

Editorial

Anaphylaxis in obstetrics – double the trouble

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Anaphylaxis is a rare but life-threatening event which an individual anaesthetist might expect to see once every seven years [1]. The 6th National Audit Project of the Royal College of Anaesthetists (NAP6) provided valuable insights into peri-operative anaphylaxis. The results were mostly reassuring for obstetric anaesthetists, but did highlight the diagnostic difficulties of maternal collapse with multiple potential causes. It also highlighted the challenges in resuscitating a pregnant woman, specifically after 20 weeks of pregnancy when caval compression becomes evident. The National Audit Project made useful recommendations for peri-operative anaphylaxis in obstetrics, to sit alongside existing advice for resuscitation in pregnancy, and these are summarised in Table 1 [2, 3].

Despite the infrequency of anaphylaxis in obstetrics, the potential diagnostic difficulties and challenges of resuscitation may heighten the anxiety around such an event. In this issue, McCall et al. provide further information with data from a pan-European study [4]. McCall et al. studied the experience of anaphylaxis in women at all stages of pregnancy and up to 48 h postpartum, identifying causal agents, management and investigation of such events. The UK, France, Belgium and the Netherlands, identified patients prospectively from their existing surveillance systems; in Finland, patients were picked up retrospectively from the Finnish Medical Birth Registry. Patients were included if a severe, life-threatening reaction occurred which the anaesthetist or obstetrician believed to be anaphylaxis. The study highlights several key points which merit further consideration.

Clinical lessons

In total, 63 cases of anaphylaxis were included in the dataset from almost 4.5 million deliveries, giving an incidence of 1.5 per 100,000. This is lower than previous estimates; in the UK, the Scottish Confidential Audit of Severe Maternal Morbidity identified 18 cases of anaphylactic shock from 2003 to 2012, giving an incidence of 3 per 100,000 births [5], and a 2-year retrospective analysis of hospital discharge records of parturients in Texas, USA, found an incidence of maternal anaphylaxis of 2.7 per 100,000 deliveries [6]. The incidence was broadly similar across all countries in the study by McCall et al., providing ‘face validity’ to their findings. Perhaps unsurprisingly, the peripartum period was identified as the time of highest risk for anaphylaxis, with 75% of reactions occurring immediately before or after delivery. Of specific relevance to anaesthesia, the majority of peripartum reactions were related to operative delivery. The most common causal agents were antibiotics, followed by neuromuscular blocking (NMB) drugs; again, in keeping with the European experience of peri-operative anaphylaxis [7, 8]. Management of patients was broadly similar across mainland Europe and was judged suboptimal in some, with only two-thirds of women receiving epinephrine, although a larger proportion did receive intravenous fluids and oxygen. In the UK, the proportion receiving epinephrine was higher, at 93%. The authors highlight an apparent reluctance to use epinephrine in obstetric patients; this is difficult to comment upon without the comparator of epinephrine use in non-obstetric patients. Mortality was comparable with quoted rates for peri-operative

Table 1 Considerations for the management of anaphylaxis in obstetrics based on the 6th National Audit (NAP6) [2] and the European Resuscitation Council Guidelines for Resuscitation [3].**Recommendations for peri-operative practice in obstetrics**

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

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 the presence of neuraxial blockade and/or aortocaval compression.

Recommendations for resuscitation of cardiac arrest during pregnancy

Manually displace the uterus to the left to remove caval compression. Add left lateral tilt if this is feasible. The method used for tilting will depend on where the patient is and what is available.

Early tracheal intubation decreases this risk of pulmonary aspiration of gastric contents in pregnancy.

Attempt defibrillation using standard energy doses.

After 20 weeks' gestation when initial resuscitation attempts fail, delivery of the fetus may improve the chances of successful resuscitation of both the mother and fetus. This requires that caesarean section starts at about 4 min after cardiac arrest.

Perimortem caesarean section should not be delayed by moving the woman. It should be performed where maternal collapse has occurred and resuscitation is taking place.

anaphylaxis, at 3.5%, but the outcome for babies was noted to be poor, with one third requiring admission to neonatal intensive care [1,9]. By comparison, of the eight obstetric patients identified in NAP6, there were no poor maternal outcomes; one baby was delivered after the onset of anaphylaxis, but the outcome is not known [2].

It is noteworthy that in this series no cases of anaphylaxis were attributed to chlorhexidine. Recent studies of peri-operative anaphylaxis in countries which test routinely for chlorhexidine have shown this agent to be responsible for 10–15% of all life-threatening anaphylaxis [1, 10–12]. Chlorhexidine use is ubiquitous throughout healthcare settings, and the incidence of allergic reactions it causes looks set to rise as we continue to sensitise patients through repeated exposure [12]. However, it is frequently overlooked as a potential causal agent at the time of the reaction. This may be due to delayed onset of symptoms, a lack of visibility as a trigger or lack of knowledge about chlorhexidine-containing substances. A typical scenario would be that a lubricating, chlorhexidine-containing gel (such as Instillagel®) that is used for urethral catheterisation in the operating theatre, results in the onset of symptoms a variable time later. The link between these two events is easy to miss, resulting in misattribution of the event to another cause. Also of note, the authors found that suxamethonium was the only neuromuscular blocking drug to cause anaphylaxis during caesarean section in the cohort studied. This is perhaps surprising given that NAP6 found rocuronium to be the most

common cause of peri-operative anaphylaxis among all NMB drugs [1]. This finding probably reflects the predominant use of suxamethonium over rocuronium for rapid sequence induction in the obstetric patient, in contrast to other patient groups [13, 14]. Although there is debate in the literature around the relative merits of each of these drugs in the obstetric setting [15], there is evidence of growing interest in the use of rocuronium as the neuromuscular blocker of choice in general anaesthesia for caesarean section. It is important to remember that sugammadex can itself cause anaphylaxis; indeed, work from Japan suggests that sugammadex is highly allergenic with an incidence of anaphylaxis of 1 per 2000 administrations [16].

Low incidence

A key finding in this study is the very low incidence of anaphylaxis in obstetric patients. The reasons for this are not clear and have not been explored by the authors. One obvious explanation might be that obstetric patients are less likely to receive drugs during hospital admission compared with other patient groups, and in particular to receive the drugs known to cause the majority of cases of peri-operative anaphylaxis. Around one quarter of obstetric patients undergo operative delivery requiring antibiotics, and only a very small minority of these will receive general anaesthesia. Therefore, exposure to common causal agents is relatively low. Another reason might be that the obstetric patient group is a younger population, compared with other patient

groups, with less opportunity for previous drug exposures and therefore fewer opportunities to become sensitised; risk of drug allergy increases with age, and the obstetric population may simply represent a 'naïve' cohort [17]. Lastly, the effects of pregnancy on the immune system are unpredictable, leading to a worsening of some immune-mediated conditions and amelioration of others. Drug hypersensitivity reactions may be less frequent during pregnancy, as a result of as yet undefined immunomodulatory changes.

Significant effort was made in this study to identify all cases of anaphylaxis and ensure uniform case definition across countries. However, the dataset is subject to the same limitations as all studies in this field. Case inclusion was, necessarily, dependent on the anaesthetist or obstetrician recognising that anaphylaxis might have occurred. It is widely accepted that anaphylaxis is under-reported in the peri-operative setting; this is supported by a limited number of prospective studies which have attempted to define the true incidence of anaphylaxis [18, 19]. It is possible that the McCall et al. cohort represents only a proportion of all cases, although there is nothing to suggest that anaphylaxis in obstetric patients would be under-reported to a greater extent than any other patient group. Of greater concern in this dataset, however, are the methods for confirming the diagnosis of anaphylaxis and the causal agent. Mast cell tryptase measurements are key to establishing whether anaphylaxis has occurred, but were only known in 54% of the cases in mainland Europe and 86% of the UK cases (72% of cases overall). Among these, only half demonstrated a rise in mast cell tryptase. This means that the diagnosis of anaphylaxis remains unconfirmed in up to 60% of cases. The negative predictive power of mast cell tryptase is not 100%, and false-negative results are therefore possible, but most of the adverse events where the mast cell tryptase was normal would likely have been caused by something other than anaphylaxis [20].

In terms of identifying the causal agent, the investigators relied on serum-specific IgE testing alone and did not consider other testing modalities such as skin testing or drug provocation testing. The latter is the gold standard test for allergy; the drug is administered in incremental doses, and the patient observed for signs of reaction [21]. The other tests used for investigation of drug allergy are imperfect, and their interpretation relies heavily on the clinical context. Evidence of IgE sensitisation with skin or blood testing demonstrates prior exposure to that drug, but does not predict clinical allergy. Only in the context of an adverse reaction temporally related to drug administration does this sensitisation become clinically-relevant [17, 20].

Furthermore, both skin and blood tests are themselves imperfect, with specificity and sensitivity below 100% [17, 20]. Serum IgE testing is, in general, less accurate than skin testing, which further limits its utility [17, 21]. In this study, the only testing appears to be for serum IgE; nine patients were tested of whom only seven had a positive result. From the data presented, the causal agent for the vast majority of cases, therefore, remains unconfirmed and is based purely on what the anaesthetist or obstetrician perceived to be the most likely cause. We know from NAP6 that anaesthetists misattribute a causal agent up to 25% of the time, and other important causal agents are likely to have been missed in the cohort presented [2].

Antibiotics

Lastly, this study highlights some important considerations around antibiotic use in parturients. As with peri-operative anaphylaxis in all other groups, antibiotics were the single most common causal agent. Half of the antibiotic reactions occurred after the baby had been delivered, and the authors state that the burden of infant morbidity might have been higher had all antibiotics been administered at the start of surgery. This is an area in need of urgent review. A Cochrane review of 95 studies involving 15,000 women in 2014 showed no evidence of lower infection rates if antibiotics were administered after cord clamping, as opposed to before [22]; this contradicted earlier work demonstrating reduced infection rates in women given the antibiotic before skin incision, on which the 2011 NICE guidance for antibiotic use at caesarean section was based [23]. There is also an evidence gap for the effects of maternal antibiotic use on the long-term health of babies [24]; this is an area of active research. It is our opinion that in the absence of compelling evidence of benefit to the mother and the potential for fetal harm, risk-benefit analysis may favour giving antibiotics after cord clamping, with possible exceptions for women with additional risk factors for postoperative infection, for example, obesity. This would minimise the effects of maternal hypotension and hypoxia on the baby should maternal anaphylaxis occur, and may also improve the quality of maternal resuscitation since aortocaval compression will be reduced.

The authors noted that three episodes of anaphylaxis occurred following administration of penicillin to patients with a documented penicillin allergy. They rightly highlight the avoidable nature of these reactions and the importance of the World Health Organization (WHO) checklist as a means of reducing medical error. They further suggest that this concept be extended to vaginal deliveries, although do

not detail at what point in the patient journey this is best achieved. The issue of prescribing errors is not confined to obstetrics, but the time pressure and anxiety associated with emergency operative delivery only serves to increase the risk of error; reinforcing the imperative for the WHO checklist among all theatre staff should be a vital part of drill training and education of the team.

The work by McCall et al. is a world first and should be reassuring to patients and anaesthetists alike, since it demonstrates the very low risk of anaphylaxis in obstetric patients. Nevertheless, given the risk of under-reporting, the potential for associated poor outcomes in mother and baby, and the imperative to correctly identify the culprit drug to ensure future safety during anaesthesia, this important differential should not be overlooked when a patient deteriorates unexpectedly.

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