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REVIEW ARTICLE

CME

Anaphylaxis in the Clinical Setting of Obstetric Anesthesia: A Literature Review

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The prevalence of anaphylaxis occurring during pregnancy is approximately 3 cases per 100,000 deliveries. The management of anaphylaxis occurring during the third trimester of pregnancy may be challenging because of the additive effects of aortocaval compression and cardiovascular disturbances of anaphylaxis. In this review, we identify the clinical signs of anaphylaxis occurring during labor and cesarean delivery, discuss the more common allergens that cause anaphylaxis during this clinical setting, and develop a rational approach to the identification of the offending allergen. We also suggest strategies for the management of anaphylaxis occurring during the third trimester of pregnancy, including the prompt administration of epinephrine and emergency cesarean delivery in cases of severe reactions. Evidence is limited to case reports and extrapolation from nonfatal and fatal cases, interpretation of pathophysiology, and consensus opinion. (Anesth Analg 2013;117:1357–67)

Anaphylaxis is a clinical condition that may be life threatening, especially when occurring during the third trimester of pregnancy, because of the additive effects of aortocaval compression on the cardiovascular disturbances of anaphylaxis. The aims of this review are to increase awareness of anaphylaxis as a possible diagnosis in the obstetric setting, as well as to ensure focus on rapid diagnosis and appropriate management. Thus, this review seeks to: (1) identify the clinical signs of anaphylaxis occurring during labor or cesarean delivery; (2) discuss the more common allergens that cause anaphylaxis in these clinical settings; (3) discuss the management of anaphylaxis occurring during the third trimester of pregnancy; and (4) briefly discuss a rational approach to the identification of the offending allergen and prevent recurrences.

METHODS

For evidence on immediate hypersensitivity occurring in the labor and delivery setting, we performed a literature search in PubMed® database by using the following Medical Subject Heading (MeSH) terms: "Pregnancy and Anaphylaxis—Delivery," "Obstetric and Anaphylaxis—Cesarean Section" and "Anaphylaxis—Latex Hypersensitivity and Pregnancy." Several guidelines on the perioperative management of anaphylaxis ($n = 4$) have been published since 2000.[1–4] Therefore, we searched for studies and case reports published during the last decade, that is, between January 1, 2000 and December 31, 2011. We focused our search on English and French language studies, studies of pregnant adults, and to the following study types: meta-analysis ($n = 0$), systematic review ($n = 0$), retrospective study ($n = 1$),[5] prospective study ($n = 1$),[6] clinical cases ($n = 22$),[7–22] and report on maternal deaths ($n = 5$).[23–27]

Although the case reports did not use any particular grading system for the definition of anaphylaxis, we used the modified Ring and Messmer 4-step grading scale that is currently used in the anesthesiology allergy literature to classify the severity of immediate hypersensitivity.[1,2,4,28]

Definitions

Although different definitions of anaphylaxis have been proposed by European and North American academic authorities, an attempt has been made to streamline these definitions.[29–32] The American Academy of Allergy, Asthma, and Immunology defines anaphylaxis as often life threatening and almost always an unanticipated reaction.[32] The European Academy of Allergology and Clinical Immunology defines it as a severe, life-threatening, generalized, or systemic immediate hypersensitivity reaction.[29,30] The use of the word "anaphylactoid" reaction is now discouraged by the European Academy.[29,30] However, the American academy continues to use the word anaphylactoid for non-IgE mediated reactions producing a clinical response similar to anaphylaxis.[32] Two types of immediate clinical reactions are differentiated. Nonallergic immediate hypersensitivity refers to reactions in which an immunologic mechanism

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Table 1. Clinical Severity Scale of Immediate Hypersensitivity Reactions According to the Modified Ring and Messmer 4-Step Grading Scale[1,2,4,28]

Grades	Clinical signs
I	Cutaneous-mucous signs: generalized erythema, urticaria with or without angioedema
II	Moderate multivisceral signs: cutaneous-mucous signs ± hypotension ± tachycardia ± dyspnea ± gastrointestinal disturbances
III	Life-threatening mono or multivisceral signs: cardiovascular collapse, tachycardia or bradycardia ± cardiac dysrhythmia ± bronchospasm ± cutaneous-mucous signs ± gastrointestinal disturbances
IV	Cardiac arrest

can be excluded; allergic immediate hypersensitivity refers to those where an immunologic mechanism can be proven (usually immunoglobulin [Ig]E-mediated).[29,30]

Clinical Scale of Severity: The Ring and Messmer 4-Step Grading Scale

Drug- or latex-induced immediate hypersensitivity is usually described according to the modified Ring and Messmer 4-step grading scale (Table 1).[1,2,4,28] Grades I and II are usually not life-threatening conditions, whereas grades III and IV correspond to clinical settings, necessitating urgent resuscitation. The initial diagnosis of immediate hypersensitivity is presumptive and is suspected based on the features and severity of clinical signs and the timing between the introduction of a suspected allergen and the onset of symptoms.[28] The etiologic diagnosis of an immediate hypersensitivity reaction relies on a triad that includes the description of the ongoing clinical reaction, as well as the biologic and allergologic evidence.[1–4,28] Although the Ring and Messmer scale does not consider the pathophysiologic mechanisms, it is appropriate for grading the clinical severity and guiding the clinical care of perioperative immediate hypersensitivity reactions.[4,28]

EPIDEMIOLOGY

During the triennium 2003 to 2005, 845 cases of severe maternal morbidity were reported in Scotland, of which 5 were because of anaphylactic shock. Anaphylaxis had an incidence of 3 per 100,000 maternities (95% confidence interval 1–7 per 100,000 maternities).[23] During the same period (2004–2005), the analysis of a hospital discharge database in Texas demonstrated a prevalence of 2.7 cases per 100,000 deliveries, with β-lactam antibiotics being the most common agents leading to anaphylaxis.[5] No fatalities were reported during this 2-year period. More recently, a case series of anaphylactic reactions during cesarean deliveries demonstrated a frequent incidence of latex allergy (1:310) over a 1-year period in Italy.[17] There were no cases of drug-induced anaphylaxis in this report. The same authors also reported a higher prevalence of latex sensitization in the obstetric population (5.1 vs 1.7%, respectively) compared with a nonpregnant population undergoing gynecologic surgery.[6] However, these data cannot necessarily be extrapolated to other countries, because the quality and quantity of latex and the use of latex-free products varies among countries.

In the latest 2 reports of the *Confidential Enquiries into Maternal Deaths in the United Kingdom* (triennium 2003–2005 and 2006–2008), in which 295 and 261 deaths were reported, respectively, 2 deaths were because of anaphylaxis. One death was attributed to nalbuphine,[23] and another fatality was attributed to an antibiotic (not specified) administered during labor.[26] The *Confidential Enquiry into Maternal and Child Health* also publishes a perinatal mortality surveillance report. There were no reported cases of perinatal death attributable to anaphylaxis since 2000 in that report.[24] In the most recent report of anesthesia-related maternal mortality in the United States (1991–2002), no death attributed to anaphylaxis was reported.[27] The latest data from France report 3 maternal deaths because of suspected neuromuscular-blocking drug-induced anaphylaxis between 2001 and 2006.[25]

Little is known about the epidemiology of immediate allergic hypersensitivity occurring during delivery. Antibiotics and latex appear to be the main culprit agents. The incidence of immediate hypersensitivity occurring during labor and delivery appears to be low; deaths attributed to anaphylaxis are rarely reported.[23,25,26] However, the exact incidence is probably underestimated, because perioperative immediate reactions are likely to be underdiagnosed and underreported.

Immediate Hypersensitivity in Obstetrics

Cardiovascular disturbances are the hallmark of anaphylaxis.[2–4,28,33] Immediate hypersensitivity occurring during the third trimester of pregnancy is a clinical condition that can be life threatening. The pregnant uterus compresses the inferior vena cava impeding venous return and thereby reducing cardiac output. The low-flow state is worsened by the peripheral vasodilatation and interstitial capillary leakage induced by anaphylaxis.[28,34] Thus, persistent hypotension, cardiovascular collapse as the sole feature, or cardiac arrest may be the inaugural event.[2–4,28] The vital prognosis of the patient is linked to the restoration of hemodynamic stability. Mucocutaneous signs and symptoms (facial angioedema, erythema, urticaria) are usually present. However, the subcutaneous vascular bed is susceptible to vasoconstrictive influences from the early stage of anaphylaxis, and mucocutaneous signs may therefore only appear after the normalization of the arterial blood pressure indicating restoration of peripheral perfusion.[28,35] Consequently, the absence of cutaneous vasodilatation does not exclude the diagnosis of anaphylaxis.[3,4,28] One series demonstrated that slightly more than one-quarter of cases of anaphylaxis during pregnancy had a mucocutaneous sign or symptom on first presentation.[5] Other clinical features such as respiratory (cough, wheezing, dyspnea and/or bronchospasm) or digestive (vomiting, diarrhea) may also be present.

Clinical Presentation and Causes

Less than 30 cases reporting immediate hypersensitivity occurring before or during the course of labor and during cesarean delivery have been published since 2000 (Tables 2

Table 2. Clinical Cases Reported Since 2000: IgE-Mediated Anaphylaxis Occurring Before or During the Course of Labor

Reference	Gestation (weeks)/ Agent	Grade	Time onset and clinical signs	Treatment	Mode of delivery	Allergological assessment	Diagnosis
Eckhout and Ayad,[7] 2001	32/Latex	II	*"Within several min"* Generalized urticaria BP: 78/40 mm Hg HR: 98 bpm Dyspnea, wheezing	Ephedrine IV: 10 mg Crystalloids: 500 mL	Vaginal delivery	None	Presumptive
Shingai et al.,[9] 2002	38/Latex	II	*"A few min after vaginal examination"* Generalized urticaria Facial angioedema Dyspnea	Epinephrine intratracheal: 1 mg	Cesarean delivery (120 min after anaphylaxis onset)	Latex IgE >100 U/mL (normal <0.34)	Presumptive
Gei et al.,[10] 2003	40/Amoxicillin	II	*"During the antibiotic infusion"* Urticaria, itching BP: 80/17 mm Hg HR: 170 bpm Shortness of breath Nausea	Epinephrine IV: 3 × 100 μg Epinephrine infusion (1–3.3 μg/min) (3.5 h) Crystalloids: 2000 mL	Vaginal delivery	None	Presumptive
Kaneko and Maruta,[11] 2003	40/Ranitidine	III	*"A few min after ranitidine infusion"* Cutaneous flushing and swelling SAP: 60 mm Hg Undetectable pulse Dyspnea, nausea	Ephedrine IV: 20 mg Epinephrine IV: 2 mg	Emergent cesarean delivery	None	Presumptive
Vercauteren et al.,[12] 2003	28/Pentastarch	II	*"Within the first min after pentastarch"* Erythema Facial angioedema BP: 100/77 mm Hg Bronchospasm Spo_2: 88%	Ephedrine IV: 40 mg	Cesarean delivery (the next day)	None	Presumptive
Berardi et al.,[13] 2004	37/Ampicillin	III	*"Five min after ampicillin infusion"* Pruritus, urticaria Undetectable BP	Etilefrine IV:? mg Fluid therapy:? mL	Emergent cesarean delivery	None	Presumptive
Jao et al.,[15] 2006	38/Cefazolin	III	*"At the beginning of the antibiotic infusion"* Diffuse itching + burning Diffuse urticaria BP: 40/20 mm Hg HR: 180 bpm Dyspnea, wheezing Nausea	Ephedrine IV: 10 mg Epinephrine infusion (1–3.3 μg/min) (for?) Crystalloids: 2000 mL	Cesarean delivery (10 min after anaphylaxis onset)	None	Presumptive
Vatsgar et al.,[16] 2006	24/Dextran	IV	*"Shortly after Macrodex infusion"* Cardiac arrest	Epinephrine IV + intratracheal: 0.3 + 2 × 0.5 + 4 × 1 mg Norepinephrine: (0.2–0.4 μg/kg/min) (6 h) CPR	Cesarean delivery (15 min after anaphylaxis onset)	Tryptase: 95 μg/L (normal <24)	Presumptive
Sheikh[19] 2007	?/Penicillin G	III	*"Within a min after penicillin infusion"* Profound hypotension Dyspnea	Epinephrine: route and dose:?	Emergent cesarean delivery	Penicillin G IgE: 3.1 kU/L Penicillin V IgE: 2.7 kU/L (normal <0.35)	Presumptive
Khan et al.,[20] 2008	38/Ceftriaxone	II	*"7 min after ceftriaxone injection"* Urticaria, erythema Palpebral angioedema SAP: 70 mm Hg HR: 160 bpm	Epinephrine IV: 10 μg Crystalloids: 1000 mL Colloids: 1000 mL	Cesarean delivery (60 min after anaphylaxis onset)	None	Presumptive

(*Continued*)

Table 2. Continued

Reference	Gestation (weeks)/Agent	Grade	Time onset and clinical signs	Treatment	Mode of delivery	Allergological assessment	Diagnosis
Sengupta and Kohli,[21] 2008	?/Cefotaxime	II	*"30 min after antibiotic infusion"* SAP <70 mm Hg Spo_2 <90% Mild cough, dyspnea Vomiting	Epinephrine infusion: ? µg/min Fluid therapy: ? mL	Cesarean delivery (12 h after anaphylaxis onset)	None	Presumptive
Chaudhuri et al.,[22] 2009	40/Penicillin G	III	*"Within a few min after the start of the infusion"* Diffuse erythema BP: 40/20 mm Hg HR: 155 bpm then undetectable BP	Ephedrine IV: 15 mg Epinephrine IV: 100 + 300 + 600 µg	Cesarean delivery (30 min after anaphylaxis onset)	None	Presumptive
Sleth et al.,[36] 2009	38/Amoxicillin	III	*"Within 5 min after amoxicillin injection"* Generalized erythema Vomiting Cardiovascular collapse Tachycardia	Epinephrine IV: 200 + 200 µg	Cesarean delivery (10 min after anaphylaxis onset)	Tryptase: 19 µg/L (normal <13.5) Amoxicillin IgE: – Skin tests amoxicillin: +	Proven

BP = arterial blood pressure; HR = heart rate; SAP = systolic arterial blood pressure; - = negative; + = positive.

and 3). No neuraxial analgesia was performed near the time of the occurrence of immediate hypersensitivity before or during the course of labor. In contrast, immediate hypersensitivity has been reported during cesarean delivery performed under spinal and general anesthesia.

Timing

Labor

Thirteen clinical cases of immediate hypersensitivity occurring before or during the course of labor have been reported since 2000 (Table 2).[7,9–13,15,16,19–22,36] No neuraxial analgesia was performed in these cases. Drug-induced immediate hypersensitivity (n = 11)[10–13,15,16,19–22,36] was the most frequently reported, followed by latex (n = 2).[7,9] β-lactam antibiotics including amoxicillin, ampicillin, penicillin G, cefazolin, ceftriaxone, and cefotaxime were the most common drugs (n = 8).[10,13,15,19–22,36] Other agents included ranitidine (n =1) and colloid solutions (n =2) (pentastarch and dextran).[11,12,16] Clinical features of drug-induced reactions were moderate (grade II, n = 4) or severe (grade III, n = 6 and grade IV, n = 1) and appeared within the first few minutes after drug administration. Latex-induced reactions were graded as moderate and appeared within minutes after latex contact.[7,9]

Cesarean Delivery

Fourteen cases of immediate hypersensitivity have been reported during cesarean delivery under spinal (n = 11)[17,18,37–41] and general anesthesia (n = 3)[8,14,36] (Table 3). In this clinical setting, cardiovascular signs of immediate hypersensitivity may have been aggravated by caval compression and the cardiovascular effects of anesthesia (i.e., either spinal or general anesthesia), causing negative inotropic effects and/or vasodilation.

Type of Anesthesia

Neuraxial Anesthesia

Latex was frequently involved in cases of immediate hypersensitivity occurring during the course of cesarean delivery performed under spinal anesthesia (n = 10)[17,18,37,38,40,41] (Table 3). Clinical features were either moderate (grade I: n = 3; grade II: n = 1) or severe (grade III: n = 5; grade IV: n = 1) and appeared within 10 to 30 minutes after the start of the cesarean delivery[17,37,38] or within minutes of administering exogenous oxytocin (4 cases).[18,37,40,41] Following uterine manipulation, oxytocin-induced uterine contractions may favor the absorption of latex particles. These particles were most likely derived from latex gloves and released into the systemic circulation.[38,42] A severe (grade III) immediate hypersensitivity reaction was reported after IV administration of a gelatin-based colloid.[39]

No immediate hypersensitivity reactions attributed to local anesthetics administered during labor, or cesarean delivery were reported during the last decade. Allergy to local anesthetics is frequently reported by patients, but it is rare to encounter an IgE-mediated allergic reaction to local anesthetics.[2–4] Reports of an anxiety attack, a vasovagal episode, and the intravascular injection of epinephrine were associated with reactions after local anesthetic injection.[2–4] The vast majority of adverse effects to local anesthetics are because of systemic absorption of local anesthetic or epinephrine.

General Anesthesia

Only 3 cases of succinylcholine-induced immediate hypersensitivity reactions have been reported (Table 3).[8,14,36] Clinical features were always severe (grade III: n = 2; grade IV: n = 1) and occurred within minutes after succinylcholine administration. Patients exhibited severe cardiovascular signs associated with bronchospasm. No cutaneous signs were observed in these 3 cases.

Maternal and Fetal Outcomes After Maternal Anaphylaxis

Labor

No maternal morbidity or mortality was observed when maternal anaphylaxis occurred during labor. Neonatal neurological abnormalities, including rigidity of the extremities, seizure-like movements, brain damage, hypoxic encephalopathy, and neonatal death were reported in 46% of these cases.[9,11,13,19,20,22] Parturients experiencing anaphylaxis had a

Table 3. Clinical Cases Reported Since 2000: IgE-Mediated Anaphylaxis Occurring During the Course of Cesarean Section

Reference	Gestation (weeks)/ agent	Anesthesia	Grade	Time onset Clinical signs	Treatment	Allergological assessment	Diagnosis
Stannard and Bellis,[8] 2001	38/Succinylcholine	GA	IV	*"Soon after intubation"* Unrecordable BP HR: 40 bpm $EtCO_2$ <10 mm Hg Spo_2: 50% Bronchospasm	Epinephrine IV: 1 + 4 mg Colloid: 500 mL	Tryptase >200 μg/L (normal <?) PT succinylcholine: +	Proven
Biermann et al.,[14] 2005	26/Succinylcholine	GA	III	*"Immediately after induction"* Unrecordable BP HR: 160 bpm Bronchospasm	Ephedrine IV: 18 mg Epinephrine IV: 0.1 mg + 1.5 mg/h (for?)	Increased tryptase ST succinylcholine: +	Proven
Draisci et al.,[17] 2007	41/Latex	SA	I	*"30 min after skin incision"* Facial edema Generalized erythema	No vasoconstrictor	Latex IgE: 1.3 kU/L (normal <0.35) PT latex: +	Proven
	41/Latex	SA	I	*"30 min after the start of the procedure"* Facial edema Erythema	No vasoconstrictor	Latex IgE <0.35 kU/L (normal <0.35) PT latex: +	Proven
	38/Latex	SA	III	*"30 min after the start of the procedure"* Hypotension Bronchospasm	Epinephrine IV: ? mg Fluid therapy: ? mL	Latex IgE >100 kU/L (normal <0.35) PT latex: +	Proven
	39/Latex	SA	I	*"30 min after the start of the procedure"* Facial edema, urticaria	No vasoconstrictor	Latex IgE: 11 kU/L (normal <0.35) PT latex: +	Proven
Ogata and Minami,[18] 2007	?/Latex	SA	III	*"Just after oxytocin infusion"* Itching Marked flushing (face, upper limbs) BP: 59/34 mm Hg Dyspnea	Ephedrine IV: ? mg Phenylephrine IV:? μg Epinephrine IV: ? mg Cristalloid: 3000 mL	Latex IgE: 14 IU/mL (normal <?) PT latex: +	Proven
Delaunay and Blasco,[37] 2008	?/Latex	SA	III	*"10 min after oxytocin injection"* Urticaria Cardiovascular collapse Bronchospasm	Epinephrine IV:? mg	Tryptase: 68 μg/L (normal <13.5) Latex IgE: 26 kU/L (normal <0.1) PT latex: +	Proven
	36/Latex	SA	IV	*"Within minutes following foetal extraction"* Cardiac arrest	Epinephrine IV: ? mg CPR	Latex IgE: 20 kU/L (normal <0.1) PT latex: +	Proven
Turillazzi et al.,[38]2008	38/Latex	SA	III	*"10 min after the start of surgical procedure"* Persistent hypotension Severe bronchospasm	Inotropes:? Fluid therapy: ? mL	Latex IgE: 14 U/L (normal <0.1)	Presumptive
Karri et al.,[39] 2009	?/Gelatine-based colloid	SA	III	*"Within few min following gelatine"* Facial itching SAP: 65 mm Hg	Epinephrine IV: 0.1 mg	Tryptase: 41 μg/L (normal <?) PT gelatine: +	Proven
Pant et al.,[40] 2009	37/*Attributed to oxytocin* but probably due to latex	SA followed by GA	III	*"Within a min following oxytocin"* Sneezing Throat itching Facial flushing, edema BP: 86/50 mm Hg HR: 86 bpm then unrecordable BP + tachycardia	Ephedrine IV: ? mg Epinephrine IV: 0.4 + 0.6 mg + infusion (up to 15 μg/min) replaced by norepinephrine (30 μg/min) Crystalloid + colloid:? mL	None	Presumptive

(Continued)

Table 3. Continued

Reference	Gestation (weeks)/ agent	Anesthesia	Grade	Time onset Clinical signs	Treatment	Allergological assessment	Diagnosis
Sleth et al.,[36] 2009	37/Succinylcholine	GA	III	*"Immediately after the induction"* SAP: 40 mm Hg Bronchospasm	Ephedrine IV: 30 mg Epinephrine IV: 100 + 100 µg	Tryptase: 35 µg/L (normal <13.5) PT succinylcholine: +	Proven
Ikeda et al.,[41] 2010	37/Latex	SA	II	*"Five min after oxytocin infusion"* BP: 70/40 mm Hg HR: 130 bpm Chest discomfort	Ephedrine IV: ? mg Phenylephrine IV:? µg Epinephrine infusion: ? µg.min^{-1}	Tryptase: 9 ng/mL (normal <?) Latex IgE: +	Presumptive

GA = general anesthesia; SA = spinal anesthesia; BP = arterial blood pressure; HR = heart rate; SAP = systolic arterial blood pressure; PT = prick-test; ST = skin tests; CPR = cardiopulmonary resuscitation.

delayed cesarean delivery after anaphylaxis onset[9,20–22] or did not receive epinephrine despite undetectable arterial blood pressure.[13] Others received excess IV epinephrine for the grade of the reaction[11] or received delayed epinephrine.[22] Epinephrine was the first drug injected in only one-third of grade III reactions,[19,36] while other vasoconstrictors such as ephedrine or etilefrine were injected as first-line therapy in the remaining two-third of cases.[11,13,15,22] A 2008 review found that in most cases of severe anaphylaxis, permanent damage occurred in the neonate.[22] There were 9 cases common to our series in that review.[7,10,13,15,17,19]

Neonatal deaths and neurological abnormalities were associated with maternal anaphylaxis (grade II and III reactions) during labor. Inappropriate doses or delayed epinephrine may have contributed to these poor outcomes. Cesarean delivery was delayed in many cases. In contrast, fetal outcome was uneventful when appropriate doses of epinephrine were given according to the severity of the reaction, and cesarean delivery was performed promptly (within 10–15 minutes) after the onset of anaphylaxis, even in cases of severe reactions (grade III and IV).[15,16,19,36]

Cesarean Delivery

No neonatal neurological abnormalities or death were reported when maternal anaphylaxis occurred during cesarean delivery.[8,14,17,18,36–41] In contrast, maternal morbidity, including severe hypertension associated with pulmonary edema, acute respiratory distress syndrome with acute renal failure,[8] acute respiratory distress syndrome with disseminated intravascular coagulation,[37] and increased liver enzymes with abnormal renal function[40] were reported in 20% of cases. Epinephrine was the first drug injected in 60% of severe reactions (grade III or IV),[8,17,37,39] while other vasoconstrictors such as ephedrine or phenylephrine were injected as first-line therapy in 40% of the cases.[14,18,36,40] Maternal morbidity was likely because of the excess dose of epinephrine for the grade of the reaction in 2 cases,[8,40] and the cause of morbidity was inconclusive in another case in the absence of details.[37] In 1 case, maternal death was because of unrecognized latex-induced anaphylaxis.[38]

In summary, maternal morbidity was mainly reported when anaphylaxis occurred during cesarean delivery and may be attributable to delayed recognition and/or inappropriate management of maternal anaphylaxis. No neonatal neurological damage and/or death were observed in this clinical setting, probably because fetal extraction was concurrently performed during maternal resuscitation. Neonatal morbidity was reported primarily if anaphylaxis occurred during labor. Thus, anaphylaxis may be catastrophic to the mother and/or fetus. Review of these cases suggests that poor maternal and/or neonatal outcomes are likely because of inappropriate management of maternal anaphylaxis.

Management of Anaphylaxis During the Third Trimester of Pregnancy

The management steps for the treatment of an immediate hypersensitivity reaction during pregnancy are listed in Table 4.

Epinephrine

Epinephrine is the first-line therapy for perioperative anaphylaxis management.[1–4,28] Early use of epinephrine, dosed according to the clinical presentation, must be the rule after a severe immediate hypersensitivity reaction (i.e., grades III and IV).[2–4,43] Previous reports demonstrated poor outcomes, including deaths, associated with either inadequate or excessive epinephrine doses during anaphylaxis.[44] Absent or late administration of epinephrine was also associated with significant morbidity and mortality.[44] Garvey et al.[45] investigated the use of epinephrine in 270 patients experiencing perioperative anaphylaxis. Epinephrine was the first drug injected in only 24% of patients with grade III reactions; ephedrine and phenylephrine were commonly used as first-line therapy. These authors point out that "treatment with epinephrine can be delayed because of difficulties in diagnosing anaphylaxis and reluctance to administer epinephrine, even if the correct diagnosis has been made." Some authors have expressed concerns regarding the use of epinephrine during pregnancy because of its potential to reduce uteroplacental blood flow.[22] Although epinephrine increases uterine vascular resistance through its α-adrenergic-mediated blood vessel vasoconstriction, an appropriate dose of an alpha-adrenergic agonist, being titrated to response, will increase systemic vascular resistance, cardiac output, and uteroplacental perfusion.[46] During attempted resuscitation of a pregnant woman, the best hope for fetal survival is maternal survival.[43] Therefore, epinephrine should be the treatment of choice for anaphylaxis during pregnancy, as recognized by the latest French Guidelines[4] and the *Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom*.[26] Although the latest Scandinavian[2] and British[3]

guidelines, as well as the American practice parameter,[32] on perioperative anaphylaxis highlight the important role of epinephrine for the treatment of anaphylaxis during anesthesia, they do not specifically discuss the use of epinephrine in the parturient. The therapeutic range of epinephrine plasma concentrations necessary for successful anaphylaxis treatment remains unknown. Therefore, epinephrine should be used with careful titration according to the hemodynamic response[2–4,28] (Table 5). Epinephrine should not be injected during grade I reactions; small titrated boluses may sometimes be necessary during grade II reactions. Titrated IV bolus administration is required during grade III reactions; repeated doses may be required. A continuous infusion may be initiated to minimize the need for repeated bolus injections.[1,4,28] Grade IV reactions (cardiac arrest) require cardiopulmonary resuscitation and high doses of epinephrine.[47] Advanced Cardiovascular Life Support guidelines for cardiac arrest during pregnancy recommend the use of the same dosages used during resuscitation of adults.[43]

Arginine Vasopressin

Desensitization of adrenergic receptors may be one of the factors contributing to catecholamine failure during anaphylaxis; thus, arginine vasopressin (AVP) may be an alternative treatment. AVP works through its vasoconstrictive effects mediated by nonadrenergic vascular V_1 receptors. Increased nitric oxide synthesis contributes to the hypotension and resistance to vasopressors during vasodilatory shock[48] and is another factor that may contribute to catecholamine failure.[28] AVP directly decreases intracellular concentrations of the nitric oxide second messenger, guanosine 3′, 5′-cyclic monophosphate, and thus might act during anaphylaxis as an anti-inflammatory agent.[49] Accordingly, several case reports suggest that AVP might be considered a potential rescue therapy during anaphylaxis refractory to epinephrine, norepinephrine, and/or phenylephrine.[50–55] Further studies are necessary to clarify the use of AVP during anaphylaxis. There are no data available regarding the use of AVP during pregnancy.

Fluid Therapy

Fluid therapy initiated with either crystalloid or colloid solutions is essential to compensate for the peripheral vasodilatation and interstitial capillary leakage.[2–4,34] Changes in vascular permeability may cause more than half of the intravascular fluid to translocate into the interstitial space within 15 minutes after onset of anaphylactic shock.[56] Therefore, a large volume of crystalloids and/or colloids should be administered via large-bore IV access from the early stage of anaphylaxis.[1–4] While the French guidelines recommend that colloids be used after the crystalloid dose exceeds 30 mL/kg,[1,4] others estimate that there is no evidence that one is better than the other.[2,3] Although these guidelines indicate that large volumes of fluid may be required, they do not indicate the dose to be used.[1–4] The dose requirement for fluid therapy during anaphylaxis remains unknown.

Table 4. Management Steps for the Treatment of an Immediate Hypersensitivity Reaction During Pregnancy

- **W**ithdraw the **suspected culprit** drug or agent
- **I**mmediately **call for help**, especially for grade III and IV reactions
- **Discontinue anesthetic agents** likely to cause vasodilation and negative inotropic effects
- **P**osition the patient in **left lateral uterine displacement** to relieve aortocaval compression
- **A**dminister early **intravenous epinephrine** in cases of grade III or IV reactions
- **G**ive a **large fluid** bolus **(crystalloid/colloid)**
- **E**stablish or secure the airway with **100% oxygen** to compensate for the increased oxygen consumption
- **A** plan for a **cesarean delivery** is necessary when the diagnosis of anaphylaxis has been made, as it may lead to cardiac arrest

Cesarean Delivery

Emergent cesarean delivery should be considered early in cases of persistent maternal hemodynamic instability despite resuscitation.[4,43] Since a stable maternal hemodynamic status during anaphylaxis does not guarantee appropriate placental perfusion and fetal oxygenation, normal fetal heart rate variability provides reassurance about fetal status.[57] Persistent nonreassuring fetal heart rate patterns despite aggressive medical management are an indication for emergency delivery.[58]

Additional Therapy

Treatment with inhaled β_2-agonist (salbutamol or albuterol) is recommended for isolated bronchospasm.[1–4,28] Epinephrine remains the first-line therapy when cardiovascular collapse and bronchospasm occur together.[2–4,28] α_1- and β_1-adrenergic receptors activation by epinephrine counteracts the vasoplegic component of anaphylaxis, while its β_2-effect is effective in relieving bronchoconstriction. Glucocorticoid therapy (i.e., methylprednisolone 1 mg/kg) is considered a secondary treatment to decrease airway inflammation.[1–4,28,59] H_1- and/or H_2-receptor antagonists may be administered as the second line of treatment, but never before epinephrine.[1–4,28] However, their effects have never been evaluated.

Cardiac Arrest

The 2010 *Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care from the American Heart Association* make it clear that there should be no delay in delivering the usual treatment during the management of cardiac arrest in pregnancy, including standard drug doses.[43] Cesarean delivery should be initiated within 4 minutes of the arrest if the resuscitation has not been successful with the goal of delivering the fetus within 5 minutes of the arrest.[43] Emptying the uterus removes aortocaval compression, resulting in 60% to 80% increase in cardiac output, thereby increasing the likelihood of maternal survival.[60] Unfortunately, very few cases of perimortem cesarean delivery are within the recommended time period. Survival of the mother has been reported with perimortem cesarean delivery performed up to 15 minutes after the onset of maternal cardiac arrest.[60,61] The *Eighth Report of the Confidential Enquiries into Maternal Deaths in the United Kingdom* reported the death of a woman after suffering an anaphylactic reaction to an antibiotic given during labor.[26] A careful review demonstrates that "the failure to initiate perimortem caesarean section on the labor ward within 4 minutes of cardiac arrest to deliver the fetus may have contributed to the unsuccessful maternal resuscitation," and

Table 5. Epinephrine Dose According to the Grade of the Immediate Reaction

Grades	IV epinephrine
I	None
II	10- to 20-μg bolus dose sometimes necessary
III	100- to 200-μg bolus dose required, repeated every 1 to 2 min. according to the hemodynamic response ± continuous infusion (0.05–0.1 μg/kg/min) to minimize the need for repeated bolus injections
IV	1-mg bolus dose repeated every 3 to 5 min.

adds that "acute anaphylaxis requires an immediate medical response including treatment with epinephrine."[26]

Etiological Diagnosis of Immediate Hypersensitivity

While the initial diagnosis of peripartum immediate hypersensitivity relies on the clinical symptoms and the chronology of events, the etiological diagnosis is based on serologic and skin tests.[2–4,28] The interpretation of the allergological assessment should be done in the context of the clinical history. This analysis helps to ensure an accurate diagnosis necessary to determine the pathophysiological mechanism, to identify the culprit agent, and to provide subsequent recommendations for further anesthetic procedures.[2–4,28]

The diagnosis of IgE-mediated allergic hypersensitivity was proven in 44% of the reported cases in this review (confirmation by the clinical history and positive skin tests to the culprit agent) (Tables 2 and 3).[8,14,17,18,36,37,39] If measured, serum tryptase was always elevated. Serum-specific IgE measured during documented latex-induced reactions was always positive. The diagnosis of IgE-mediated anaphylaxis remained presumptive in the remaining 56% of cases.[7,9–13,15,16,19–22,38,40,41] Although the clinical history was suggestive of immediate allergic hypersensitivity, tryptase was not measured in most of these cases, and skin tests were not performed. Therefore, it is difficult to draw conclusions from these uninvestigated cases because the evidence is quite limited.

Biochemical Tests and In Vitro Assays Measurements

Plasma Histamine

Plasma histamine is an inflammatory mediator stored in mast cell and basophil granules. An increased concentration of plasma histamine indicates in vivo release and is observed during both allergic and nonallergic immediate reactions. The peak of plasma histamine is immediate, and its plasma half-life is short, approximately 15 to 20 minutes.[4] However, serum histamine is not a good marker following anaphylaxis after the first trimester of pregnancy, because it is metabolized by the histamine-degrading diamine oxidase enzyme; this enzyme is released by the placenta.[62] The balance between histamine and the diamine oxidase seems to be crucial for an uncomplicated course of pregnancy.[63] Plasma histamine measurement is therefore not helpful in the diagnosis of anaphylaxis after the first trimester of pregnancy because of false negative results.[4]

Serum Tryptase

Tryptases are neutral serine proteases stored predominantly in mast cells. Two major forms can be measured in vivo: pro-α tryptase that reflects the mast cell burden and is increased in mastocytosis,[64] and mature β-tryptase preferentially stored in mast cells granules and released during mast cell activation, such as during IgE-mediated anaphylaxis.[65] The total tryptase level, measured in serum by fluoroimmunoassay, measures mature β-tryptase in addition to pro-α tryptase.[66] The median serum tryptase level was reported to be 5.1 μg/L (range: 1–30.7 μg/L) in a general adult population.[67] Serum total tryptase concentrations reach a peak at 1 hour after the onset of the immediate reaction, decline under first-order kinetics with a half-life of approximately 2 hours, and correlate with the clinical severity of the reaction.[2–4] While an increase in tryptase can be measured 30 to 60 minutes after onset of symptoms in cases of mild reactions, sampling is recommended between 30 minutes and 2 hours in cases of grade III and IV reactions.[4] Tryptase may not be increased in mild reactions. An increase in tryptase is highly suggestive of mast cell activation as seen in IgE-mediated anaphylaxis, but its absence does not preclude the diagnosis. To compare the concentrations during an immediate reaction with baseline levels, a tryptase measurement may be performed after >24 hours following a reaction or when the patient is referred for investigation.[1–4]

Specific Serum IgE Measurement

IgE-antibody testing may be performed at the time of the reaction or later.[1–4] Specific serum IgE measurement is available for some drugs including β-lactam drugs (e.g., ampicillin and amoxicillin, penicillins G and V), succinylcholine, morphine, chlorhexidine and protamine, but the test sensitivity is low.[1–4] IgE-antibody assay is also commercially available for latex and has a similar sensitivity as a skin prick test.[68] In the United States, Food and Drug Administration-approved specific serum IgE measurements are only available for penicillins G, V and latex. Identification of serum IgE provides possible evidence of IgE sensitization; this result should be correlated with clinical symptoms at the time of contact or administration of the allergen.

Skin Tests

Skin tests should be performed as suggested by the clinical history. All drugs and substances (e.g., latex, chlorhexidine) to which the patient was exposed before the reaction should be tested. Skin testing should be performed at least 4 to 6 weeks after an anaphylactic reaction to avoid false negative results.[3,4] Skin test can be performed at any point during the pregnancy, especially for local anesthetics, latex, and neuromuscular-blocking drugs.[4]

A suggestive clinical history with a mild reaction without an increase in tryptase and a negative skin test is indicative of a nonallergic reaction, such as histamine release.[1–4] Conversely, immediate hypersensitivity reactions requiring emergency treatment, and associated with an increased

tryptase and positive skin tests to the suspected drug/agent, constitute evidence of an IgE-mediated mechanism.[1–4] In this latter condition, the identified drug/agent should be avoided in the future. The sensitivity of skin tests for neuromuscular-blocking drugs in patients having experienced anaphylaxis after a neuromuscular-blocking drug injection is >95%, and their reproducibility is excellent.[1,69] Therefore, negative skin-tested drugs can be used for further procedures (i.e., negative skin-tested neuromuscular-blocking drugs during the diagnostic approach of a documented neuromuscular-blocking drug-induced IgE-mediated anaphylaxis).[4] In selected cases, drug challenges are the "gold standard" after a negative skin test to address drug hypersensitivity to certain drugs such as penicillins.[70,71]

PREVENTION

As no prospective randomized studies evaluating the use of a specific protocol of premedication for the prevention of perioperative anaphylaxis have been published, it is critical to identify at-risk patients before any surgical procedure.[2–4,28] A careful and complete review of the clinical history is essential before any procedure in patients with previous uninvestigated perioperative immediate reactions because they are at increased risk of a recurrence during subsequent anesthetics.[2–4,28] An allergological assessment linked to the clinical history should then be considered to identify and avoid the culprit drug or latex.[2–4,28] Therefore, it is quite important that health care facilities have institutional guidelines for precautions used during management of patients with latex allergy, including the use of latex-free gloves and medical equipment.

CONCLUSION

Even though anaphylaxis is not common during pregnancy, it is important to recognize it rapidly and treat it effectively, because the cardiovascular disturbances may be catastrophic to both mother and fetus. Causes of anaphylaxis include drugs and environmental agents to which obstetric patients are commonly exposed. Accordingly, the most common triggers are penicillin administered for prophylaxis against neonatal group B streptococcal infection, other β-lactam antibiotics (e.g. cephalosporins) administered for surgical prophylaxis, and latex. No anaphylaxis to local anesthetics has been reported during the past decade. The vast majority of adverse effects to local anesthetics are because of systemic absorption of local anesthetic or epinephrine. The management of anaphylaxis occuring during the third trimester of pregnancy may be challenging. As stated in the latest report of the *Confidential Enquiries into Maternal Deaths in the United Kingdom*, a formal anaphylaxis protocol should be immediately available for all clinical staff.[26] The use of cognitive aids, such as anaphylaxis checklists, have been demonstrated to improve medical care in a simulated clinical environment.[72,73] Treatment with epinephrine should be grade specific, and cesarean delivery should be considered in cases of severe reactions. Finally, patients who experience anaphylaxis during pregnancy should have a follow-up assessment from an allergy/immunology specialist to confirm the trigger for anaphylaxis, prevent recurrences, and propose alternatives for further procedures.

DISCLOSURES

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