



ELSEVIER

www.obstetanaesthesia.com

REVIEW ARTICLE

Allergic reactions during labour analgesia and caesarean section anaesthesia

I. Adriaensens,^a M. Vercauteren,^a F. Soetens,^b L. Janssen,^c J. Leysen,^d D. Ebo^d

^a Department of Anaesthesia, Antwerp University Hospital, Antwerp, Belgium

^b Department of Anaesthesia, AZ Turnhout, Turnhout, Belgium

^c Department of Anaesthesia, St Dimpna Hospital, Geel, Belgium

^d 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.

© 2013 Elsevier Ltd. All rights reserved.

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

Introduction

Anaphylactic reactions during anaesthesia are rare in the general population.¹ 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,^{2–4} 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.^{5,6} Recently, the estimated annual incidence of allergic

reactions during anaesthesia in France was reported to be 100.6 per million procedures (1:9940).⁴ In contrast, a retrospective study at a large United States centre reported approximately one referral per 34000 anaesthetics.⁷ Associated mortality rates range from 3.4% to as high as 6%.^{1,8} A significant female predominance has been observed, independent of the causal agent.^{3,4,9}

An IgE-mediated reaction is involved in approximately 50–70% of cases.^{4,7} 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%).^{3,4} 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%.^{7,10} 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.^{11–13} In addition, exposure to certain drugs, such as pholcodine in Norway, may pre-sensitize patients for cross-reactivity to NMBDs.¹⁴

Stephens analyzed intensive care unit (ICU) admissions from an obstetric hospital.¹⁵ Of 24161 anaesthetics in 10 years, five cases involved an allergic reaction. As

Accepted April 2013

Correspondence to: Marcel Vercauteren, Department of Anaesthesia, Antwerp University Hospital, Wilrijkstraat 10, 2650 Edegem, Belgium.
 E-mail address: marcel.vercauteren@uza.be

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.¹⁶ Similarly, Mulla et al.¹⁷ 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%.¹⁷ Draisci et al, however, reported an incidence as high as 1:310 of latex anaphylactic reactions in caesarean section patients.¹⁸

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.^{19,20} 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.^{1,2}

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.²¹ Oestrogen and progesterone concentrations are greatly increased during pregnancy and are considered immunomodulating hormones.²¹ 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;²¹ however, it is unclear if they predispose the parturient to anaphylaxis or affect its severity.²²

The placenta plays a role in protecting the fetus against maternal anaphylactic reactions, as it prevents the passage of high-molecular-weight IgE antibodies.²³ 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.^{24–27} After anaphylactic shock at 27 weeks of gestation, multicystic bilateral encephalomalacia of both hemispheres and atrophy of the corpus callosum have been reported.²⁸ Sleth et al.²⁹ 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.³⁰ 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.² In 90% of cases, symptoms appear within minutes of administration of the triggering substance.^{1,31} 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.³¹ The most common clinical features are cardiovascular symptoms (73.6%), cutaneous reactions (69.6%) and bronchospasm (44.2%).^{1,2,30,31} 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.³¹

Clinical manifestations appear more severe in patients with true IgE-mediated anaphylaxis in comparison with those suffering what was previously called an

Table 1 Clinical manifestations of a suspected anaphylactic reaction

	Symptom	Sign	Specific sign during labour or anaesthesia
Cutaneous	Pruritus	Piloerection	
	skin	Rash, erythema, flushing	
	vulva	Urticaria	
	vagina	Peri-orbital or peri-oral oedema	
Respiratory	Hoarseness	Stridor (laryngeal oedema)	Difficult ventilation
	Dysphonia	Wheezing (bronchospasm)	↑ Peak airway pressure
	Dyspnoea	Pulmonary oedema	↓ SpO ₂
		Cyanosis	↑ EtCO ₂
Cardiovascular	Angina	Tachycardia	↓ EtCO ₂
	Light-headedness	Hypotension, cardiac arrest	↑ Haematocrit
	Faintness	Dysrhythmias	
		Fetal heart rate changes	
Abdominal	Nausea	Vomiting	
	Abdominal pain	Diarrhoea	
	Uterine cramps	Preterm labour	Fetal asphyxia

SpO₂: arterial haemoglobin oxygen saturation; EtCO₂: end-tidal carbon dioxide concentration.

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%).^{3,9}

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.³² During obstetric anaesthesia, other conditions may mimic an allergic reaction. Cardio-respiratory 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.³³ 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 neuraxial 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.³⁴ 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.^{35–37} 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.^{37,38} Not surprisingly, AFE has been called the ‘anaphylactoid syndrome of pregnancy’.^{39,40} 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.³⁴ 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-in-

duced 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.⁴⁴ 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,⁷⁴ 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

sometimes used in cases of suspected penicillin allergy, carries a low risk of anaphylactic reactions, but is a potent histamine-releasing drug that can cause severe hypotension and flushing.⁷⁵ However, to date there are no reports of allergic reactions to vancomycin use in obstetrics.

All reported allergic reactions occurred within minutes of administration of the antibiotic. All but two presented with cardiovascular signs ranging from mild hypotension to severe cardiovascular shock with or without accompanying cutaneous and/or respiratory symptoms. All responded well to treatment with favourable maternal outcome. Nevertheless, in half the cases fetal outcome was poor with neurological damage and in two cases intrauterine fetal demise. Although poor fetal outcome might be correlated with cardiovascular collapse seen in antibiotic-triggered allergic reactions, another explanation may be that antibiotics are not infrequently administered when the anaesthetist or resuscitation team are not present.

Colloids

Maternal hypotension is common following spinal anaesthesia for caesarean section.⁷⁶ Colloids are frequently used as prophylaxis or treatment since they have been found to be more effective than crystalloids.^{77,78} Dextran, 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.⁷⁹ 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 1:821.⁸⁰ 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.^{79,81} Because of several reports of severe fetal distress and at least one neonatal death,^{79–83} 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%).⁸⁴ Seven obstetric cases were published several decades ago with a further report in 2009.^{85,86} HES

solutions are associated with the lowest allergic risk (0.006–0.058%).⁸⁴ An anaphylactic reaction to HES during caesarean section has been reported in a patient with haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.⁸⁷

Uterotonics

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:^{88–95} none proved to be IgE-mediated. Allergic reactions to carbeto-cin have not been reported. One case of hypersensitivity to methylergometrine has been reported although simultaneous administration of oxytocin might also have been involved.⁹³ Another report described collapse in a patient with Raynaud's disease, which was suggested to be caused by hypersensitivity to ergometrine.⁹⁶

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.⁹⁷ A recent UK survey found a much lower rate of <1%.⁹⁸ Ester local anaesthetics are more likely to provoke IgE-mediated anaphylaxis because of the metabolite para-aminobenzoic acid which is a documented allergen.³¹ In addition, preservatives, such as methylparaben and metabisulphite, can also produce an allergic response.⁹⁸ Amide local anaesthetics have been reported to be involved in 0.33–0.6% of all perioperative allergic reactions.^{3,4} Only three obstetric cases have been reported with proven allergy for amide local anaesthetics.^{99–101} Diphenhydramine was suggested as an alternative agent for episiotomy repair in a case of local anaesthetic hypersensitivity.¹⁰¹ Cross-reactivity to both ropivacaine and levobupivacaine has also been reported.¹⁰²

When a parturient has a history of suspected hypersensitivity to local anaesthetics, appropriate testing is mandatory.^{98,103} Intradermal skin testing for local anaesthetics is associated with frequent false positive reactions in 8–15% and therefore not reliable.¹⁰⁴ 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.^{103,104} 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.¹⁰⁴

Neuromuscular blocking drugs

Many reports have shown NMBDs to be the leading cause of perioperative allergic reactions, responsible for >50% of all cases.^{1–4,31} 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.^{29,105–108} 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.¹⁰⁹ Furthermore, hypersensitivity to sugammadex has been reported.^{110–112}

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 benzyloquinolones d-tubocurarine, atracurium and mivacurium.³¹ 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.^{3,4,9,31}

Cross-reactivity among NMBDs is frequent, ranging from 60% to 70%.^{1,3,31} It is common among the groups of steroidal or benzyloquinolines 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.^{31,107}

Histamine H₂-receptor antagonists

Allergic reactions associated with histamine H₂-receptor antagonists in obstetric patients have been related to ranitidine only:^{113–116} 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.^{117,118} 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.^{119,120}

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.¹²¹ True allergic reactions to opioids are rare and mostly seen with 'natural' compounds such as morphine,

whereas reactions to (semi-) synthetic compounds are rare.¹²¹ Fentanyl hypersensitivity after epidural use for caesarean section has been reported.¹²²

General anaesthetic induction agents

An anaphylactic reaction with cardiac arrest has been reported during caesarean section anaesthesia induced with propanidid.²³ 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.¹²³

Chlorhexidine

Several topical preparations for skin or mucosal disinfection and lubrication gels for urologic and gynaecologic procedures contain chlorhexidine.^{124,125} It is also present in soaps, cosmetics, toothpaste and mouthwash which may cause sensitization of the general population. Hypersensitivity reactions range from contact dermatitis to generalised urticaria and life-threatening anaphylaxis.¹²⁴ 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.^{47,125}

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, phyto-menadione and insect stings.^{28,126–133}

Management and specific considerations for the parturient

Management should be tailored to the severity and combination of clinical features in each patient,¹³⁴ and is similar to the approach in the general population with some additional considerations (Table 2)^{22,135}. 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.^{2,136} 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.^{2,134} When there is no obvious causative agent, colloids, latex, chlorhexidine, antibiotics and blood products should be removed.^{134,137} Discontinuation of anaesthesia, if possible, avoids additional cardiovascular depression.¹ When bronchospasm is the sole symptom, volatile anaesthetics can be

Table 2 Management of a suspected anaphylactic reaction

Initial management

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

Second-line therapy

1. Histamine H₁-receptor antagonist (intramuscular promethazine 50 mg or intravenous 25 mg)
2. Histamine H₂-receptor antagonist (intravenous ranitidine 50 mg)
3. Vasopressor infusion (noradrenaline 1–4 µg/min starting dose)
4. Nebulized bronchodilator (salbutamol, fenoterol, ipratropium)
5. Corticosteroids: (intravenous hydrocortisone 5 mg/kg)
6. Others: tranexamic acid, glucagon, aminophylline

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.^{1,134,136,138} If airway patency is compromised, which is signified by hoarseness, lingual oedema, stridor or oropharyngeal swelling,¹²⁰ tracheal intubation should be performed without delay and preferably by the most experienced person available.

Fluid resuscitation is of paramount importance to compensate for the large fluid shifts resulting from vasodilation and increased capillary permeability.^{1,136–138} Volume expansion of 2–4 L may be needed.^{1,2} There is no evidence supporting the use of colloids over crystalloids in this setting,^{1,119} and colloids may also trigger an allergic reaction.⁸⁴ 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.²

Adrenaline is the cornerstone of treatment of anaphylactic reactions.^{1,2,119,134–138} 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.^{119,120} 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.¹¹⁹ 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.^{136–138} 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.¹³⁶ In cases of cardiac arrest, cardiopulmonary resuscitation and high doses of adrenaline (1 mg every 2 min) are required.^{119,120} 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.¹³⁷

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.^{22,135} Concerns regarding the use of adrenaline have been raised because of its potential to reduce

uterine blood flow through α -adrenergic-mediated vasoconstriction in the placenta, which may worsen fetal distress.^{24,25,51} Indeed, small doses of 10–20 μ 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.^{27,64,66,67} Ephedrine is a direct-acting adrenergic agonist but also a weak indirect-acting sympathomimetic agent (α - and β -agonist, releasing noradrenaline from adrenergic nerve terminals) with a more prominent β -adrenergic activity. It produces venoconstriction to a greater degree than arteriolar constriction causing redistribution of blood centrally, improving venous return (preload), cardiac output and uterine perfusion.¹³⁹ However, it may be less effective than adrenaline as a vasopressor in severe anaphylactic shock.²⁵ Furthermore, most observations of adrenaline effects on the uterine vasculature were obtained in absence of a vasoplegic haemodynamic state.

Fetal mortality and neurological sequelae associated with adrenaline treatment of maternal anaphylaxis have been reported.^{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.⁶⁸ Another report described delivery of a vigorous baby after maternal cardiac arrest due to dextran with adrenaline 1.3 mg administered before delivery.⁸¹

Although rarely used in parturients, β -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.^{136,137,140} Phenylephrine, a selective α -adrenergic agonist, is increasingly recommended to treat hypotension in the parturient. Despite concerns about potential constrictive effects on the uteroplacental circulation, doses up to 100 μ 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, vasopressin, metaraminol and methoxamine have been proposed.^{119,120,134,136} Arginine vasopressin (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.^{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.^{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 vasopressors 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.^{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.^{1,141–144} Although, little evidence supports the use of histamine H_2 -receptor antagonists,¹¹⁹ 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.^{142,144} Although corticosteroids may decrease airway swelling,² and prevent or shorten protracted reactions,^{119,137} there is a lack of strong evidence for their benefit in anaphylaxis because they require several hours to become fully effective.¹⁴⁵ Bronchospasm 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 uteroplacental perfusion. However, bronchospasm may be resistant, necessitating inhalational bronchodilator therapy with β_2 -agonists (e.g. salbutamol) and/or anticholinergics (e.g. ipratropium). When persistent, intravenous administration of salbutamol (5–25 μ 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.^{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.³¹

Mast cell tryptase is a neutral serine protease 99% located within mast cells. A serum tryptase level $>25 \mu\text{g/L}$ is highly indicative of mast cell degranulation.^{134,146} 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.^{2,134,146} The recommended time points to measure tryptase are: immediately after resuscitation, at 1–2 h and at 24 h or any time after this.¹⁴⁷ 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%).⁹ However, it does not differentiate between an IgE-mediated reaction and mast cell activation from other causes.¹⁴⁶

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.¹⁴⁸ Skin tests are performed using the undiluted drug introduced in the epidermis by pricking 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.³¹ Intradermal testing is performed by injecting 0.01–0.02 mL of the diluted drug on the volar surface of the forearm.¹⁴⁸ 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,^{31,143} all available agents should be tested, also allowing identification of possible safe alternatives for future anaesthetics. 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.¹⁴⁷ Other assays detect changes to molecules present on the basophil surface using flow cytometry as an indicator of activation.¹⁴⁹ 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, chlorhexidine, 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.¹⁴⁷ 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

1. Levy J. The allergic response. In: Barash P, Cullen B, Stoelting R, editors. *Clinical anesthesia*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 1298–312.
2. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003;**97**:1381–95.
3. Mertes PM, Laxenaire MC; GERAP. Anaphylactic and anaphylactoid reactions occurring during anaesthesia in France. Seventh epidemiologic survey (January 2001–December 2002). *Ann Fr Anesth Reanim* 2004;**23**:1133–43.
4. Mertes PM, Alla F, Tréchet P, Auroy Y, Jouglu E. Groupe d'études des réactions anaphylactoides perianesthésiques. Anaphylaxis during anaesthesia in France: an 8-year national survey. *J Allergy Clin Immunol* 2011;**128**:366–73.
5. Fisher MM, Baldo BA. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. *Ann Fr Anesth Reanim* 1993;**12**:97–104.
6. Fasting S, Gisvold SE. Serious intraoperative problems – a five-year review of 83,844 anesthetics. *Can J Anaesth* 2002;**49**:545–53.
7. Gurrieri C, Weingarten TN, Martin DP, et al. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg* 2011;**113**:1202–12.
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.
9. Mertes PM, Laxenaire MC, Alla F. Anaphylactic and anaphylactoid reactions occurring during anesthesia in France in 1999–2000. *Anesthesiology* 2003;**99**:536–45.
10. Harboe T, Guttormsen AB, Irgens A, Dybendal T, Florvaag E. Anaphylaxis during anesthesia in Norway: a 6-year single-center follow-up study. *Anesthesiology* 2005;**102**:897–903.

11. Levy JH, Castells MC. Perioperative anaphylaxis and the United States perspective. *Anesth Analg* 2011;**113**:979–81.
12. Levy JH, Gottge M, Szlam F, Zaffer R, McCall C. Weal and flare responses to intradermal rocuronium and cisatracurium in humans. *Br J Anaesth* 2000;**85**:844–9.
13. Dhonneur G, Combes X, Chassard D, Merle JC. Skin sensitivity to rocuronium and vecuronium: a randomized controlled prick-testing study in healthy volunteers. *Anesth Analg* 2004;**98**:986–9.
14. Johansson SG, Florvaag E, Oman H, et al. National pholcodine consumption and prevalence of IgE-sensitization: a multicenter study. *Allergy* 2010;**65**:498–502.
15. Stephens ID. ICU admissions from an obstetrical hospital. *Can J Anaesth* 1991;**38**:677–81.
16. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mothers' Lives: Reviewing maternal deaths to make motherhood safer – 2003–2005. In: *The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom*. London: CEMACH; 2007.
17. Mulla ZD, Ebrahim MS, Gonzales JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. *Ann Allergy Asthma Immunol* 2010;**104**:55–9.
18. Draisci G, Nucera E, Pollastrini E, et al. Anaphylactic reactions during cesarean section. *Int J Obstet Anesth* 2007;**16**:63–7.
19. Johansson SG, Hourihane JO, Bousquet J, et al. A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;**56**:813–24.
20. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol* 2005;**115**:584–91.
21. Zen M, Ghirardello A, Laccarino L, et al. Hormones, immune response and pregnancy in healthy woman and SLE patients. *Swiss Med Wkly* 2010;**140**:187–201.
22. Heinly TL, Lieberman P. Anaphylaxis in pregnancy. *Immunol Allergy Clin North Am* 2000;**20**:831–8.
23. Baraka A, Sfeir S. Anaphylactic cardiac arrest in a parturient. Response of the newborn. *JAMA* 1980;**243**:1745–6.
24. Khan R, Anastasakis E, Kadir RA. Anaphylactic reaction to ceftriaxone in labour. An emerging complication. *J Obstet Gynaecol* 2008;**28**:751–3.
25. Chaudhuri K, Gonzales J, Jesurun CA, Ambat MT, Mandal-Chaudhuri S. Anaphylactic shock in pregnancy: a case study and review of the literature. *Int J Obstet Anesth* 2008;**17**:350–7.
26. Berardi A, Rossi K, Cavalleri F, et al. Maternal anaphylaxis and fetal brain damage after intrapartum chemoprophylaxis. *J Perinat Med* 2004;**32**:375–7.
27. Berthier A, Sentilhes L, Hamou L, Renoult-Litzler D, Marret S, Marpeau L. Antibiotics at term. Questions about five severe allergic accidents. *Gynecol Obstet Fertil* 2007;**35**:464–72.
28. Luciano R, Zuppa AA, Maragliano G, Gallini F, Tortorolo G. Fetal encephalopathy after maternal anaphylaxis. *Biol Neonate* 1997;**71**:190–3.
29. Sleth JC, Lafforgue E, Cherici O, Nagy P. Anaphylaxis in terminal pregnancy: two case studies and review of the literature. *Ann Fr Anesth Reanim* 2009;**28**:790–4.
30. Fisher M, Baldo B. Persistence of allergy to anaesthetic drugs. *Anaesth Intensive Care* 1992;**20**:143–6.
31. Mertes PM, Lambert M, Gueant-Rodriguez RM, et al. Perioperative anaphylaxis. *Immunol Allergy Clin North Am* 2009;**29**:429–51.
32. Jacobsen J, Lindekaer AL, Ostergaard HT, et al. Management of anaphylactic shock evaluated using a full-scale anaesthesia simulator. *Acta Anaesthesiol Scand* 2001;**45**:315–9.
33. Boutonnet M, Faitot V, Katz A, Salomon L, Keita H. Mallampati class changes during pregnancy, labour, and after delivery: can these be predicted? *Br J Anaesth* 2010;**104**:67–70.
34. Harboe T, Benson MD, Or H, Softeland E, Bjorge L, Guttormsen AB. Cardiopulmonary distress during obstetrical anaesthesia: attempts to diagnose amniotic fluid embolism in a case series of suspected allergic anaphylaxis. *Acta Anaesth Scand* 2006;**50**:324–30.
35. Farrar SC, Gherman RB. Serum tryptase analysis in a woman with amniotic fluid embolism. A case report. *J Reprod Med* 2001;**46**:926–8.
36. Nishio H, Matsui K, Miyazaki T, Tamura A, Iwata M, Suzuki K. A fatal case of amniotic fluid embolism with elevation of serum mast cell tryptase. *Forensic Sci Int* 2002;**126**:53–6.
37. Benson MD, Kobayashi H, Silver RK, Oi H, Greenberger PA, Terao T. Immunologic studies in presumed amniotic fluid embolism. *Obstet Gynecol* 2001;**97**:510–4.
38. Fineschi V, Gambassi R, Gherardi M, Turillazzi E. The diagnosis of amniotic fluid embolism: an immunohistochemical study for the quantification of pulmonary mast cell tryptase. *Int J Legal Med* 1998;**111**:238–43.
39. Kretzschmar M, Zahm D-M, Remmler K, Pfeiffer L, Victor L, Schirrmeyer W. Pathophysiological and therapeutic aspects of amniotic fluid embolism (anaphylactoid syndrome of pregnancy): case report with lethal outcome and overview. *Anaesthesist* 2003;**52**:419–26.
40. Gilmore DA, Wakim J, Secrest J, Rawson R. Anaphylactoid syndrome of pregnancy: a review of the literature with latest management and outcome data. *AANA J* 2003;**71**:120–6.
41. Draisci GD, Zanfini BA, Nucera E, et al. Latex sensitization. A special risk for the obstetric population? *Anesthesiology* 2011;**114**:565–9.
42. Jorrot JC, Mercier F, Pecquet C, Jacquinet P, Conseiller C. Perioperative anaphylactic shock to latex gloves. *Ann Fr Anesth Reanim* 1989;**8**:278–9.
43. Obenhaus T. Intraoperative anaphylaxis to latex in pregnancy. *Anesthesist* 1995;**44**:119–22.
44. Stewart PD, Bogod D. Latex anaphylaxis during late pregnancy. *Int J Obstet Anesth* 1995;**4**:48–50.
45. Deusch E, Reider N, Marth C. Anaphylactic reaction to latex during cesarean delivery. *Obstet Gynecol* 1996;**88**:727.
46. Péchinot M. Allergie au latex au décours d'une césarienne. *Ann Fr Anesth Reanim* 1997;**16**:79–80.
47. Porter BJ, Acharya U, Ormerod AD, Herriot R. Latex/chlorhexidine-induced anaphylaxis in pregnancy. *Allergy* 1998;**53**:455–7.
48. Santos R, Hernandez-Ayup S, Galache FG, Batiza VA, Montoya DII. Severe latex allergy after vaginal examination during labor: a case report. *Am J Obstet Gynecol* 1997;**177**:1543–4.
49. Takamatsu I, Karasawa F, Kamei M, et al. A case of emergency caesarean section as a result of anaphylaxis to latex. *Masui* 1999;**48**:83–5.
50. Nawa Y, Imaizumi H, Masuda Y, et al. A case of anaphylactic shock due to latex glove used on internal examination and on the probe of intrauterine echogram. *Masui* 2000;**49**:1027–9.
51. Eckhout GV, Aya S. Anaphylaxis due to airborne exposure to latex in a primigravida. *Anesthesiology* 2001;**95**:1034–5.
52. Shingai Y, Nakagawa K, Kato T, et al. Severe allergy in a pregnant woman after vaginal examination with a latex glove. *Gynecol Obstet Invest* 2002;**54**:183–4.
53. Gillis-Haegerstrand C, Lindblad U, Johansson SG, Rösblad PG. Latex caused two cases of anaphylactic shock during cesarean section. *Lakartidningen* 2007;**104**:1987–8.
54. Turillazzi E, Greco P, Neri M, Pomara C, Riezzo I, Fineschi V. Anaphylactic latex reaction during anaesthesia: the silent culprit in a fatal case. *Forensic Sci Int* 2008;**179**:e5–8.
55. Delaunay F, Blasco V. Latex induced anaphylactic shock during caesarean section: two cases from Guadeloupe. *Ann Fr Anesth Reanim* 2008;**27**:1023–5.
56. Kanamori R, Kamata K, Komatsu R, Ozaki M. Case of latex allergy manifested during cesarean section. *Masui* 2010;**59**:375–8.
57. Ikeda N, Oda Y, Tanaka K, Nakamura T, Asada A. A case of anaphylactic shock induced by latex during cesarean section. *Masui* 2010;**59**:1294–7.

58. Hepner DL, Castells MC. Latex allergy: an update. *Anesth Analg* 2003;**96**:1219–29.
59. Lieberman P. Anaphylactic reactions during surgical and medical procedures. *J Allergy Clin Immunol* 2002;**110**:S64–9.
60. Kam PC, Lee MS, Thompson JF. Latex allergy: an emerging clinical and occupational health problem. *Anaesthesia* 1997;**52**:570–5.
61. Dakin MJ, Yentis SM. Latex allergy: a strategy for management. *Anaesthesia* 1998;**53**:774–81.
62. Ogata J, Minami K. Synthetic oxytocin and latex allergy. *Br J Anaesth* 2007;**98**:845–6.
63. Bloomberg RJ. Cefotetan-induced anaphylaxis. *Am J Obstet Gynecol* 1988;**159**:125–6.
64. Gallagher JS. Anaphylaxis in pregnancy. *Obstet Gynecol* 1988;**71**:491–3.
65. Heim K, Alge A, Marth C. Anaphylactic reaction to ampicillin and severe complication in the fetus. *Lancet* 1991;**337**:859–60.
66. Konno R, Nagase S. Anaphylactic reaction to cefazolin during pregnancy. *J Obstet Gynaecol* 1995;**21**:577–9.
67. Dunn AB, Blomquist J, Khouzami V. Anaphylaxis in labor secondary to prophylaxis against group B Streptococcus. A case report. *J Reprod Med* 1999;**44**:381–4.
68. Gei AF, Pacheco LD, Vanhook JW, Hankins GDV. The use of continuous infusion of epinephrine for anaphylactic shock during labor. *Obstet Gynecol* 2003;**102**:1332–5.
69. Jao MS, Cheng PJ, Shaw SW, Soong YK. Anaphylaxis to cefazolin during labor secondary to prophylaxis for group B Streptococcus: a case report. *J Reprod Med* 2006;**51**:655–8.
70. Sheikh J. Intrapartum anaphylaxis to penicillin in a woman with rheumatoid arthritis who had no prior penicillin allergy. *Ann Allergy Asthma Immunol* 2007;**99**:287–9.
71. Sengupta A, Kohli JK. Antibiotic prophylaxis in cesarean section causing anaphylaxis and intrauterine fetal death. *J Obstet Gynaecol Res* 2008;**34**:252–4.
72. Verani JR, McGee L, Schrag SJ. Prevention of perinatal group B streptococcal disease. Revised guidelines from CDC. *MMWR Recomm Rep* 2010;**59**:1–36.
73. Smail FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane Database Syst Rev* 2010;**1**:CD007482.
74. Lamont RF, Sobel J, Kusanovic JP, et al. Current debate on the use of antibiotic prophylaxis for cesarean section. *BJOG* 2011;**118**:193–201.
75. Veien M, Sziam F, Holden J, Yamaguchi K, Denson D, Levy J. Mechanisms of nonimmunological histamine and tryptase release from human cutaneous mast cells. *Anesthesiology* 2000;**92**:1074–81.
76. Rout CC, Rocke DA, Levin J, Gouws E, Reddy D. A reevaluation of the role of crystalloid preload in the prevention of hypotension associated with spinal anesthesia for elective cesarean section. *Anesthesiology* 1993;**79**:262–9.
77. Cyna AM, Andrew M, Emmett RS, Middleton P, Simmons SW. Techniques for preventing hypotension during spinal anaesthesia for caesarean section. *Cochrane Database Syst Rev* 2006;**4**:CD002251.
78. Dahlgren G, Granath F, Pregner K, Rosblad PG, Wessel H, Irestedt L. Colloid vs. crystalloid preloading to prevent maternal hypotension during spinal anesthesia for elective cesarean section. *Acta Anaesthesiol Scand* 2005;**49**:1200–6.
79. Berg EM, Fasting S, Sellevold OFM. Serious complications with dextran-70 despite hapten prophylaxis. Is it best avoided prior to delivery? *Anaesthesia* 1991;**46**:1033–5.
80. Paull J. A prospective study of dextran-induced anaphylactoid reactions in 5745 patients. *Anaesth Intensive Care* 1987;**15**:163–7.
81. Vatsgar TT, Ingebrigtsen O, Fjose LO, Wikstrom B, Nilsen JE, Wik L. Cardiac arrest and resuscitation with an automatic mechanical chest compression device (LUCAS) due to anaphylaxis of a woman receiving caesarean section because of pre-eclampsia. *Resuscitation* 2006;**68**:155–9.
82. Fanous LH, Gray A, Felmingham J. Severe anaphylactoid reactions to dextran 70. *Br Med J* 1977;**2**:1189–90.
83. Barbier P, Jonville AP, Autret E, Coureau C. Fetal risks with dextrans during delivery. *Drug Saf* 1992;**7**:71–3.
84. Laxenaire MC, Charpentier C, Feldman L. Anaphylactoid reactions to colloid plasma substitutes: incidence, risk factors, mechanisms. A French multicenter prospective study. *Ann Fr Anesth Reanim* 1994;**13**:301–10.
85. Lund N. Anaphylactoid reaction to infusion of polygelatin (Haemacel). A study in pregnant women. *Anaesthesia* 1980;**35**:655–9.
86. Karri K, Raghavan R, Shahid J. Severe anaphylaxis to volplex, a colloid during cesarean section: a case report and review. *Obstet Gynecol Int* 2009;**2009**:374791.
87. Vercauteren MP, Coppejans HC, Sermeus L. Anaphylactoid reaction to hydroxyethylstarch during cesarean delivery in a patient with HELLP syndrome. *Anesth Analg* 2003;**96**:859–61.
88. Slater RM, Bowles BJM, Pumphrey RSH. Anaphylactoid reaction to oxytocin in pregnancy. *Anaesthesia* 1985;**40**:655–6.
89. Kawarabayashi T, Narisawa Y, Nakamura K, Sugimori H, Oda Y, Taniguchi Y. Anaphylactoid reaction to oxytocin during cesarean section. *Gynecol Obstet Invest* 1988;**25**:277–9.
90. Pradines B, Rakotonarivo J, Bergis A, Jaulin L. Perianaesthetic iterative allergic accident; apropos of a case involving oxytocin. *Agressologie* 1989;**30**:297–300.
91. Maycock EJ, Russell WC. Anaphylactoid reaction to Syntocinon. *Anaesth Intensive Care* 1993;**21**:211–2.
92. Morris WW, Lavies NG, Anderson SK, Southgate HJ. Acute respiratory distress during caesarean section under spinal anaesthesia. A probable case of anaphylactoid reaction to Syntocinon. *Anaesthesia* 1994;**49**:41–3.
93. Shimo T, Nishiike S, Masuoka M, Seki S, Tsuchida H. Intraoperative anaphylactic shock induced by methylergometrine and oxytocin. *Masui* 2006;**55**:447–50.
94. Lin MC, Hsieh TK, Liu CA, et al. Anaphylactoid shock induced by oxytocin administration – a case report. *Acta Anaesthesiol Taiwan* 2007;**45**:233–6.
95. Pant D, Vohra VK, Pandey SS, Sood J. Pulseless electrical activity during caesarean delivery under spinal anaesthesia: a case report of severe anaphylactic reaction to Syntocinon. *Int J Obstet Anesth* 2009;**18**:85–8.
96. Valentine BH, Martin MA, Phillips NV. Collapse during operation following i.v. ergometrine. A case report. *Br J Anaesth* 1977;**49**:81–2.
97. Fisher MM, Bowey CJ. Alleged allergy to local anaesthetics. *Anaesth Intensive Care* 1997;**25**:611–4.
98. Bhole MV, Manson AL, Seneviratne SL, Misbah SA. IgE-mediated allergy to local anaesthetics: separating fact from perception: a UK perspective. *Br J Anaesth* 2012;**108**:903–11.
99. Erkkola R, Kanto J, Maenpaa J, Kero P, Hovi-Viander M, Viander M. Allergic reaction to an amide local anesthetic in segmental epidural analgesia. *Acta Obstet Gynecol Scand* 1988;**67**:181–4.
100. Thomas AD, Caunt JA. Anaphylactoid reaction following local anaesthesia for epidural block. *Anaesthesia* 1993;**48**:50–2.
101. Horikawa Y, Mitsuhata H, Saito J, Kawakami T, Hiruta M, Seo N. Diphenhydramine is useful in a parturient with hypersensitivity to local anesthetics to manage her delivery. *Masui* 2002;**51**:493–7.
102. Calderon AL, Diot N, Benatir F, et al. Immediate allergic cross-reactivity to levobupivacaine and ropivacaine. *Anaesthesia* 2013;**68**:203–5.
103. Browne IM, Birnbach DJ. A pregnant woman with previous anaphylactic reaction to local anesthetics: a case report. *Am J Obstet Gynecol* 2001;**185**:1253–4.

104. Balestrieri PJ, Ferguson JE. Management of a parturient with a history of local anesthetic allergy. *Anesth Analg* 2003;**96**:1489–90.
105. Matthews MD, Ceglarski JZ, Pabari M. Anaphylaxis to suxamethonium – a case report. *Anaesth Intensive Care* 1977;**5**:235–8.
106. Skogvoll E, Hoel TM, Smith-Erichsen N, Melsom R. Anaphylactic shock caused by suxamethonium (Curacit). *Tidsskr Nor Lægeforen* 1989;**109**:3323–5.
107. Guttormsen AB, Husby P, Elsayed S. Anaphylactic shock during elective cesarean section. Sensitizing mechanisms and follow-up. *Tidsskr Nor Lægeforen* 1989;**109**:3321–3.
108. Stannard L, Bellis A. Maternal anaphylactic reaction to a general anaesthetic at emergency caesarean section for fetal bradycardia. *BJOG* 2001;**108**:539–40.
109. Clarke RC, Sadleir PH, Platt PR. The role of sugammadex in the development and modification of an allergic response to rocuronium: evidence from a cutaneous model. *Anaesthesia* 2012;**67**:266–73.
110. Peeters PA, van den Heuvel MW, van Heumen E, et al. Safety, tolerability and pharmacokinetics of sugammadex using single high doses (up to 96 mg/kg) in healthy adult subjects: a randomized, double-blind, crossover, placebo-controlled, single-centre study. *Clin Drug Investig* 2010;**30**:867–74.
111. Menendez-Ozcoidi L, Ortiz-Gomez JR, Olaguibel-Ribero JM, Salvador-Bravo MJ. Allergy to low dose sugammadex. *Anaesthesia* 2011;**66**:217–9.
112. Godai K, Hasegawa-Moriyama M, Kuniyoshi T, et al. Three cases of suspected sugammadex-induced hypersensitivity reactions. *Br J Anaesth* 2012;**109**:216–8.
113. Greer IA, Fellows K. Anaphylactoid reaction to ranitidine in labour. *Br J Clin Pract* 1990;**44**:78.
114. Barry JE, Madan R, Hewitt PB. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesthesia* 1992;**47**:360–1.
115. Powell JA, Maycock EJ. Anaphylactoid reaction to ranitidine in an obstetric patient. *Anaesth Intensive Care* 1993;**21**:702–3.
116. Kaneko K, Maruta H. Severe anaphylactoid reaction to ranitidine in a parturient with subsequent fetal distress. *J Anesth* 2003;**17**:199–200.
117. Son WJ, Kim MH, Lee SM, et al. Two cases of H2-receptor antagonist hypersensitivity and cross-reactivity. *Allergy Asthma Immunol Res* 2011;**3**:128–31.
118. Cho HJ, Yoo HS, Park SY, et al. A case of cimetidine-induced immediate hypersensitivity. *J Investig Allergol Clin Immunol* 2012;**22**:216–8.
119. Soar J, Perkins GD, Abbas G, et al. Section 8. Cardiac arrest in special circumstances. *Resuscitation* 2010;**81**:1400–33.
120. Vanden Hoek TL, Morrison LJ, Shuster M, et al. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Part 12: cardiac arrest in special situations. *Circulation* 2010;**122**:S829–861.
121. Blunk JA, Schmelz M, Zeck S, Skov P, Likar R, Koppert W. Opioid-induced mast cell activation and vascular responses is not mediated by opioid receptors: an in vivo microdialysis study in human skin. *Anesth Analg* 2004;**98**:364–70.
122. Zucker-Pinchoff B, Ramanathan S. Anaphylactic reaction to epidural fentanyl. *Anesthesiology* 1989;**71**:599–601.
123. Inal MT, Memis D, Vatan I, Cakier U, Yildiz B. Late-onset pulmonary edema due to propofol. *Acta Anaesthesiol Scand* 2008;**52**:1015–7.
124. Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetized patients – four cases of chlorhexidine allergy. *Acta Anaesthesiol Scand* 2001;**45**:1290–4.
125. Krauthaim AB, Jermann TH, Bircher AJ. Chlorhexidine anaphylaxis: case report and review of the literature. *Contact Dermatitis* 2004;**50**:113–6.
126. Hadar A, Holcberg G, Mazor M. Anaphylactic shock after diclofenac sodium (Voltaren). *Harefuah* 2000;**138**:211–2.
127. Cuciti C, Mayer DC, Arnette R, Spielman FJ. Anaphylactoid reaction to intravenous sodium ferric gluconate complex during pregnancy. *Int J Obstet Anesth* 2005;**14**:362–4.
128. Olivieri P, Berchet-Montaut MP, Thomas P. Analgésie obstétricale chez une femme allergique à l'oxyde d'éthylène. *Ann Fr Anesth Réanim* 1988;**7**:346–8.
129. Guharoy SR, Barajas M. Probable anaphylactic reaction to corn-derived dextrose solution. *Vet Hum Toxicol* 1991;**33**:609–10.
130. Soulat JM, Bouju P, Oxeda C, Amiot JF. Anaphylactoid shock due to metabisulfites during cesarean section under peridural anesthesia. *Cah Anesthesiol* 1991;**39**:257–9.
131. Anderson TH, Hindsholm KB, Follingborg J. Severe complication to phytomenadione after intramuscular injection in woman in labor. Case report and review of literature. *Acta Obstet Gynecol Scand* 1989;**68**:381–2.
132. Habek D, Cerkez-Habek J, Jalsovec D. Anaphylactic shock in response to wasp sting in pregnancy. *Zentralbl Gynakol* 2000;**122**:393–4.
133. Rizk DE, Mensah-Brown E, Lukic M. Placental abruption and intrauterine death following an ant sting. *Int J Gynaecol Obstet* 1998;**63**:71–2.
134. Harper NJN, Dixon T, Dugue P, et al. Suspected anaphylactic reactions associated with anaesthesia. *Anaesthesia* 2009;**64**:199–211.
135. Simons F, Schatz M. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012;**130**:597–606.
136. Mertes PM, Tajima K, Regnier-Kimmoun MA, et al. Perioperative anaphylaxis. *Med Clin North Am* 2010;**94**:761–89.
137. Norred CL. Anesthetic-induced anaphylaxis. *AANA J* 2012;**80**:129–40.
138. Levy JH, Adkinson NF. Anaphylaxis during cardiac surgery: implications for clinicians. *Anesth Analg* 2008;**106**:392–403.
139. Lawson NW, Johnson JO. Autonomic nervous system: physiology and pharmacology. In: Barash P, Cullen B, Stoelting R, editors. *Clinical anesthesia*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 275–333.
140. McLean-Tooke AP, Bethune CA, Fay AC, Spickett GP. Adrenaline in the treatment of anaphylaxis: what is the evidence? *BMJ* 2003;**327**:1332–5.
141. Hepner D, Castells M. Anaphylaxis during the perioperative period. *Anesth Analg* 2004;**97**:1381–95.
142. Levy J. Anaphylaxis: what is monitored to make a diagnosis? How is therapy monitored? *Anesthesiol Clin North America* 2001;**19**:705–15.
143. Mertes P, Laxenaire M. Allergic reactions occurring during anesthesia. *Eur J Anaesthesiol* 2002;**19**:240–62.
144. McKinnon R, Wildsmith J. Histaminoid reactions in anaesthesia. *Br J Anaesth* 1995;**74**:217–28.
145. Choo KJL, Simons FER, Sheikh A. Glucocorticoids for the treatment of anaphylaxis. *Cochrane Database Syst Rev* 2012;**4**:CD007596.
146. Ebo DG, Fisher MM, Hagendorens MM, Bridts CH, Stevens WJ. Anaphylaxis during anaesthesia: a diagnostic approach. *Allergy* 2007;**62**:471–87.
147. Nel L, Eren E. Peri-operative anaphylaxis. *Br J Clin Pharmacol* 2011;**71**:647–58.
148. Fisher M. Intradermal testing after anaphylactoid reaction to anaesthetic drugs: practical aspects of performance and interpretation. *Anaesth Intensive Care* 1984;**12**:115–20.
149. Leysen J, Bridts CH, De Clerck LS, et al. Allergy to rocuronium: from clinical suspicion to correct diagnosis. *Allergy* 2011;**66**:1014–9.