and delivery
Antibiotics‡
NRL
Neuromuscular blockers
Oxytocin
Local anesthetics
Transfusion of blood or blood products

Data are taken from references 1 to 10 and 12 to 29.

*Most commonly, antibiotics and nonsteroidal anti-inflammatory medications; other medications, such as intravenous iron and intravenous vitamins B1, B6, and B12 which are used for the treatment of hyperemesis gravidarum in some countries.

†Occupational allergens, including stinging insect venoms and NRL, aeroallergens (rare), radiocontrast media, and exercise. Idiopathic anaphylaxis also occurs.

‡Most commonly penicillin and other β -lactam antibiotics injected intrapartum for prevention of neonatal GBS infection or prevention of maternal infection after cesarean delivery.

in perioperative settings, including neuromuscular blockers, epidural medications, general anesthetics, NRL, and chlorhexidine, have also been implicated.^{1,3,7,19-26}

During labor, exercise rarely induces anaphylaxis.²⁷ Maternal anaphylaxis during breast-feeding is also rare; onset occurs in the first 3 days postpartum and is attributed to rapidly decreasing levels of progesterone. Anaphylaxis during breast-feeding is reported to be amplified in some women by concurrent use of nonsteroidal anti-inflammatory drugs.^{8,9,28} Rapid change in progesterone levels might be important because increased progesterone levels during the second and third trimesters of pregnancy are also rarely associated with anaphylaxis that is relieved by delivery.²⁹

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of anaphylaxis is based primarily on a detailed history of the episode and recognition of sudden onset and rapid progression of characteristic symptoms and signs, within minutes to a few hours after exposure to a likely or known allergen. More than 1 body organ system is typically involved (Table II).^{10,30,31} Hypotension and shock are not necessarily present. Anaphylactic and anaphylactoid reactions do not need to be distinguished with regard to diagnosis and acute treatment. The term "anaphylactoid" should no longer be used.^{10,30}

Potential symptoms and signs of anaphylaxis in pregnancy include intense itching in the vulvar and vaginal areas, low back pain, uterine cramps, fetal distress, and preterm labor (Table III and Fig 1).^{1,10,30} Based on case series of patients of all ages with anaphylaxis, skin and mucosal involvement is observed in 80% to 90%, respiratory tract involvement in up to 70%, gastrointestinal tract involvement in up to 45%, cardiovascular involvement in up to 45%, and central nervous system involvement in up to 15%. Symptom patterns vary from one patient to another and even from one anaphylactic episode to another in the same patient. Only a few symptoms might be present during a given episode.^{10,30}

Although there are no specific data on the usefulness of serum total tryptase measurements for confirming the clinical diagnosis of anaphylaxis in pregnant women, in some patients with anaphylaxis,

such as those with insect sting- or medication-induced anaphylaxis, the clinical diagnosis can be confirmed based on increased serum total tryptase levels. Blood samples for this test should optimally be obtained 15 minutes to 3 hours after symptom onset. Serial measurements (eg, at presentation, 1-2 hours later, and at resolution) appear to increase the sensitivity of the test.³² The total tryptase assay takes several hours to perform and is not helpful with initial diagnosis and management, although the results can be useful later. Increased total tryptase levels are not specific for anaphylaxis. They are also found in patients with myocardial infarction and amniotic fluid embolism (AFE), both of which need to be considered in the differential diagnosis of anaphylaxis during labor and delivery (Table IV).^{1,4,10,31,33-44} Moreover, total tryptase levels within the normal reference range of 1 to 11.4 ng/mL cannot be used to refute the clinical diagnosis of anaphylaxis because tryptase levels are seldom increased in patients with food-induced anaphylaxis or those in whom blood pressure remains normal during anaphylaxis.^{10,32}

During the first 3 trimesters, before labor and delivery, the differential diagnosis of anaphylaxis in pregnancy is similar to the differential diagnosis of anaphylaxis in nonpregnant patients. Common diagnostic dilemmas involve acute asthma, acute generalized urticaria, acute angioedema, syncope (fainting), and acute panic or anxiety attack^{10,33-35}; however, many other diagnoses, including mastocytosis,³⁶ need to be considered (Table IV).

During labor and delivery, the differential diagnosis of anaphylaxis includes all other causes of maternal respiratory distress or cardiovascular compromise, such as pulmonary embolism, pulmonary edema, cardiomyopathy, acute coronary syndrome, mitral stenosis, hypotension, cerebrovascular accident, and AFE (Table IV).^{4,31,37-44}

Laryngeal obstruction, a frequent and potentially life-threatening symptom of anaphylaxis, must be differentiated from laryngopathia gravidarum, particularly the acute form that occurs immediately before parturition in women with preeclampsia.⁴ In patients with laryngopathia gravidarum, onset of laryngeal symptoms is typically slower than in those with anaphylaxis, and the correct diagnosis is supported by the presence of hypertension, peripheral edema, urinary abnormalities, or a history of preeclampsia. Laryngeal edema caused by hereditary angioedema rarely presents for the first time in pregnancy; although the frequency of attacks often increases in pregnancy, especially in the third trimester, the most common presentation involves abdominal symptoms.^{34,35}

Hypotension associated with anaphylaxis must be differentiated from more common causes of hypotension during pregnancy, including spinal block, local anesthetic administration, and hemorrhage.³¹ Sudden onset of urticaria, itching, angioedema, stridor, or wheezing concomitantly with hypotension strongly supports the diagnosis of anaphylaxis (Table IV).

AFE, a rare and catastrophic cause of acute respiratory or cardiovascular collapse with a case fatality rate of greater than 20%, causes 10% of all maternal deaths in the United States. Diagnosis is based on a clinical presentation that can include 1 or more of the following: profound hypotension, cardiovascular collapse, arrhythmias, cyanosis, dyspnea, respiratory distress, hemorrhage, disseminated intravascular coagulation, and altered mental status, in the absence of other medical explanations for the clinical course. Bronchospasm, absence of large-volume blood loss, and absence of coagulopathy suggest anaphylaxis rather than AFE^{31,40-44}; however, activation of the coagulation system can also occur in patients with anaphylaxis.⁴⁵ A proposed mechanism

TABLE II. Clinical criteria for diagnosis of anaphylaxis during pregnancy

Anaphylaxis is highly likely when any 1 of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized urticaria, itching or flushing, swollen lips-tongue-uvula)

AND at least 1 of the following:

1. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
2. Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

OR

2. Two or more of the following that occur rapidly after exposure to a *likely allergen** for that patient (minutes to several hours):

1. Involvement of the skin-mucosal tissue (eg, generalized urticaria, itch-flush, swollen lips-tongue-uvula)
2. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, hypoxemia)
3. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
4. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

OR

3. Reduced blood pressure after exposure to *known allergen** for that person (minutes to several hours) defined as systolic blood pressure of <90 mm Hg or >30% decrease from that person's baseline value†‡

Unique aspects of diagnosis of anaphylaxis in pregnancy are highlighted in boldface below. Data are taken from references 10, 30, and 31.

*Or other trigger, such as immunologic but IgE independent or nonimmunologic (direct) mast cell activation.

†For example, after an insect sting, reduced blood pressure might be the only manifestation.

‡Normal values for vital signs are different in late pregnancy. Respiratory rate increases by 10% and heart rate increases by 15%. Systolic blood pressure does not change but diastolic blood pressure decreases by 15%. Supine hypotension syndrome occurs in more than 10% of pregnant women. It results from obstruction of the inferior vena cava by the gravid uterus when a woman lies in the supine position.

TABLE III. Symptoms and signs of anaphylaxis during pregnancy

Skin, subcutaneous tissue, and mucosa*†

Flushing, itching, urticaria (hives), angioedema, morbilliform rash, pilor erection

Periorbital itching, erythema, edema, conjunctival erythema, tearing

Itching and/or swelling of lips, tongue, palate, uvula, external auditory canals, palms, and soles

Respiratory*

Nasal itching, congestion, rhinorrhea, sneezing

Throat itching, tightness, dysphonia, hoarseness, dry staccato cough, stridor

Lower airways: increased respiratory rate, shortness of breath, chest tightness, deep cough, wheezing

Cyanosis

Respiratory arrest

Gastrointestinal*

Abdominal pain, dysphagia, nausea, vomiting (stringy mucus), diarrhea

Cardiovascular system*

Chest pain

Tachycardia, bradycardia (less common), other dysrhythmias, palpitations

Hypotension, feeling faint, incontinence, shock

Cardiac arrest

Central nervous system*

Aura of impending doom, uneasiness; headache (before epinephrine), altered mental status, dizziness, confusion, tunnel vision, loss of consciousness

Other*

Intense itching of the vulvar/vaginal regions, uterine cramps, low back pain, **fetal distress, preterm labor**

Metallic taste in mouth

Symptoms and signs unique to pregnancy are highlighted in boldface. Data are taken from references 1, 10, and 30.

*Sudden onset of symptoms and signs is characteristic of anaphylaxis.

†A detailed list of symptoms and signs is provided to aid in prompt recognition of anaphylaxis and to indicate the possibility of rapid progression to multiorgan system involvement.

in AFE is a non-IgE-mediated immunologic reaction to fetal antigens leading to mast cell degranulation, release of histamine and tryptase, and involvement of the complement and coagulation pathways. Low complement levels and increased serum tryptase and urinary histamine levels have been reported in some patients. Sialyl Tn, a potential marker for severe AFE, is reported to be predictive for life-threatening or fatal episodes.⁴²

PATHOPHYSIOLOGY

Effects of anaphylaxis on fetal oxygenation

Anaphylaxis has a potentially devastating effect on fetal oxygenation. Oxygen delivery to the fetus is a function of the

Fick principle; specifically, each volume of blood passing through the uterus and placenta gives up an amount of oxygen that reflects the PO₂ difference between the fetal and maternal circulation. The total oxygen delivered is a function of the quantity of oxygen delivered by 1 mL of blood multiplied by blood flow. A relatively high uterine blood flow rate (942 mL/min at 36 weeks gestation) is needed for normal fetal oxygenation to compensate for inefficiencies of the placenta and high oxygen consumption. Arterial PO₂ in the fetus is approximately one third to one fourth that of arterial PO₂ in the mother. Fetal oxygenation is directly compromised by maternal hypoxemia and indirectly compromised by maternal hypotension or vasoconstriction leading to reduced uterine blood flow.⁴⁶

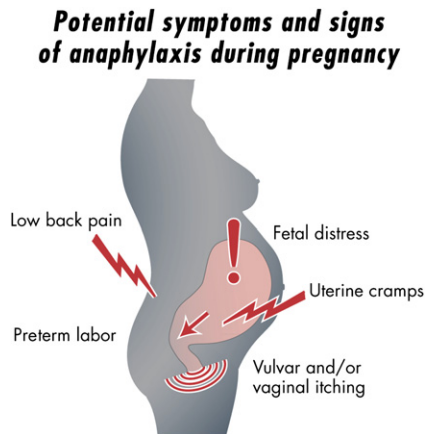


FIG 1. Potential symptoms and signs of anaphylaxis during pregnancy. Sudden onset of multisystem symptoms and signs is characteristic; most symptoms and signs are similar to those in nonpregnant patients with anaphylaxis. Itching in the vulvar/vaginal areas, low back pain, uterine cramps, fetal distress, and preterm labor can occur. Data are taken from references 1, 10, and 30.

Fetal and maternal outcomes

The fetus compensates for decreased blood flow by means of redistribution of blood to vital organs, including the brain, heart, placenta, and adrenal glands; increased oxygen uptake and tissue oxygen extraction; and decreased body movements (Fig 1). The level and duration of fetal hypoxia that exceed these compensatory mechanisms, although not precisely defined in human beings, are affected by fetal reserve and gestational age. When these mechanisms fail, the fetus is at risk of hypoxic-ischemic encephalopathy and permanent central nervous system damage, which occur more commonly in the infant than in the mother, and of death, which can occur despite maternal survival.¹

Maternal cardiac arrest is potentially devastating to the fetus and mandates immediate cesarean delivery.^{38,47} Although 90% of neonates delivered within 5 minutes are neurologically intact, fewer than 60% of those delivered within 15 minutes are likely to be neurologically intact.

MANAGEMENT

Management of anaphylaxis in pregnancy is similar to management of anaphylaxis in the general population, with additional caveats as listed below (Table V and Fig 2).^{1,4,10,47-56}

Basic initial treatment

Preparation by the physician and his or her team is the key to successful outcomes (Table V and Fig 2). A written anaphylaxis emergency protocol should be posted in all medical and surgical settings. Removal of exposure to the trigger should be expedited, if possible; as an example, an intravenous medication should be discontinued. Maternal circulation, airway, breathing, mental status, skin, and body weight should be assessed.

A call for assistance should be placed to emergency medical services in community settings or to a resuscitation team (potentially including an anesthesiologist, obstetrician, and neonatologist) in hospital settings (Table V and Fig 2).^{10,48} Epinephrine (adrenaline) should be promptly injected intramuscularly in the mid-outer thigh using a first aid dose of 0.3 mg (0.3 mL) of a 1 mg/mL (1:1000) solution. This dose can be repeated every 5

to 15 minutes, depending on the clinical response.¹⁰ Epinephrine injection leads to decreased mediator release from mast cells and should not be delayed by taking time to administer second-line medications with no immediate life-saving benefit, such as H₁-antihistamines, H₂-antihistamines, or glucocorticoids.^{10,48,50}

High-flow humidified supplemental oxygen (up to 100%) should be administered promptly through a close-fitting face mask or oropharyngeal airway (Table V and Fig 2). The mother's lower extremities should be elevated, and she should be placed on her left side to prevent the gravid uterus from compressing the inferior vena cava and obstructing venous return to the heart; manual displacement of the uterus (by placing the hands on the right side of her abdomen and gently pushing the uterus towards the left side) might be necessary. If the mother is dyspneic or vomiting, she should be placed in a position of comfort. She should not sit or stand suddenly because this can lead to cardiac arrest caused by the empty inferior vena cava/empty ventricle syndrome.

Intravenous access should be established with two 14- to 16-gauge catheters; when indicated for hypotension, administer 5 to 10 mL/kg 0.9% (isotonic) saline rapidly (within the first 5-10 minutes; Table V and Fig 2).^{10,48,50} Continuous noninvasive electronic monitoring of maternal blood pressure, heart rate, oxygenation (by using pulse oximetry), and fetal heart rate should be instituted. Cardiopulmonary resuscitation should be performed when indicated. Resuscitation can be difficult because of changes in body habitus during pregnancy; it is not easy to perform high-quality chest compressions in a fully gravid woman. For fetal distress, emergency cesarean delivery should be performed when indicated (see the "Obstetrical management" section).^{10,48,50}

Anaphylaxis refractory to basic initial treatment

Airway and blood pressure support. For upper or lower airway obstruction unresponsive to initial medical management, intubation and, rarely, tracheostomy might be required. Endotracheal tube insertion should be performed by the most experienced health care professional available because it can be difficult when there is pregnancy-associated edema of the upper airway, if the tongue is swollen, or if the larynx and other landmarks in the upper airway are obscured because of edema and mucus.^{10,48,50}

As described above, hypotension should be reversed promptly with large volumes of intravenous fluid; up to 7 liters of fluid might be needed. A minimum maternal systolic blood pressure of 90 mm Hg should be maintained to ensure adequate perfusion of the placenta.^{48,50}

Vasopressor use during labor and delivery. Patients experiencing hypotension or shock refractory to basic initial treatment with first aid doses of epinephrine and intravenous fluid resuscitation require intravenous vasopressors administered through an infusion pump, with frequent dose titration based on continuous noninvasive monitoring of heart rate, blood pressure, and oxygenation. Ideally, this should be carried out by a team of physicians, nurses, and technicians who are trained, experienced, and equipped to provide optimal shock management because even under optimal conditions, potentially fatal adverse events, including ventricular arrhythmias, hypertensive crises, and pulmonary edema, can occur.^{10,48,50}

Traditionally, ephedrine, which has both α - and β -adrenergic receptor agonist effects and also enhances norepinephrine release from neurons, has been used for treatment of hypotension associated with spinal block and treatment of

TABLE IV. Differential diagnosis of anaphylaxis during pregnancy

A. First 3 trimesters, before labor and delivery
Common diagnostic dilemmas, such as acute asthma, acute generalized urticaria, acute angioedema, syncope/fainting, panic attack, acute anxiety attack
Postprandial syndromes, such as scombroidosis, pollen-food allergy syndrome (oral allergy syndrome), monosodium glutamate reaction, sulfite reaction, food poisoning
Upper airway obstruction (other forms), such as nonallergic angioedema (no accompanying urticaria or itching): includes hereditary angioedema types I, II and III
Shock (other forms), such as hypovolemic, septic, cardiogenic
Nonorganic diseases, such as vocal cord dysfunction, hyperventilation, psychosomatic episode, Munchausen stridor
Other: excess endogenous histamine, such as mastocytosis/clonal mast cell disorder; flush syndromes, such as carcinoid syndrome; certain tumors; system capillary leak syndrome
B. Labor and delivery
Pulmonary embolism (thrombotic) and pulmonary edema
Cardiac conditions (acquired and congenital)*
Hypotension caused by spinal block, local anesthetic, or hemorrhage, for example, secondary to abruptio placentae or uterine rupture
Cerebrovascular accident
AFE
Preeclampsia/eclampsia-associated symptoms, such as laryngopathia gravidarum and seizures
Other

Unique aspects of the differential diagnosis of anaphylaxis during pregnancy are highlighted in boldface. Data are taken from references 4, 10, 31, and 33 to 44.

*Pregnancy, labor, and delivery can lead to cardiovascular decompensation in patients with coexisting heart disease. In pregnancy and labor intravascular fluid volume increases by 35%. In pregnancy cardiac output increases by approximately 40% and can increase an additional 30% to 45% above prelabor values during labor and delivery, leading to congestive heart failure and pulmonary edema. Cardiac conditions that place mothers at risk of decompensation include the following: myocarditis, cardiomyopathy (including cardiomyopathy of pregnancy), acute coronary syndrome, mitral stenosis, mitral regurgitation, tetralogy of Fallot, Eisenmenger syndrome, primary pulmonary hypertension, thrombosed mechanical prosthetic heart valve, coarctation of the aorta, Marfan syndrome, and aortic dissection.

TABLE V. Basic management of anaphylaxis

Preliminary steps
1. Have a posted, written emergency protocol for recognition and treatment of anaphylaxis; rehearse it regularly.
2. Remove exposure to the trigger, if possible (eg, discontinue an intravenous diagnostic or therapeutic agent that seems to be triggering symptoms).
3. Assess circulation, airway, breathing, mental status, skin, and body weight (mass).
Promptly and simultaneously*
4. Call for help. This might involve a multispecialty resuscitation team (anesthesiologist, obstetrician, neonatologist) in a hospital setting or emergency medical services in a community setting.
5. Inject epinephrine (adrenaline) intramuscularly in the mid-outer aspect of the thigh, 0.01 mg/kg of a 1 mg/mL (1:1000 solution; typical first aid dose of 0.3 mg, maximum first aid dose of 0.5 mg); record dose and time; repeat dose in 5 to 15 minutes, if needed; most patients respond to 1 or 2 doses.†
6. Administer high-flow humidified supplemental oxygen (up to 100%, 6-8 L/min) through a face mask or oropharyngeal airway.
7. Place the woman on her left side (or in a position of comfort if there is respiratory distress and/or vomiting), and elevate her lower extremities. Manual displacement of the gravid uterus to the left might be necessary. Positioning on the back might lead to inferior vena caval compression and reduced venous return to the heart. Fatality can occur within seconds if she stands or sits suddenly.
8. Establish intravenous access with two 14- to 16-gauge catheters. When indicated, administer 5 to 10 mL/kg 0.9% (isotonic) saline rapidly (within the first 5-10 minutes); large intravenous fluid volumes might be needed (eg, 7 L).
9. Start continuous electronic monitoring of maternal blood pressure, cardiac rate and function, respiratory status, and oxygenation and start continuous electronic fetal monitoring. If continuous electronic monitoring is not available, monitor maternal vital signs and fetal heart rate every 5 minutes or more frequently. Maintain a minimum maternal systolic blood pressure of 90 mm Hg.‡
10. When indicated at any time, prepare to perform cardiopulmonary resuscitations, initiating continuous chest compressions before rescue breathing. Compressions should be started at a rate of 100 to 120 per minute and a depth of 5 to 6 cm before giving rescue breaths. High-quality chest compressions can be difficult to perform in a fully gravid woman.
11. When indicated at any time, perform emergency cesarean delivery for anaphylaxis refractory to medical management as outlined above or for fetal distress.

Unique aspects of management of anaphylaxis in late pregnancy, labor, and delivery are highlighted in boldface. Data are taken from references 1, 4, 10, and 47 to 50.

*Steps 4, 5, 6, and 7 should be performed promptly and simultaneously as soon as anaphylaxis is diagnosed or strongly suspected. If precious minutes are lost early in the treatment of an acute anaphylactic episode, subsequent management can become more difficult.

†Epinephrine (adrenaline) injection is the first-line treatment. Second-line medications include:

Inhaled β -adrenergic agonist (eg, 2.5-5 mg of albuterol [salbutamol] in 3 mL saline) administered through a nebulizer and face mask for additional relief of bronchospasm

H₁-antihistamine (eg, 25-50 mg of diphenhydramine 25-50 intravenously): not life-saving; given for additional relief of urticaria and itching

H₂-antihistamine (eg, 50 mg of ranitidine intravenously): not life-saving; note that there are case reports of anaphylaxis to ranitidine in parturients

Glucocorticoid (eg, 125 mg/d methylprednisolone intravenously): no immediate life-saving benefits, administered to prevent biphasic or protracted anaphylaxis

‡The duration of monitoring in a medically supervised setting should be individualized.

hypotension in pregnancy.⁴ However, in a series of randomized controlled trials in pregnant women undergoing elective cesarean delivery, intravenous phenylephrine has been found

to be significantly more effective than intravenous ephedrine in maintaining maternal blood pressure without decreasing uterine or placental blood flow or increasing fetal distress or

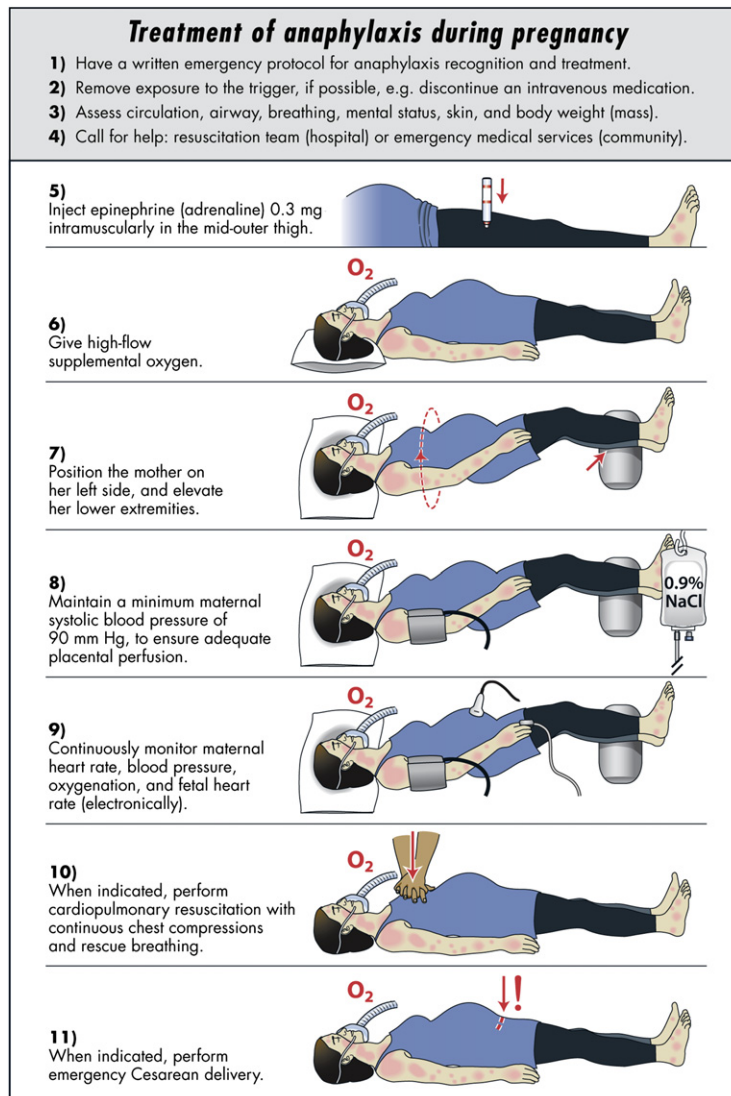


FIG 2. Treatment of anaphylaxis during pregnancy. This involves prompt intramuscular injection of 0.3 mg (0.3 mL) of epinephrine using a 1 mg/mL (1:1000) dilution; high-flow supplemental oxygen; the mother positioned on her left side to improve venous return to the heart; maintenance of a minimum systolic blood pressure of 90 mm Hg for adequate placental perfusion; continuous electronic monitoring; cardiopulmonary resuscitation when indicated; and emergency cesarean delivery when indicated. Data are taken from references 1, 4, 10, 30, 47, 48, and 50.

acidosis.⁵¹⁻⁵⁴ Intravenous epinephrine with careful dose titration and continuous noninvasive electronic monitoring of the mother and fetus has also been used successfully on an empiric basis⁵⁵ and is the currently recommended vasopressor.^{48,56} Randomized controlled trials of the pros and cons of various sympathomimetic agents in pregnant women are ongoing. A timely admonition is “keep the blood pressure up, and don’t spare the vasoconstrictors.”⁵⁴

Obstetrical management. Fetal distress, as evidenced by late repetitive decelerations of fetal heart rate with each uterine contraction, should be treated by prompt aggressive maternal medical management with correction of hypoxemia, hypotension, or both. The potential benefits of emergency cesarean delivery in patients with anaphylaxis refractory to medical treatment need to be balanced against the potential risks of surgery in a gravida with hypoxemia, hypotension, or both and the potential risk of

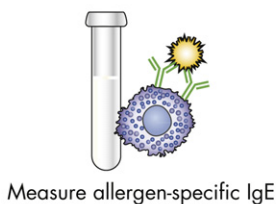
neonatal morbidity and mortality caused by prematurity, especially if gestational age is less than 32 weeks.^{47,48,50}

PREVENTION

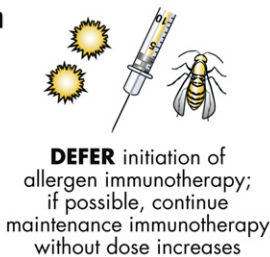
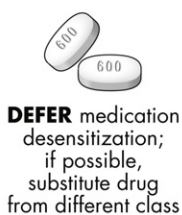
The principles of prepregnancy risk assessment and risk management to prevent recurrent anaphylaxis are similar to the principles of risk assessment and risk management in nonpregnant patients at risk of recurrent anaphylaxis.¹⁰ During pregnancy, the benefits of skin tests, challenge/provocation tests, desensitization, and immunotherapy with allergens need to be weighed against the small, finite risks of iatrogenic anaphylaxis induced by these procedures. If they are being contemplated in a pregnant woman, physicians should be aware that there is little published guidance about selection of patients and that good clinical judgment is essential (Fig 3).^{5,10,11,14,57-65}

Anaphylaxis during pregnancy: Risk assessment and risk reduction

Confirm anaphylaxis trigger(s)



Avoidance and immunomodulation



Emergency preparedness

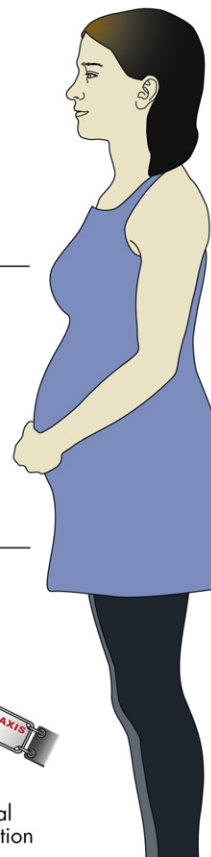
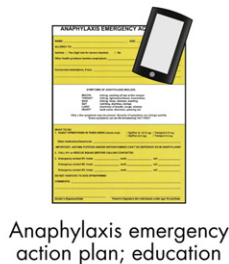


FIG 3. Anaphylaxis during pregnancy: risk assessment and risk reduction. (1) Etiology suggested by history should be confirmed by measuring allergen-specific IgE levels in serum. (2) Strict avoidance of relevant confirmed allergen triggers is recommended. Initiation of allergen immunotherapy and desensitization to medications are usually deferred until after parturition because of the small associated risk of anaphylaxis. (3) Patients should be taught to self-inject epinephrine in the mid-outer thigh and equipped with a personalized anaphylaxis emergency action plan and medical identification. Data are taken from references 5, 10, 11, 14, and 57 to 65.

Prepregnancy assessment and management

Many pregnancies are unplanned. The allergy/immunology specialist can therefore play an important role in prevention of anaphylaxis during pregnancy by ensuring that in his or her practice, all women of child-bearing age with a history of clinical reactivity (symptoms and signs of an acute systemic reaction) on exposure to allergens receive timely and appropriate prepregnancy assessments, including skin tests and challenge tests when indicated, and appropriate prepregnancy management, including desensitization and immunotherapy when indicated. The allergy/immunology specialist also plays an important role in the long-term management of women at risk for anaphylaxis who have comorbidities such as asthma or mastocytosis that increase the risk of severe or fatal anaphylaxis.

Confirmation of anaphylaxis etiology during pregnancy

The etiology of clinical reactivity to an allergen or allergens should be confirmed by testing for sensitization to the allergens

suggested by the history of the reaction. Quantitative *in vitro* tests, such as ImmunoCAP (Thermo Fisher Scientific, Asheville, NC), are now widely available for measurement of serum allergen-specific IgE levels to inhalants, foods, stinging insect venoms, and NRL.¹⁰ Allergen skin tests and allergen challenge tests are deferred until after parturition, if possible, because of the small risk of anaphylaxis associated with these procedures (Fig 3).

Prevention of anaphylaxis during pregnancy

Strategies for prevention of anaphylaxis during pregnancy focus on strict avoidance of relevant foods, stinging insects, medications, NRL, or other triggers associated with a previous anaphylactic episode. Patients should be provided with written personalized information about how to avoid their confirmed trigger, personalized written information about appropriate substitutes, and a short list of reliable Web sites that provide up-to-date information about anaphylaxis (Fig 3).¹⁰

Subcutaneous allergen immunotherapy during pregnancy. As outlined in the 2011 Allergen Immunotherapy

Practice Parameter, the physician must be aware of the benefits versus potential risks of immunotherapy in pregnant patients.¹¹ Allergen immunotherapy is usually not initiated during pregnancy because of concerns about the potential adverse effects of systemic reactions and their resultant treatment on the fetus, mother, or both, such as fetal hypoxia, premature labor, and loss of the infant.¹¹ If pregnancy occurs during the build-up phase and the patient is receiving a dose that is unlikely to be therapeutic, discontinuation of immunotherapy should be considered.¹¹ Allergen immunotherapy maintenance doses can be continued during pregnancy.¹¹ The recommended precautions for the prevention of adverse reactions during immunotherapy are important to the pregnant patient because of the possible effects on the fetus, as well as the mother.¹¹

Sublingual immunotherapy is reported to be safe for use during pregnancy⁵⁷; however, additional studies of its efficacy and safety are needed in this vulnerable population.

Three examples of the modified assessment and management approach will be given, as follows.

Stinging insect venom-induced anaphylaxis. Pregnant women with a history suggestive of clinical reactivity to a stinging insect should have sensitization confirmed by measurement of venom-specific IgE levels in serum. Venom skin tests are usually deferred. Those at increased risk should be instructed in insect avoidance measures and emergency preparedness for self-treatment of anaphylaxis in community settings.¹⁰

As outlined in the 2011 Allergen Immunotherapy Practice Parameter, "the initiation of immunotherapy might be considered during pregnancy when the clinical indication for immunotherapy is a high-risk medical condition such as anaphylaxis caused by Hymenoptera hypersensitivity.¹¹ When a patient receiving immunotherapy reports that she is pregnant, the dose of immunotherapy is usually not increased.¹¹ The recommended precautions for prevention of adverse reactions are important in the pregnant patient because of the possible effects of anaphylaxis on the fetus as well as the mother."^{11,58}

An example of a clinical situation in which the benefits of venom skin testing and initiation of venom immunotherapy during pregnancy potentially outweigh the small risk of anaphylaxis from these procedures and the risk of sting-induced anaphylaxis if venom immunotherapy is deferred might involve a pregnant woman with a history of clinical reactivity to stinging insects and occupational exposure.

β -Lactam antibiotic-induced anaphylaxis. Pregnant women with a history of clinical reactivity to penicillin should be evaluated promptly because the need for prophylactic penicillin during labor and delivery cannot be predicted in advance; moreover, antibiotic prophylaxis against GBS infection is ineffective if given to the neonate after delivery.^{5,14,17} Patients with a history of penicillin allergy cannot be optimally evaluated by using measurement of penicilloyl G- and penicilloyl V-specific IgE levels in serum because of the suboptimal sensitivity of these tests.⁵⁹ Although skin testing for penicillin allergy can be performed in pregnant women,^{5,14} it is usually deferred until after parturition, especially if the history suggests an acute systemic allergic reaction such as anaphylaxis.¹⁴

For women with positive GBS cultures and a history of penicillin allergy, the US Centers for Disease Control and Prevention recommend the following alternative intrapartum intravenous antibiotics.⁶⁰ First, women with penicillin allergy who do not have a history of anaphylaxis or acute respiratory

distress, angioedema, or urticaria after administration of a penicillin or cephalosporin should receive 2 g of cefazolin administered intravenously (initial dose) followed by 1 g administered intravenously every 8 hours until delivery. Second, women with a history of anaphylaxis or acute respiratory distress, angioedema, or urticaria after receiving a penicillin or cephalosporin should not receive a penicillin or cephalosporin. They should have antimicrobial sensitivity testing performed on antenatal GBS cultures. If their GBS isolates are susceptible to clindamycin, they should receive 900 mg of clindamycin administered intravenously every 8 hours until delivery. If their GBS isolates are intrinsically resistant to clindamycin or demonstrate inducible resistance to clindamycin or if susceptibility is unknown, they should receive 1 g of vancomycin administered intravenously every 12 hours until delivery. Third, erythromycin is no longer an acceptable alternative for intrapartum GBS prophylaxis in women with penicillin allergy because of high GBS resistance to this agent.⁶⁰

An example of a clinical situation in which the benefits of penicillin skin testing and, when relevant, desensitization⁶¹ potentially outweigh the small risk of anaphylaxis from these procedures might involve a pregnant woman with syphilis, because penicillin is the only antimicrobial agent recommended for eradication of maternal syphilis and prevention of congenital syphilis.^{62,63} During antepartum treatment of spirochetal infections with penicillin, an acute Jarisch-Herxheimer reaction, including fever, tachycardia, uterine contractions, and fetal heart rate decelerations, can occur.⁶⁴

NRL-induced anaphylaxis. Pregnant women with a history of clinical reactivity to NRL should be evaluated promptly because of potential NRL exposure in health care settings and in the community. Serum IgE levels to NRL should be measured to confirm sensitization; the US Food and Drug Administration-cleared assay for NRL-specific IgE levels is useful for this purpose.⁶⁵ Skin testing with NRL should be deferred until after parturition. Commercial NRL skin test reagents are not standardized and not widely available.

Written instructions for NRL avoidance in health care and community settings should be provided to the patient. Her obstetrician and other personal physicians should be advised in writing (with a copy to her) that she requires a latex-free environment during labor and delivery.

Breast-feeding-related anaphylaxis. Anaphylaxis associated with breast-feeding resolves spontaneously with cessation or suppression of lactation. Nonsteroidal anti-inflammatory drugs, a potential cofactor, should be avoided. When breast-feeding-related anaphylaxis occurs in successive pregnancies, prophylaxis with an H₁-antihistamine, a glucocorticoid, or both has been successful.⁹

Communication with other health care professionals

The patient's allergies should be listed in ribbons or menus in the electronic medical record or, where paper charts are still in use, in a prominent place on the outside front cover. Written communication between the allergy/immunology specialist and the patient's obstetrician and other personal physicians (with a copy to the patient) is imperative, particularly for women who are sensitized to medications such as penicillin or to agents such as NRL that are commonly encountered in medical and surgical settings.

Emergency preparedness

Pregnant women who are at risk of recurrent anaphylaxis in the community setting should be trained how to self-inject a first aid dose of 0.3 mg of epinephrine intramuscularly in the mid-outer thigh from an autoinjector and should carry 1 or more epinephrine autoinjectors with them at all times (Fig 3). A personalized anaphylaxis emergency action plan should be developed for them. This plan should list common anaphylaxis symptoms to facilitate self-recognition of an episode and recommend prompt self-injection of epinephrine, along with concurrently calling 911 or the appropriate emergency medical services number. All patients at risk of anaphylaxis should wear accurate up-to-date medical identification jewelry at all times, listing their confirmed anaphylaxis triggers and comorbidities (if any), such as asthma, cardiovascular disease, or mastocytosis.¹⁰

SUMMARY

Many pregnancies are unplanned; therefore allergy/immunology specialists can play an important role in the prevention of anaphylaxis in pregnancy through prepregnancy risk assessment and risk reduction strategies in all women of child-bearing age. A modified approach to assessment and management of patients at risk of anaphylaxis during pregnancy based on the principle “first, do no harm” is recommended to minimize the risk of iatrogenic anaphylaxis in pregnant women, because anaphylaxis during pregnancy, labor, and delivery can be catastrophic for the mother and, especially, the infant. Prospective interdisciplinary studies of anaphylaxis during pregnancy are needed.

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