REVIEW ARTICLE

Allergic reactions during labour analgesia and caesarean section anaesthesia

I. Adriaensens, M. Vercauteren, F. Soetens, L. Janssen, J. Leysen, D. Ebo

Department of Anaesthesia, Antwerp University Hospital, Antwerp, Belgium
Department of Anaesthesia, AZ Turnhout, Turnhout, Belgium
Department of Anaesthesia, St Dimpna Hospital, Geel, Belgium
Department of Immunology, Antwerp University Hospital, Antwerp, Belgium

ABSTRACT

Allergic reactions in the parturient are challenging for the anaesthetist who is dealing with both mother and baby, often in circumstances when there is a need for delivery. While most previous reviews have focused on specific substances in individual cases, this review focuses on allergic reactions during the peripartum period, the differential diagnosis and specific treatment options. Immunoregulation and susceptibility to allergic reactions may change during pregnancy. Compared with non-pregnant patients, in whom neuromuscular blocking drugs are the most common triggering substances, allergic reactions in parturients mostly occur following contact with latex, injection of antibiotics and uterotonics, and infusion of colloids. With the exception of latex, where patient history may raise suspicion, allergic reactions may occur without prior exposure to triggering agents. Most drugs used for resuscitation of the non-pregnant patient are suitable for the parturient. Some substances, such as H2-receptor antagonists for aspiration prophylaxis or corticosteroids for prematurity, may have been given before the event. Although fetal outcome is important, the mother is the primary focus of care.

Keywords: Anaesthesia; Allergy; Anaphylaxis; Labour; Caesarean section

Introduction

Anaphylactic reactions during anaesthesia are rare in the general population. Management of the parturient is challenging since the welfare of both mother and fetus must be considered. There have been many reviews on anaphylaxis during anaesthesia in general, but other than case reports, only a few reviews have been written specifically about obstetric patients. Haemodynamic changes are common during obstetric anaesthesia which may delay the diagnosis of an allergic reaction. The present review aims to increase awareness of possible allergic reactions and highlight the different triggering agents and treatment options.

Epidemiology

There is large variability in the reported incidence of intraoperative anaphylactic reactions, ranging from 1:10000 to 1:20000 in Australia to 1:6000 in Norway. Recently, the estimated annual incidence of allergic reactions during anaesthesia in France was reported to be 100.6 per million procedures (1:9940). In contrast, a retrospective study at a large United States centre reported approximately one referral per 34000 anaesthetics. Associated mortality rates range from 3.4% to as high as 6%. A significant female predominance has been observed, independent of the causal agent. An IgE-mediated reaction is involved in approximately 50–70% of cases. French epidemiological surveys revealed neuromuscular blocking drugs (NMBDs) to be involved in 54–58% of cases, followed by latex (19.6–22.3%) and antibiotics (12.8–14.7%). Whereas a Norwegian study reported NMBDs as the responsible allergen in 93.2%, the United States report found NMBDs to be causative in only 11.1%. These discrepancies may be caused by the potential of NMBDs to produce positive skin tests, as demonstrated in volunteers, independent of mast cell degranulation, which may explain the high but probably false incidence of alleged allergic reactions. In addition, exposure to certain drugs, such as pholcodine in Norway, may presensitize patients for cross-reactivity to NMBDs.

Stephens analyzed intensive care unit (ICU) admissions from an obstetric hospital. Of 24161 anaesthetics in 10 years, five cases involved an allergic reaction.
only cases requiring ICU admission were included, the true incidence may have been underestimated. Prospective surveys of ‘near-accidents’ in the UK revealed five cases in the period 2003–2005, giving an incidence of 3 in 100,000 pregnancies. Similarly, Mulla et al. reviewed the hospital discharge data of Texan parturients during 2004–2005 and noted an incidence of maternal anaphylaxis of 2.7 per 100,000 deliveries. No maternal deaths were reported and 14 out of 19 parturients presenting with anaphylaxis (74%) were delivered by caesarean section. Antibiotics were the trigger in 68%, Drasici et al. however, reported an incidence as high as 1:310 of latex anaphylactic reactions in caesarean section patients.

**Definition, pathophysiology and alterations during pregnancy**

Although there are different types of allergic reactions, clinical symptoms are similar, making them clinically indistinguishable. The classification of allergic reactions has often changed, but since 2001 consensus has been achieved with respect to terminology. ‘Anaphylactic’ is now the preferred term to describe any reaction, whereas the term ‘anaphylactoid’ should be abandoned. A diagnostic work-up may elucidate whether an event was IgE-mediated, non-IgE-mediated or a non-immunological hypersensitivity reaction. In an IgE-mediated reaction, B-lymphocytes produce IgE antibodies during first exposure to an antigen, which bind to receptors on the surface of mast cells and basophils. On repeated exposure, the antigen bridges two adjacent IgE antibodies resulting in release of mediators such as histamine, tryptase, and chemotactic factors from storage granules, as well as newly synthesized mediators (leukotrienes, prostaglandins, platelet activating factor) from the cell membrane and also cytokines. Other mechanisms involve either immunological (IgG or IgM) or non-immunological complement activation, with the release of complement fragments, known as anaphylatoxins, which induce subsequent release of mediators from mast cells and basophils. Finally, a direct non-immune-mediated hypersensitivity reaction is also possible, causing release of histamine by mast cells in a dose-dependent fashion with symptoms that are usually mild.

During pregnancy, hormonal changes may be responsible for alterations of the immune system. Modification of autoimmune diseases during pregnancy, such as systemic lupus erythematosus which tends to develop or worsen, or rheumatoid arthritis which tends to improve, supports an alteration in immunoregulation. Oestrogen and progesterone concentrations are greatly increased during pregnancy and are considered immunomodulating hormones. Progesterone promotes type 2 T helper (Th2) cell polarization by inhibiting type 1 T helper (Th1) cell cytokine production and inducing Th2 cytokines and interleukin 10 production. These alterations serve to prevent rejection of the fetus, however, it is unclear if they predispose the parturient to anaphylaxis or affect its severity.

The placenta plays a role in protecting the fetus against maternal anaphylactic reactions, as it prevents the passage of high-molecular-weight IgE antibodies. Furthermore, the high diamine oxidase activity of the maternal decidua catalyzes oxidative deamination of histamine and other amines released during anaphylaxis. Maternal hypotension can result in fetal hypoxia causing thalamic and basal ganglia lesions with adverse outcome. After anaphylactic shock at 27 weeks of gestation, multicystic bilateral encephalomalia of both hemispheres and atrophy of the corpus callosum have been reported. Sleth et al. postulated that fetal asphyxia is the result of both maternal cardiovascular collapse and chorio-umbilical vasoconstriction due to release of mediators.

**Clinical manifestations**

Table 1 summarizes symptoms associated with allergic reactions, some or all of which may occur depending on receptor location, reaction severity and anaesthetic modality. During neuraxial anaesthesia, early signs such as malaise, pruritus, nausea and dyspnoea may be apparent in the awake patient. With general anaesthesia, however, they may be unrecognized and bronchospasm or cardiovascular collapse may be the first recognizable signs. In 90% of cases, symptoms appear within minutes of administration of the triggering substance. If the appearance of signs is delayed until after induction or during maintenance of anaesthesia, allergy to latex, antibiotics, disinfectants or local anaesthetics should be suspected. The most common clinical features are cardiovascular symptoms (73.6%), cutaneous reactions (69.6%) and bronchospasm (44.2%). Although a combination usually raises suspicion of an allergic reaction, symptoms may appear in isolation and thus delay the diagnosis.

The severity of clinical manifestations related to allergic reactions can be classified in four grades:

- Grade I: cutaneous symptoms.
- Grade II: measurable but not life-threatening symptoms including hypotension, tachycardia and respiratory disturbance (cough, difficulty to inflate).
- Grade III: life-threatening symptoms including collapse, tachycardia or bradycardia, arrhythmias and bronchospasm.
- Grade IV: cardiac and/or respiratory arrest.

Clinical manifestations appear more severe in patients with true IgE-mediated anaphylaxis in comparison with those suffering what was previously called an
anaphylactoid reaction. Mertes et al. revealed that the majority of anaphylactic reactions involved Grade II (23%) and Grade III (60%) reactions, whereas most anaphylactoid reactions were Grade I (55%) and Grade II (30%) reactions. Grade IV was only noted in true anaphylaxis (6%). Differential diagnosis with special reference to obstetrics

Simulation has revealed that anaesthetists may require at least 10 min before making the correct diagnosis of an anaphylactic reaction. During obstetric anaesthesia, other conditions may mimic an allergic reaction. Cardiorespiratory collapse may be due to local anaesthetic-induced sympathetic block or toxicity, haemorrhage or amniotic fluid embolism. Other conditions that may partially mimic an anaphylactic reaction are laryngeal oedema, laryngopathia gravidarum (pregnancy-related laryngeal dysfunction, likely to be most severe just before delivery), hereditary angio-oedema, bronchospasm, vasovagal reaction and opioid-induced pruritus.

A change in upper airway anatomy and/or tissue swelling may cause intubation difficulty in parturients, while Mallampati scores can increase during pregnancy and labour. The isolated presentation of laryngeal oedema due to an allergic reaction is extremely rare. It is more likely to be associated with other conditions such as preeclampsia, laryngopathia gravidarum and hereditary angio-oedema. Bronchospasm, not causally related to injected substances, may also be seen in patients suffering from bronchial asthma. Difficulty with intubation in the presence of an allergic reaction should be anticipated.

High or total spinal block or local anaesthetic toxicity during neur axial anaesthesia may be confused with an allergic reaction, although cutaneous reactions and bronchoconstriction are absent. Neuraxial opioids may cause pruritus, malaise, nausea and respiratory problems, which may have similarities to an allergic reaction. Vasovagal reactions can result in hypotension, bradycardia and flushing. Embolic complications may cause cardiovascular collapse and arrest.

Amniotic fluid embolism (AFE) may present with cardiovascular collapse, respiratory distress and blood loss due to coagulopathy, and is difficult to distinguish from an allergic event; diagnosis is often based upon suspicion or exclusion. Currently, understanding of the pathophysiology of AFE has changed from an obstructive embolic event to a maternal immune response. Although it has been suggested that AFE symptoms might result from maternal allergy against fetal antigens, it is unclear how the mother can tolerate these foreign antigens during pregnancy. Some case reports have found elevated serum tryptase levels during AFE, although levels are lower than those seen in anaphylactic syndromes; others have found normal tryptase levels. In addition, increased pulmonary mast cells have been found in subjects who died from AFE as well as abnormally low levels of complement. This, however, is a poor indicator because it may be found in both AFE and anaphylactic reactions. Not surprisingly, AFE has been called the 'anaphylactoid syndrome of pregnancy'. Although the differential diagnosis between an anaphylactic reaction and AFE may be difficult in survivors, the presence of bronchospasm favours an anaphylactic reaction while profuse bleeding and increased levels of specific markers such as Sialyl TN (STN) indicate AFE. Lastly, haemorrhage can also result in a hypovolemic shock with cardiovascular collapse; again, skin reactions or bronchoconstriction are not seen.

### Triggering agents in obstetric analgesia and anaesthesia

The predominant use of neuraxial anaesthesia in obstetrics limits exposure to various trigger agents. Most...
commonly involved are latex, antibiotics, colloids, oxytocics, local anaesthetics and neuromuscular blocking agents.

**Latex**

There are multiple case reports of latex triggering allergic reactions in parturients.\(^{18,41-62}\) Latex products are composed of two substances capable of causing an adverse reaction. Firstly, natural rubber latex (NRL) proteins can provoke a type I IgE-mediated hypersensitivity reaction in sensitized patients. Secondly, added chemical antioxidants and rubber accelerators may cause allergic contact dermatitis, which is a type IV hypersensitivity reaction. This reaction, resulting from T-cell-mediated sensitization, is characterized by a delayed onset but is not life-threatening. Contact dermatitis is also possible with latex products because of their alkaline pH and this usually develops minutes to hours after exposure.\(^{58}\)

The incidence of latex-related allergic reactions has rapidly increased during recent decades. Epidemiological surveys in France demonstrate an increase in latex allergic reactions from 0.5% in 1984–1989 to about 20% in the early years of the 21st century.\(^{3,4}\) Overall, latex has been found to be the second most common cause of anaphylaxis during anaesthesia.\(^{3,4}\) The incidence of latex sensitization in the general population is about 1:100. Several high-risk groups have been identified: patients with spina bifida and/or urogenital abnormalities, healthcare workers, and patients with a history of multiple surgical procedures or allergies to kiwi fruit, peach, banana, chestnuts, nuts, avocado, figs, pineapple, melon, tomato, or potato.\(^{18,41}\) A significant female predominance for latex-related reactions (about 70%) has been found.\(^{3,9,59}\) This may be related to the higher predisposition to allergic diseases observed in women, more frequent exposure to products containing NRL during everyday life and a greater mucosal contact with latex through contraceptives.\(^{60,61}\) Moreover, obstetric and gynaecological procedures appear to be the most common setting for latex-related anaphylaxis, accounting for approximately 50% of all latex-related allergic reactions.\(^{41,59}\) This probably represents the existence of one or more additional risk factors in the obstetric population such as extensive and repeated contact of highly absorptive membranes with surgical gloves during vaginal examinations or delivery.\(^{47,50,52}\)

This raises the suspicion of an increased risk for latex anaphylaxis in the parturient, as suggested by recent studies. In 2004, Draisci et al.\(^{18}\) retrospectively analyzed 1240 consecutive caesarean sections. Patients suspected to have suffered intraoperative anaphylactic reactions were questioned about previous adverse reactions to latex and drugs, atopic diseases and other risk factors, and underwent allergy testing. A high incidence of intraoperative anaphylactic reactions against latex (1:310) was reported. In 2008, Delaunay et al.\(^{55}\) reported two cases of latex-induced anaphylactic shock during caesarean section in Guadeloupe during a 5-year period when there were a total of 2138 caesarean sections. The absence of laboratory testing for allergy (tryptase, specific IgE) in Guadeloupe complicated diagnostic management and consequently the reported number of cases is probably an underestimation. In addition, Guadeloupe’s population differs from the general population as there is abundant availability of exotic fruits and the Hevea brasiliensis tree, enhancing the risk of latex sensitization. Draisci et al. found latex sensitization to be more common in the obstetric population compared with non-pregnant nulliparous women (5.1% versus 1.7%).\(^{41}\)

One case report described an allergic reaction after introducing a latex-containing urethral catheter.\(^{64}\) However, the majority of latex-related allergic reactions in parturients develop after vaginal examination with latex gloves or during caesarean section, particularly after oxytocin infusion.\(^{42,45-49,52,55,57}\) The injection of oxytocin seems to play a fundamental role in triggering these reactions. This may be explained by uterine contractions provoking the release of latex particles into the bloodstream.\(^{59}\) Another mechanism may be cross-reactivity between synthetic oxytocin and latex; in those sensitized to latex, subsequent administration of oxytocin could facilitate antigen recognition, causing an anaphylactic response.\(^{62}\)

The increased risk of latex-related anaphylaxis in pregnant patients makes thorough preoperative risk stratification mandatory.\(^{18}\) Careful questioning about previous symptoms of latex intolerance after wearing gloves, inflating balloons, previous clinical examinations with latex gloves or during the use of latex condoms is recommended since symptoms suggestive of latex sensitization before an anaphylactic reaction are present in up to 30% of cases.\(^{3,9}\) If latex allergy is confirmed or suspected, precautions are indicated such as creation of a latex-free environment. A total latex-free approach for all obstetric patients has to be considered especially as latex anaphylaxis is often misdiagnosed because of delayed symptomatology.

**Antibiotics**

There have been many case reports of antibiotic-induced allergy in parturients.\(^{25,27,29,63-71}\) Antibiotics are mainly used prophylactically during delivery to reduce the incidence of endometritis and wound infection following caesarean section.\(^{72,73}\) For the latter, it is currently recommended to administer antibiotics before incision rather than after clamping the umbilical cord,\(^{79}\) although this exposes the fetus to the consequences of an anaphylactic reaction if it occurs. A recent survey from Mulla et al.\(^{17}\) found β-lactam antibiotics to be the most common triggers of allergic reactions in obstetric patients. β-lactam antibiotics that have been implicated include penicillin, ampicillin, amoxicillin, cefotaxime, cefazolin, ceftriaxone, and cefotetan. Vancomycin, which is
Colloids

Maternal hypotension is common following spinal anaesthesia for caesarean section. Colloids are frequently used as prophylaxis or treatment since they have been found to be more effective than crystalloids. Dextrans, gelatins and hydroxyethyl starch (HES) all carry a potential allergic risk. Dextran-induced allergic reactions (DIAR) occur when dextran molecules form large immune-complexes with circulating dextran-reactive antibodies (DRA). These antibodies may have been formed in response to exposure to high-molecular-weight polysaccharides such as bacterial polysaccharides present in gut microflora, or after ingestion of dextrans as contaminants of sucrose or as components of dental plaque. DRA exist in low concentration in most individuals. Patients developing the most serious DIAR usually have high DRA titers. A prospective study in 5745 gynaecologic and obstetric patients found an overall incidence of DIAR of 1:383 (0.3%) with an incidence of severe (Grade II–IV) reactions of 1:821. Despite the use of hapten prophylaxis, during which a low-molecular-weight dextran is first administered to block the antigen combining sites of the preformed DRA without causing any immunological reaction, adverse maternal and/or fetal consequences are still possible. A case of neonatal resuscitation with subsequent severe brain damage and another of prolonged cardiac arrest in a woman with preeclampsia have been reported. Because of several reports of severe fetal distress and at least one neonatal death, dextrans have been largely abandoned during pregnancy and delivery. It may also be best to avoid gelatins in obstetric patients because they carry the highest risk of allergic reactions (0.35%). Seven obstetric cases were published several decades ago with a further report in 2009. HES solutions are associated with the lowest allergic risk (0.006–0.058%). An anaphylactic reaction to HES during caesarean section has been reported in a patient with haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

Uterotonic

Rapid intravenous administration of synthetic oxytocin analogues can cause transient hypotension and reflex tachycardia which may need to be differentiated from an allergic reaction. However, despite their widespread use, only a few allergic reactions have been reported. None proved to be IgE-mediated. Allergic reactions to carboplatin have not been reported. One case of hypersensitivity to methylergometrine has been reported although simultaneous administration of oxytocin might also have been involved. Another report described collapse in a patient with Raynaud’s disease, which was suggested to be caused by hypersensitivity to ergometrine.

Local anaesthetics

Allergic reactions to local anaesthetics are rare. Fisher et al. reported that only 3.9% of all suspected reactions to local anaesthetics were truly allergic, of which four patients suffered an immediate (Type I) and four a delayed (Type IV) reaction. A recent UK survey found a much lower rate of <1%. Ester local anaesthetics are more likely to provoke IgE-mediated anaphylaxis because of the metabolite paraaminobenzoic acid which is a documented allergen. In addition, preservatives, such as methylparaben and metabisulphite, can also produce an allergic response. Amide local anaesthetics have been reported to be involved in 0.33–0.6% of all perioperative allergic reactions. Only three obstetric cases have been reported with proven allergy for amide local anaesthetics. Diphenhydramine was suggested as an alternative agent for episiotomy repair in a case of local anaesthetic hypersensitivity. Cross-reactivity to both ropivacaine and levobupivacaine has also been reported.

When a parturient has a history of suspected hypersensitivity to local anaesthetics, appropriate testing is mandatory. Intradermal skin testing for local anaesthetics is associated with frequent false positive reactions in 8–15% and therefore not reliable. Large series have confirmed the safety of provocative challenge testing in patients reported to be allergic to local anaesthetics, while identifying safe drugs for further use. Testing should be postponed until the fetus is viable (or after delivery) and performed in an adequately equipped environment with facilities for resuscitation and emergency caesarean section.

Neuromuscular blocking drugs

Many reports have shown NMBDs to be the leading cause of perioperative allergic reactions, responsible for >50% of all cases. In contrast, relatively few reports
of such reactions exist in parturients. This can be explained by the relatively low use of general anaesthesia for caesarean section. All case reports have involved succinylcholine. With the recent availability of sugammadex to rapidly antagonize steroidal NMBDs, it is possible that rocuronium may start to replace succinylcholine, although it may also be associated with anaphylactic reactions. Although it has been suggested that sugammadex may be useful for attenuating rocuronium-induced anaphylaxis, this was not confirmed by an experimental study, using a cutaneous model of anaphylaxis in rocuronium-sensitized patients. Furthermore, hypersensitivity to sugammadex has been reported.

Most hypersensitivity reactions to NMBDs are IgE-dependent, but they can also result from direct mast cell and basophil activation. The latter is predominantly found with the benzylisoquinolones d-tubocurarine, atracurium and mivacurium. The antigenic determinant is the quaternary ammonium ion. As succinylcholine appears to be most frequently involved, it is possible that the flexible chain between the two quaternary ammonium ions may be more potent in stimulating sensitized cells than rigid molecules like pancuronium.

Cross-reactivity among NMBDs is frequent, ranging from 60% to 70%. It is common among the groups of steroidal or benzylisoquinolines but also between succinylcholine and non-depolarizing muscle relaxants. Since quaternary ammonium ions are widely present in foods, cosmetics and household products such as disinfectants and solvents, prior sensitization with formation of specific IgE antibodies, especially in females, is a plausible explanation for IgE-mediated anaphylaxis on first exposure to NMBD.

Histamine H2-receptor antagonists
Allergic reactions associated with histamine H2-receptor antagonists in obstetric patients have been related to ranitidine only. All were considered non-IgE-mediated reactions. However, allergic reactions to cimetidine, famotidine or ranitidine with cross-reactivity have been reported in the general population in which ranitidine-specific IgE antibodies have been isolated. Cimetidine metabolites, rather than cimetidine itself, might have been responsible. The occurrence of allergic reactions due to H2-receptor antagonists blockers is surprising since they are part of second line treatment for anaphylaxis.

Opioids
Direct non-immunologic activation of mast cells with dose-dependent release of histamine and tryptase from cutaneous mast cells is a common side effect of several opioids, such as morphine, codeine and meperidine. True allergic reactions to opioids are rare and mostly seen with ‘natural’ compounds such as morphine, whereas reactions to (semi-) synthetic compounds are rare. Fentanyl hypersensitivity after epidural use for caesarean section has been reported.

General anaesthetic induction agents
An anaphylactic reaction with cardiac arrest has been reported during caesarean section anaesthesia induced with propanidid. This short-acting anaesthetic was subsequently withdrawn. Another single case report described pulmonary oedema following propofol induction for caesarean section with strongly positive subsequent skin tests.

Chlorhexidine
Several topical preparations for skin or mucosal disinfection and lubrication gels for urologic and gynaecologic procedures contain chlorhexidine. It is also present in soaps, cosmetics, toothpaste and mouthwash which may cause sensitization of the general population. Hyper-sensitivity reactions range from contact dermatitis to generalised urticaria and life-threatening anaphylaxis. Despite an increasing number of anaphylactic reports, there are few cases of anaphylaxis in pregnancy, although in one, a reaction to latex could not be excluded.

Other substances
Other isolated cases of allergic reactions in obstetric patients have also been reported. Triggering agents include foods, contrast media, diclofenac, iron, ethylene oxide, corn-derived dextrose solution, metabisulphite, phytonadione and insect stings.

Management and specific considerations for the parturient
Management should be tailored to the severity and combination of clinical features in each patient, and is similar to the approach in the general population with some additional considerations (Table 2). The main goals are cessation of exposure to the triggering agent, reducing the effects of released mediators, restoring vital signs and preventing further mediator release. Although the mother may tolerate some hypotension, systolic blood pressure should be maintained >90 mmHg to ensure adequate placental perfusion.

Initial management
In non-obstetric patients, immediate interruption or delay of the surgical procedure and removal of the suspected agent is mandatory. When there is no obvious causative agent, colloids, latex, chlorhexidine, antibiotics and blood products should be removed. Discontinuation of anaesthesia, if possible, avoids additional cardiovascular depression. When bronchospasm is the sole symptom, volatile anaesthetics can be
maintained for their bronchodilatory effects. Management in obstetric patients is modified in that rapid delivery of the fetus should be performed in cases of cardiac arrest or anaphylaxis refractory to medical treatment.

Maintenance of a patent airway is imperative and 100% oxygen should be delivered. There is no evidence supporting the use of colloids over crystalloids in this setting, and colloids may also trigger an allergic reaction. Fluid resuscitation is of paramount importance to compensate for the large fluid shifts resulting from vasodilation and increased capillary permeability. Volume expansion of 2–4 L may be needed.

There is no evidence supporting the use of colloids over crystalloids in this setting, and colloids may also trigger an allergic reaction. Administration of fluids should be monitored carefully because overzealous infusion may cause pulmonary oedema after delivery when there is enhanced venous return with relief of aortocaval compression, autotransfusion from the contracting uterus and regression of the sympathetic block in cases of neuraxial anaesthesia. Left lateral tilt and leg elevation should also be performed.

Adrenaline is the cornerstone of treatment of anaphylactic reactions. It stimulates α1-adrenergic receptors, which constrict capacitance and resistance blood vessels. In addition, β1-adrenergic activity increases myocardial contractility and stimulation of β2-adrenergic receptors dilates bronchial smooth muscles, decreases hepatic venous resistance and as a consequence increases venous return. Furthermore, stimulation of β2-adrenergic receptors present on mast cells (and basophils) increases cyclic adenosine monophosphate (cAMP), inhibiting subsequent mediator release. Guidelines recommend early administration of 0.3–0.5 mg of 1:1000 adrenaline by intramuscular injection, repeated every 5–15 min if no clinical improvement. However, because there may be inadequate tissue perfusion, intravenous administration is preferable. Since intravenous adrenaline can cause life-threatening hypertension, tachycardia, arrhythmias and myocardial ischaemia, it should be titrated carefully and in accordance with the clinical response. In the perioperative setting, higher doses may be necessary because of anaesthesia-related reduced sympathetic response. Titrated boluses of 10–50 μg should be started and if insufficient, increase to 100–200 μg every 1–2 min as required.

In cases of cardiovascular collapse, these doses should be given in combination with chest compressions. If haemodynamic instability persists, prolonged inotropic support with a continuous infusion starting at 0.05–0.1 μg/kg/min may be required. In cases of cardiac arrest, cardiopulmonary resuscitation and high doses of adrenaline (1 mg every 2 min) are required. For bradycardia, adrenaline, rather than atropine, is indicated because the cause is a paradoxical cardio-inhibitory reflex, to provide adequate ventricular filling in a massive hypovolemic state.

Although adrenaline is recommended as the gold standard for treatment of anaphylactic reactions, controversy exists about its use in parturients. Placental perfusion is mainly dependent on the maternal systolic blood pressure and cardiac output. Vascular resistance plays only a minor role as placental blood vessels are almost maximally dilated in normal pregnancy. Therefore, during an acute allergic event, prompt restoration of a maternal blood pressure is essential to ensure adequate perfusion of the placenta. Concerns regarding the use of adrenaline have been raised because of its potential to reduce

<table>
<thead>
<tr>
<th>Table 2 Management of a suspected anaphylactic reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial management</strong></td>
</tr>
<tr>
<td>1. Stop administration of the antigen and/or minimize (inhaled anaesthetics)</td>
</tr>
<tr>
<td>2. Call for help</td>
</tr>
<tr>
<td>3. 100% humidified O₂ (6–8 L/min) by mask or via tracheal tube</td>
</tr>
<tr>
<td>4. Volume expansion</td>
</tr>
<tr>
<td>5. Left lateral tilt and elevation of lower extremities</td>
</tr>
<tr>
<td>6. Extend monitoring (including fetal)</td>
</tr>
<tr>
<td>7. Intravenous adrenaline (dose depending on the severity of the reaction)</td>
</tr>
<tr>
<td>8. In cases of cardiac arrest start chest compressions</td>
</tr>
<tr>
<td>9. Obstetrical management options:</td>
</tr>
<tr>
<td>- At any time: consider emergency caesarean section</td>
</tr>
<tr>
<td>- If on-going caesarean section: proceed to deliver the fetus</td>
</tr>
<tr>
<td>- If occurs after delivery: stop surgery</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Second-line therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Histamine H₁-receptor antagonist (intramuscular promethazine 50 mg or intravenous 25 mg)</td>
</tr>
<tr>
<td>2. Histamine H₂-receptor antagonist (intravenous ranitidine 50 mg)</td>
</tr>
<tr>
<td>3. Vasopressor infusion (noradrenaline 1–4 μg/min starting dose)</td>
</tr>
<tr>
<td>4. Nebulized bronchodilator (salbutamol, fenoterol, ipratropium)</td>
</tr>
<tr>
<td>5. Corticosteroids: (intravenous hydrocortisone 5 mg/kg)</td>
</tr>
<tr>
<td>6. Others: tranexamic acid, glucagon, aminophylline</td>
</tr>
</tbody>
</table>

...
uterine blood flow through $\alpha$-adrenergic-mediated vasoconstriction in the placenta, which may worsen fetal distress.\textsuperscript{24,25,51} Indeed, small doses of 10–20 $\mu$g, as recommended for treating moderate anaphylactic reactions, result in a 30–40% reduction of the uterine blood flow. Several authors have proposed the use of ephedrine instead of adrenaline.\textsuperscript{27,64,66,67} Ephedrine is a direct-acting adrenergic agonist but also a weak indirect-acting sympatheticomimetic agent ($\alpha$- and $\beta$-agonist, releasing nor-adrenaline from adrenergic nerve terminals) with a more prominent $\beta$-adrenergic activity. It produces vеноconstriction to a greater degree than arteriolar constriction causing redistribution of blood centrally, improving venous return (preload), cardiac output and uterine perfusion.\textsuperscript{139} However, it may be less effective than adrenaline as a vasopressor in severe anaphylactic shock.\textsuperscript{25} Furthermore, most observations of adrenaline effects on the uterine vasculature were obtained in absence of a vasoplastic haemodynamic state.

Fetal mortality and neurological sequelae associated with adrenaline treatment of maternal anaphylaxis have been reported.\textsuperscript{44,47,68–71} Conversely, in one case report a healthy baby was delivered after maternal haemodynamic stabilization with continuous infusion of adrenaline over 3.5 h.\textsuperscript{68} Another report described delivery of a vigorous baby after maternal cardiac arrest due to dextran with adrenaline 1.3 mg administered before delivery.\textsuperscript{81}

Although rarely used in parturients, $\beta$-blockers cause resistance to adrenaline and more benefit may be expected from glucagon (1–5 mg intravenously) whereas patients taking antidepressants and cocaine are more sensitive to the effects of adrenaline.\textsuperscript{136,137,140} Phenylephrine, a selective $\alpha$-adrenergic agonist, is increasingly recommended to treat hypotension in the parturient. Despite concerns about potential constrictive effects on the utero-placental circulation, doses up to 100 $\mu$g may not compromise fetal outcome because the increase in maternal blood pressure exceeds the increase in uterine vascular resistance. In cases of refractory hypotension or cardiac arrest unresponsive to adrenaline, alternative vasoactive drugs such as noradrenaline, vasoressin, metaraminol and methoxamine have been proposed.\textsuperscript{119,120,134,136} Arginine vasoressin (AVP) 1–2 U has been suggested to be the preferred drug for anaphylactic shock unresponsive to adrenaline whereas for cardiac arrest 40 U is recommended.\textsuperscript{136–138} Methylene blue, which interferes indirectly with nitric oxide-mediated relaxation of vasculature through activation of guanylyl cyclase, has been proposed as an alternative.\textsuperscript{86,136–138} Amrinone and milrinone (inotropic and vasodilator) and dobutamine (inotropic and chronotropic) may not affect uterine vascular resistance while being useful in low-output heart failure. However, little or no experience exists with these alternative vasoressors in the obstetric setting.

During management of an allergic reaction, vital signs including blood pressure, heart rate and arterial oxygenation must be carefully monitored. In addition, continuous fetal monitoring should also be applied. Urgent delivery must be considered in cases of fetal distress or maternal cardiac arrest, as delivery improves resuscitation attempts by relieving aortocaval compression. Whenever cardiac arrest occurs, continuous cardiopulmonary resuscitation is necessary to maintain sufficient oxygen delivery to the vital organs until the effects of the anaphylactic reaction are resolved.\textsuperscript{81,119} Transoesophageal echocardiography may be of additional help in diagnosis and treatment of anaphylactic cardiovascular collapse.

**Second-line therapy**

After initial therapy, administration of other drugs, such as histamine $H_1$-receptor antagonists (e.g. promethazine) which compete with histamine at the receptor sites, can be considered.\textsuperscript{1,141–144} Although, little evidence supports the use of histamine $H_2$-receptor antagonists, stimulation of the $H_2$- receptor may have some beneficial effects such as coronary vasodilation, stimulation of the myocardial contractility, bronchodilation and a negative feedback on histamine release.\textsuperscript{142,144} Although corticosteroids may decrease airway swelling,\textsuperscript{2} and prevent or shorten protracted reactions,\textsuperscript{119,137} there is a lack of strong evidence for their benefit in anaphylaxis because they require several hours to become fully effective.\textsuperscript{145} Bronchospasms can be the sole symptom of an allergic reaction. In such cases, intra-tracheal drug administration may be considered to reduce the direct effects of adrenaline upon the utero-placental perfusion. However, bronchospsasm may be resistant, necessitating inhalational bronchodilator therapy with $\beta_2$-agonists (e.g. salbutamol) and/or anticholinergics (e.g. ipratropium). When persistent, intravenous administration of salbutamol (5–25 $\mu$g/min) should be considered. Intravenous aminophylline could also be used but caution is indicated since its vasodilating effects may worsen existing hypotension and pulmonary shunting.\textsuperscript{119,134,136}

**Diagnostic investigations**

A detailed clinical history is mandatory, including previous anaesthetic experience, known allergies, concurrent morbidity, all drugs used before the suspected allergic reaction, and the nature, severity and timing of symptoms.

**Intraoperative testing**

These tests can determine whether an immunologic mechanism is involved. Plasma concentration of histamine is maximal immediately after the reaction. This is not always evident as resuscitation has priority and because of a short half-life and accelerated degradation in the parturient, a high rate of false negatives is likely.\textsuperscript{31}
Mast cell tryptase is a neutral serine protease 99% located within mast cells. A serum tryptase level >25 μg/L is highly indicative of mast cell degranulation. Peak plasma concentration is seen within 30–60 min of the onset of the reaction. Because of its longer half-life (90–120 min), levels remain elevated for several hours and decrease gradually over time. The recommended time points to measure tryptase are: immediately after resuscitation, at 1–2 h and at 24 h or any time after this. An elevated serum tryptase supports the diagnosis of an allergic reaction (positive predictive value of 92.6%) whereas a normal serum tryptase level does not exclude a possible allergic reaction (negative predictive value of 54.3%). However, it does not differentiate between an IgE-mediated reaction and mast cell activation from other causes.

Postoperative testing
Delayed tests are intended to determine the substance responsible for the reaction. Skin testing is usually delayed for 4–6 weeks because until then mediator stocks are still lower than normal with an increased likelihood of a false negative test. Similarly, drugs that could modify the skin response, such as antihistamines, angiotensin-converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, neuroleptics and vasoconstrictors, have to be avoided. Skin tests are performed using the undiluted drug introduced in the epidermis by prick- ing the patient’s skin through a drop of the drug being tested. Saline (negative control) and histamine (positive control) should be tested to determine whether the skin is apt to release histamine. Intradermal testing is performed by injecting 0.01–0.02 mL of the diluted drug on the volar surface of the forearm. When a reaction is present, the size of wheel and flare formation should become more pronounced when progressively decreasing the dilution.

Because of cross-reactivity between NMBDs, all available agents should be tested, also allowing identification of possible safe alternatives for future anaesthetic. Testing local anaesthetics ends with a subcutaneous ‘challenge’ of 0.5–2 mL. A basophil activation test requires incubation of the patient’s serum with a potential allergen. Mediators released can be measured as an indicator of basophil degranulation. Other assays detect changes to molecules present on the basophil surface using flow cytometry as an indicator of activation. Despite a high specificity, its sensitivity is poor and diagnostic value limited.

Specific IgE antibodies are the most conclusive test. Radioimmunoassay: Radio-Allergo-Sorbent-Test (RAST) has been designed to identify and quantify the presence of specific IgE antibodies in a patient’s serum. Currently, non-radioactive and more automated methods (colorimetric or enzymatic reactive tests) are used. The availability of specific IgE antibody tests is restricted to succinylcholine, rocuronium, latex, chlor hexidine, antibiotics, thiopental, morphine and propofol. This test is usually performed several weeks after the reaction but, if urgent, it can be performed sooner.

A provocation or challenge test is the ultimate way to detect immune and non-immune-mediated drug reactions. However, its use is limited because of the possible risk of a life-threatening reaction. When indicated, it should only be performed by an experienced personnel when monitoring and resuscitation are available.

Conclusion
As the likelihood of a parturient developing an allergic event is very low, so may be the level of clinical suspicion. The most incriminated agents are latex, antibiotics, uterotonics and colloids. Treatment consists of instant interruption of contact with suspected trigger, 100% oxygen, airway support including intubation, volume expansion, and vasopressors where necessary. As opposed to non-obstetric conditions during which the surgical procedure is usually interrupted, it is commonly recommended to proceed to urgent delivery. When dealing with allergic reactions in pregnancy, the mother is the primary focus of care.

References
8. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. The diagnosis and management of anaphylaxis: an updated practice parameter. J Allergy Clin Immunol 2005;115:S483–523.


