20 Obstetric anaesthesia

Nuala Lucas

Key findings

- Severe perioperative anaphylaxis in obstetric patients is rare. We identified eight obstetric cases in NAP6, all of which were Grade 3.
- The NAP6 Activity Survey estimated 233,886 obstetric anaesthetics per year in the UK, giving an incidence of severe perioperative obstetric anaphylaxis of 3.4 per 100,000. This is significantly lower than the incidence in non-obstetric adult cases.
- Hospital Episode Statistics data for 2015-16 indicate 648,107 deliveries. This equates to an incidence of perioperative anaphylaxis of 1.2 per 100,000 maternities.
- Hospital Episode Statistics data for 2015-16 showed that 259,243 women were delivered by caesarean section. This gives an incidence of perioperative anaphylaxis in obstetric patients as 3.1 per 100,000 caesarean sections.
- There were no obstetric cases of anaphylaxis caused by antibiotics and no cases related to latex.
- The majority of patients were awake at the time of the event. Complaints of 'feeling unwell' preceded onset of hypotension or other clinical signs.
- Recognition of a critical event was prompt, but recognition of anaphylaxis and the starting of anaphylaxis-specific treatment was slower than in non-obstetric cases. This probably illustrates the wide differential diagnosis of hypotension in the obstetric patient and that anaphylaxis is low in the diagnostic triage.
- A consultant anaesthetist was involved in the management of all the cases.
- A specific anaphylaxis pack was used to assist management in only two cases.
- Adrenaline was administered notably less than in non-obstetric cases and phenylephrine was widely used. It was uncertain whether this was due to concerns about the impact of adrenaline on uteroplacental blood flow – which are unfounded – or because of the universal availability of phenylephrine in the obstetric setting.
- Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during neuraxial anaesthesia required tracheal intubation and there were no cardiac arrests or maternal or neonatal deaths.

What we know already

Anaphylaxis and perioperative anaphylaxis in pregnancy

Until recently, anaphylaxis specifically in obstetric patients had received only limited prospective examination, and available knowledge was limited to case reports, case series and reviews. Anaphylaxis in obstetric patients is rare. The Scottish Confidential Audit of Severe Maternal Morbidity identified 18 cases of anaphylactic shock (defined as an allergic reaction resulting in collapse with severe hypotension, difficulty breathing and swelling/rash, and broadly equivalent to severity Grade 3 as used in NAP6), over the period 2003-2012, giving an incidence of 3 per 100,000 births (Lennox 2014). Mulla reviewed the hospital discharge records of parturients in Texas over a two-year period; women who had delivered a neonate and simultaneously had a diagnosis of anaphylaxis were selected for study, and Mulla reported an incidence of maternal anaphylaxis of 2.7 per 100,000 deliveries (Mulla 2010). More recently the UK Obstetric Surveillance System (UKOSS) conducted a population-based prospective study of anaphylaxis in pregnancy from all obstetrician-led maternity units in the UK over a three-year period (McCall 2017). There were 37 confirmed cases of anaphylaxis in pregnancy: an estimated incidence of 1.6 per 100,000 maternities. Of the 37 cases, 19 occurred in association with perioperative care, caesarean section or surgical management of post-partum haemorrhage after vaginal delivery.

Immunological impact of pregnancy on anaphylaxis

Previous epidemiological studies of perioperative anaphylaxis have identified a predominance of cases in females (Mertes 2011) – though this is not seen in NAP6 (see Chapter 10, Clinical features). The immune status is altered in pregnancy, and it has been suggested that increased progesterone levels during pregnancy may predispose pregnant patients to anaphylaxis. Meggs and colleagues described a patient with recurrent anaphylaxis which worsened dramatically during pregnancy. The episodes resolved after delivery when the woman started breastfeeding (Meggs 1984), but recommenced when breastfeeding ceased. The recurrent anaphylaxis finally responded to suppression of gonadotropin by luteinising hormone-releasing hormone, and then to oophorectomy. However, given the paucity of similar reports,

and also the behaviour of other conditions in pregnancy with an immune basis, such as asthma where a significant proportion of patients report an improvement in symptoms (Vatti 2012), it seems unlikely that a generalisation of increased susceptibility to anaphylaxis can be applied to all pregnant women.

Anaphylaxis during caesarean delivery

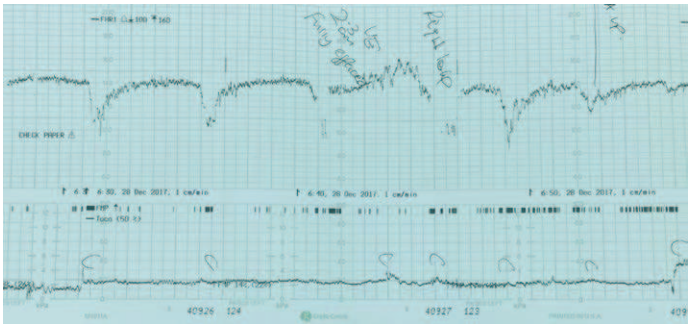
The predominant use of neuraxial techniques in obstetric anaesthesia limits the exposure to many of the widely recognised trigger agents for anaphylaxis. In a literature review of anaphylaxis in obstetric patients over an eleven-year period, 14 cases of anaphylaxis in association with caesarean section were identified, (27 obstetric cases reported in total) (Hepner 2013). The most common trigger agent was latex, occurring in ten of the 14 cases. In that series there were also three cases of anaphylaxis with suxamethonium. In the UKOSS study twelve women had a reaction to prophylactic antibiotics given at the time of caesarean delivery, with five reactions occurring when the antibiotics were given after the baby was born – which is not currently recommended practice (National Collaborating Centre for Women's and Children's Health, 2011). This raises the question of the potential impact on neonatal morbidity of anaphylaxis occurring in association with prophylactic antibiotics. The overall incidence of prophylactic-antibiotic-related anaphylaxis during caesarean delivery in the UKOSS study was 2.1 per 100,000 caesarean deliveries (McCall 2017). The agents responsible for reactions to anaesthetic drugs were suxamethonium, thiopental, and a component of spinal anaesthesia.

Maternal outcomes

Reported maternal and neonatal outcomes vary significantly, depending on the timing of onset of the anaphylactic reaction. In the UKOSS study there were two maternal deaths (giving a case fatality ratio 5%, (95%CI 0.7-18.2%), both of these deaths occurring in women who had already delivered), and 19% of women suffered one or more additional severe maternal morbidity (including haemorrhagic events, cardiac arrest and pulmonary embolism) (McCall 2017). In the Confidential Enquiries into Maternal Deaths in the UK, four deaths have been reported from anaphylaxis since 2000. In Hepner's case series no maternal morbidity or mortality was observed when maternal anaphylaxis occurred during labour (Hepner 2013). The picture appears to vary for anaphylaxis arising during caesarean section. In Hepner's series, severe maternal morbidity, pulmonary oedema, acute respiratory distress syndrome, and disseminated intravascular coagulation were reported in 20% of women who developed anaphylaxis in this setting.

Impact on the neonate

Neonatal outcomes show a different pattern, in that they appear to be worse when maternal anaphylaxis develops during labour, something which is likely to be related to poor or inadequate maternal resuscitation. The effect of maternal anaphylaxis on the foetus is largely as a result of the impact on the uteroplacental circulation arising from maternal hypotension. The placenta is metabolically active and produces diamine oxidase, a histaminase that metabolises histamine and other endogenous mediators. (Baraka 1980, Maintz 2008). In the UKOSS study no babies died, but in those babies whose mother had anaphylaxis before delivery 41% suffered morbidity (Neonatal Intensive Care Unit admissions, preterm delivery, or whole body cooling for neonatal encephalopathy (McCall 2017)). In Hepner's case series, no neonatal neurological abnormalities were reported when maternal anaphylaxis developed during caesarean delivery (Hepner 2013).



Cardiotocograph showing unprovoked fetal heart rate decelerations

Numerical analysis

We identified eight obstetric cases in NAP6, all of which were Grade 3. The NAP6 Activity Survey estimated 233,886 obstetric anaesthetics are administered per annum in the UK, giving an incidence of severe obstetric perioperative anaphylaxis of 3.4 per 100,000 (95% Confidence interval 1.48-6.74 per 100,000). The incidence in obstetric patients is therefore lower than in non-obstetric adult patients (247 cases in 2,489,428 patients: 9.92 per 100,000 95% CI 8.72 - 11.24 per 100,000, Fisher P=0.002).

Six cases occurred in association with anaesthesia for caesarean section (Category 1–2 three cases; Category 3–4: three cases). One case was related to anaesthesia for a post-partum procedure and in one case the nature of surgery was unknown.

Six patients had received neuraxial anaesthesia and two patients had received general anaesthesia.

Details of the event

All eight cases presented in the operating theatre. In five out of the six caesarean section cases anaphylaxis developed after the baby had been delivered. Three cases occurred during daytime hours Monday–Friday, with the remaining five cases occurring out of hours in evenings or at weekends. In three cases the primary anaesthetist was a consultant, in three cases an anaesthetist in training, and in two cases a non-consultant career grade anaesthetist. In all except one case a consultant was present for resuscitation. The theatre team were judged to have contributed effectively to management of the case in all except one case.

Presentation

In four out of the six patients who developed severe anaphylaxis during neuraxial anaesthesia, a common feature of presentation was that the patient complained of feeling unwell prior to the onset of hypotension or other clinical signs. All patients developed hypotension, in some cases profound.

In four of the cases (both general anaesthesia cases and two of the neuraxial cases) there was prompt recognition of the clinical event. In only one case (neuraxial anaesthesia) was the event promptly recognised as anaphylaxis.

A woman received spinal anaesthesia for caesarean section performed out of hours. She received diamorphine and bupivacaine in the spinal anaesthetic after skin preparation with chlorhexidine. She received prophylactic phenylephrine boluses for the pre-emptive management of spinal hypotension and a cephalosporin for surgical prophylaxis. Following delivery of the baby she received syntocinon and ondansetron. One hour after the spinal was sited she complained of feeling unwell and developed profound hypotension that was managed with multiple phenylephrine boluses and intramuscular adrenaline.

An obese woman underwent caesarean section. She received propofol and suxamethonium as part of a rapid sequence induction followed by atracurium, morphine and syntocinon given after delivery of the baby. Soon after delivery she developed sudden profound hypotension, and this was initially managed with phenylephrine and ephedrine boluses. However, she required a noradrenaline infusion to effectively treat the hypotension. Subsequent allergy clinic testing revealed sensitivity to atracurium.

Management

Specific treatment for anaphylaxis was initiated promptly in five cases once the clinical event was recognised as anaphylaxis. It was judged as slow in the remaining three. The vasopressors used to manage hypotension are shown in Table 1. Phenylephrine was the predominant agent used. Four patients received adrenaline as part of the management of anaphylaxis.

Table 1. Vasopressor drugs used in the management of perioperative anaphylaxis in obstetrics

	Adrenaline bolus		Ephedrine	Metaraminol	Phenylephrine
	IV	IM			
All cases (n=8)	1	3	3	2	6
GA cases (n=2)	0	1	2	0	1
Neuraxial cases (n=6)	1	2	1	2	5

Five of eight patients received chlorphenamine and six received hydrocortisone. Fluid management was deemed to be appropriate in all patients where that information was supplied (five out of eight).

A specific anaphylaxis pack was used to assist management in only two cases.

Mast cell tryptase levels to support diagnosis were measured in all cases.

The review panel were able to assess the anaesthetist's clinical management in five out of eight cases; in four cases this was judged as good' and in one 'good and poor'.

Maternal and neonatal outcomes

Maternal and neonatal outcomes were good in all cases. None of the women who experienced anaphylaxis during neuraxial anaesthesia required tracheal intubation. No woman progressed to cardiac arrest. After the anaphylaxis event two women were transferred to the critical care, two were cared for in an observation bay on the delivery suite, two were transferred to the recovery unit and two were cared for in the operating theatre. Hospital discharge was delayed for three women, but the remaining five were discharged at the time anticipated prior to the anaphylactic reaction. One woman subsequently reported anxiety about future anaesthetics. There were no reports of any woman developing post-traumatic stress disorder or any other sequelae.

In five of the six women who developed anaphylaxis in association with caesarean section, the onset of the reaction was after delivery of the baby. In one case the onset was immediately before delivery; there is no further information about neonatal outcome in this case.

Referral for investigation

Seven women were referred to an allergy clinic for investigation. At the time of referral four women were provided with written or oral information about which drugs or substances to avoid before they were seen in an allergy clinic, and three women received no information. The quality of referral to the allergy clinic was 'good' in three cases, 'good and poor' in one, 'poor' in one and 'unassessable' in two.

No cases were reported to the Medicines and Healthcare products Regulatory Agency (MHRA).

Of the eight cases, the review panel identified the agent responsible for the anaphylactic reaction in four (Table 2).

Table 2. Identified causative agents in obstetric perioperative anaphylaxis in NAP6

	Certainty of agent as cause of anaphylaxis
Suxamethonium	Definite
Atracurium	Definite
Chlorhexidine	Definite
Ondansetron	Probable

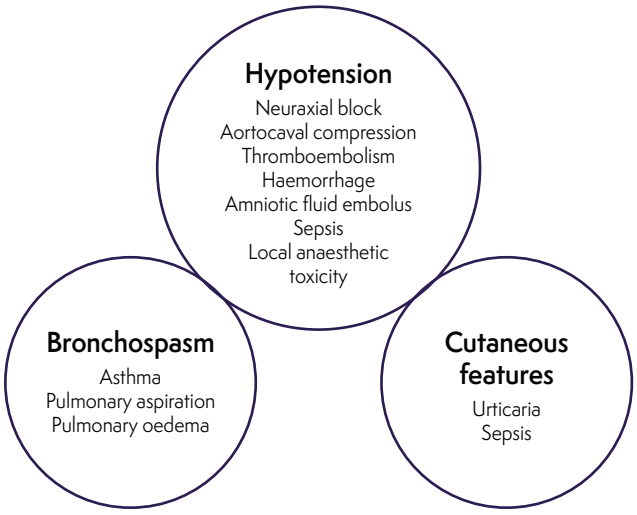
The anaesthetist made a correct judgement about the responsible agent at the time of the reaction in only one case.

Discussion

Severe perioperative anaphylaxis in obstetric patients is extremely rare. In the NAP6 dataset the outcomes for women and their babies were good. Anaesthetists however should not be complacent: anaphylaxis can still be fatal in the obstetric setting, and indeed this was reported in the most recent MBRRACE report (Knight 2017). In NAP6, delays in diagnosing anaphylaxis (as opposed to recognising an acute event) and in starting anaphylaxis-specific treatment were greater in obstetric cases than in others.

There is a broad differential diagnosis for anaphylaxis in pregnancy, including pulmonary thromboembolism, amniotic fluid embolus, cardiac disease, complications of anaesthesia (including high/total neuraxial block and local anaesthetic toxicity), sepsis, and post-partum haemorrhage (Figure 1). Disseminated intravascular coagulation (DIC) is a very common finding in amniotic fluid embolus and can develop with other obstetric complications but can also be present in anaphylaxis (Borahay 2011, Truong 2015).

Figure 1. Differential diagnosis of anaphylaxis in obstetrics



The overlapping clinical features of anaphylaxis with other acute obstetric morbidities can hinder the diagnosis of anaphylaxis, particularly during the onset or in the presence of neuraxial block. It has been suggested that, because of the altered immune response in pregnancy, the classical clinical features of anaphylaxis may be modified, such that hypotension may be the predominant or only sign (Rosen 1992), although in published case series cutaneous and respiratory manifestations were also common (Adriaensens 2013, Hepner 2013). In the absence of prophylaxis, hypotension can occur in two thirds of patients with spinal anaesthesia, though this can be effectively prevented with vasopressors. However, other conditions, such as aortocaval compression, haemorrhage, and, much more rarely, amniotic fluid or thromboembolic embolus, can lead to hypotension.

As many perioperative obstetric patients are awake, it is unsurprising that presenting features differ from anaesthetised patients. A subjective feeling of being 'unwell' is generally preceded by physiological disturbance, and this should be a key indicator for obstetric anaesthetists of the possibility of anaphylaxis.

Hypotension was the commonest objective physiological disturbance in obstetric anaphylaxis in NAP6. In four of the women who developed anaphylaxis during neuraxial blockade in NAP6, 'new' hypotension developed – that is, hypotension developing after the period of time during which spinal hypotension would have reasonably been expected. Nevertheless, whenever hypotension develops, obstetric causes are likely to be uppermost in the anaesthetist's mind when working on the labour ward, and this in itself could be a source of delay.

Adrenaline was administered to half the obstetric cases compared with 83% of all NAP6 cases. It was administered intravenously to only one of eight obstetric patients, compared to three quarters of all patients, and intramuscular adrenaline was administered in three obstetric cases and to 14% of non-obstetric cases. In contrast, phenylephrine was the vasopressor most commonly used to treat hypotension associated with obstetric anaphylaxis. Phenylephrine infusions are recommended to prevent and treat hypotension associated with spinal anaesthesia (Kinsella 2018). Phenylephrine is therefore immediately available and familiar to the anaesthetist working on the labour ward. In the presence of spinal anaesthesia, and thus effective sympathectomy, hypotension from other causes can be exacerbated and require large doses of vasopressor to treat effectively. Adrenaline is the agent recommended for the management of anaphylaxis, but in obstetric patients there might be concerns about the potential effect on the uteroplacental circulation when used to treat anaphylaxis before delivery.
The effect of adrenaline administered intravenously on uterine blood flow has largely been studied in animal models (Chestnut 1986, Hood 1986). Adrenaline causes uterine vasoconstriction and can cause uterine blood flow to decrease by as much as 40%, but this effect is short-lived and Hood has suggested that the effect is similar to the decrease that occurs during a normal uterine contraction. The uteroplacental circulation is low resistance and not subject to autoregulation. The most important determinant of uterine blood flow is maternal blood pressure. Although there are isolated case reports of poor neonatal outcome, which the authors have attributed to the detrimental effects of adrenaline on the

uteroplacental circulation (Entman 1984), in Hepner's case series fetal outcomes were good when adequate doses of adrenaline were used. Gei reported a case of anaphylaxis occurring in a woman in labour where an adrenaline infusion was used to manage hypotension for several hours (Gei 2003). The maternal and neonatal outcome was excellent. Therefore, available evidence would appear to suggest that maintenance of maternal blood pressure is the over-riding factor in ensuring fetal wellbeing, and that adrenaline should be used.

There were no particular themes in the agents identified as causative agents. The absence of antibiotics is of interest, but the numbers are so small that this is likely to be a statistical quirk. The range of agents identified does, however, highlight the fact that even low-risk agents can, on occasion, cause severe perioperative anaphylaxis.

There were no cases of anaphylaxis caused by latex. Hypersensitivity to latex increased dramatically from 0.5% in the 1980s to almost 20% of all perioperative allergic reactions in the early part of the 21st century (Mertes 2011). The obstetric population has previously been identified as being at high risk for latex sensitivity in a number of studies (Draisci 2007, Draisci 2011). There were no cases of latex anaphylaxis identified in the UKOSS investigation (McCall 2017) and, with the findings of NAP6, this suggests that strategies to screen pregnant women and also the reduction of latex-containing equipment in the theatre environment have been effective.

There were no cases of anaphylaxis attributable to an anaesthetic induction agent. A UK survey published in 2013 reported that thiopental was the preferred induction agent for caesarean section for 94% of UK obstetric anaesthetists (Murdoch 2013). In the same year the NAP5 Activity Survey (Sury 2014) found that thiopental was administered during induction in 97% of caesarean section cases. However, the NAP5 Report on Accidental Awareness during General Anaesthesia highlighted thiopental, rapid sequence induction and obstetrics as all being risk factors for accidental awareness during general anaesthesia (Pandit 2014). A change to propofol was recommended and this has subsequently been reinforced in the 2015 MBRRACE Report (Knight 2014) and by others (Lucas 2015). In the NAP6 Allergen Survey (Chapter 9) thiopental was the induction agent in 62.7% of caesarean sections and propofol in 29.7% (<3% in NAP5), demonstrating a significant change in practice.

Recommendations

Institutional

- Obstetric units should ensure immediate availability of Anaesthetic anaphylaxis treatment and investigation packs wherever general or regional anaesthesia is administered.

Individual

- An allergy history should be taken even when there is extreme urgency to deliver the baby
- Anaesthetists should be vigilant to non-obstetric causes of hypotension in obstetric patients
- Anaphylaxis in obstetric patients should be managed following the same principles as in non-obstetric patients. Adrenaline should not be withheld for fear of a detrimental effect on placental perfusion
- Anaphylaxis should be actively considered where the cause of maternal hypotension or collapse is unclear, and mast cell tryptase levels should be measured
- Anaesthetists should be aware that hypotension due to anaphylaxis can be exacerbated by neuraxial blockade and or aortocaval compression.

References

Adriaensens 2013: Adriaensens I, Vercauteren M, Soetens F, Janssen L, Leysen J, Ebo D. Allergic reactions during labour analgesia and caesarean section anaesthesia. Int J Obstet Anesth. 2013; 22: 231-42.

Baraka 1980: Baraka A, Sfeir S. Anaphylactic Cardiac Arrest in a Parturient Response of the Newborn. JAMA. 1980; 243: 1745-6.

Borahay, 2011: Borahay MA, Harirah HM, Olson G, Kilic GS, Karipcin S, Hankins GD. Disseminated Intravascular Coagulation, Hemoperitoneum, and Reversible Ischemic Neurological Deficit Complicating Anaphylaxis to Prophylactic Antibiotics during Cesarean Delivery: A Case Report and Review of Literature. AJP Rep. 2011; 1: 15-20.

Chestnut 1986: Chestnut DH, Weiner CP, Martin JG, Herrig JE, Wang JP. Effect of intravenous epinephrine on uterine artery blood flow velocity in the pregnant guinea pig. Anesthesiology. 1986; 65: 633-6.

Draisci 2007: Draisci G, Nucera E, Pollastrini E, *et al.* Anaphylactic reactions during cesarean section. Int J Obstet Anesth. 2007; 16: 63-7.

Draisci 2011: Draisci G, Zanfini BA, Nucera E, *et al.* Latex sensitization: a special risk for the obstetric population? Anesthesiology. 2011; 114: 565-9.

Entman 1984 Entman SS, Moise KJ. Anaphylaxis in pregnancy. South Med J. 1984; 77: 402.

Gei 2003: Gei AF, Pacheco LD, Vanhook JW, Hankins GD. The use of a continuous infusion of epinephrine for anaphylactic shock during labor. Obstet Gynecol. 2003; 102: 1332-5.

Hepner 2013: Hepner DL, Castells M, Mouton-Faivre C, Dewachter P. Anaphylaxis in the clinical setting of obstetric anesthesia: a literature review. Anesth Analg. 2013; 117: 1357-67.

Hood 1986: Hood DD, Dewan DM, James FM Maternal and fetal effects of epinephrine in gravid ewes. Anesthesiology. 1986; 64: 610-3.

Kinsella 2018: Kinsella SM, Carvalho B, Dyer RA, *et al.* International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia 2018; 73: 71-92.

Knight 2017: Knight M, Nair M, Tuffnell D, Shakespeare J, Kenyon S, Kurinczuk JJ (Eds.) on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care. Lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2013–15 Maternal, Newborn and Infant Clinical Outcome Review Programme 2017. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202017%20-%20Web.pdf (accessed 20 Feb 2018).

Knight 2014: Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ, eds, on behalf of MBRRACE-UK. Saving Lives, Improving Mothers' Care – Lessons Learned to Inform Future Maternity Care from the UK and Ireland. Confidential Enquiries into Maternal Deaths and Morbidity 2009-12. https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/Saving%20Lives%20Improving%20Mothers%20Care%20report%202014%20Full.pdf (accessed 20 Feb 2018).

Lennox C 2014: Lennox C, Marr L. Scottish Confidential Audit of Severe Maternal Morbidity: reducing avoidable harm. 10th Annual Report. Healthcare Improvement Scotland 2014. http://www.healthcareimprovementscotland.org/our_work/reproductive,_maternal_child/programme_resources/scasmm.aspx (Accessed 20 Feb 2018).

Lucas 2015: Lucas DN, Yentis SM. Unsettled weather and the end for thiopental? Obstetric general anaesthesia after the NAP5 and MBRRACE-UK reports. Anaesthesia 2015; 70: 375-9.

Maintz, 2008: Maintz L, Schwarzer V, Bieber T, van der Ven K, Novak N. Effects of histamine and diamine oxidase activities on pregnancy: a critical review. Hum Reprod Update. 2008; 14: 485-95.

McCall 2017: McCall SJ, Bunch KJ, Brocklehurst P *et al.* The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. BJOG. 2017. doi: 10.1111/1471-0528.15041. [Epub ahead of print].

Meggs 1984: Meggs WJ, Pescovitz OH, Metcalfe D, Loriaux DL, Cutler G Jr, Kaliner M. Progesterone sensitivity as a cause of recurrent anaphylaxis. N Engl J Med. 1984; 311: 1236-8.

Mertes 2011: Mertes PM, Alla F, Tréchot P, Auroy Y, Jougla E; Groupe d'Etudes des Réactions Anaphylactoïdes Peranesthésiques. Anaphylaxis during anesthesia in France: an 8-year national survey. J Allergy Clin Immunol. 2011; 128: 366-73.

Murdoch 2013: Murdoch H, Scrutton M, Laxton CH. Choice of anaesthetic agents for caesarean section: a UK survey of current practice. Int J Obstet Anesth. 2013; 22: 31-5.

National Collaborating Centre for Women's and Children's Health 2011: National Collaborating Centre for Women's and Children's Health. Caesarean section. RCOG Press at the Royal College of Obstetricians and Gynaecologists. https://www.nice.org.uk/guidance/cg132/evidence/full-guideline-pdf-184810861 (Accessed 20 Feb 2018).

Pandit 2014: Pandit JJ, Andrade J, Bogod DG, *et al.* 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth. 2014; 113: 549-59.

Rosen 1992: Rosen M, Harmer M. Anaphylactic reactions during anaesthesia in pregnancy: safe in our hands? Int J Obstet Anesth. 1992; 1: 183-4.

Sury 2014: Sury MJR, Palmer JHMacG, Cook TM, Pandit JJ. The state of UK anaesthesia: a survey of National Health Service Activity in 2013. Br J Anaesth 2014; 113: 575-84.

Truong 2015: Truong HT, Browning RM. Anaphylaxis-induced hyperfibrinolysis in pregnancy. Int J Obstet Anesth. 2015; 24: 180-4.

Vatti 2012: Vatti RR, Teuber SS. Asthma and pregnancy. Clin Rev Allergy Immunol. 2012; 43: 45-56.