

CORRESPONDENCE

Anaphylaxis-related mortality in the obstetrical setting: analysis of the French National Confidential Enquiry into Maternal Deaths from 2001 to 2012

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Editor—Anaphylaxis is an unpredictable and severe systemic immediate hypersensitivity reaction after exposure to an antigen. During pregnancy, this complication is rare, with an estimated incidence of 1.6–2.7 per 100 000 deliveries, but it is associated with significant morbidity for mother and the fetus.^{1–3} Few data are available on anaphylaxis-related maternal death. The specific anaphylaxis-related maternal mortality ratio (MMR) was recently estimated to be 0.09 per 100 000 live births (95% confidence interval [CI], 0.01–0.30) over the period 2012–14 in the UK, but the specific epidemiology of anaphylaxis-related maternal death was not analysed.³

The study of maternal mortality in France benefits from an enhanced national surveillance system with a dual epidemiological and clinical audit objective, the National Confidential Enquiry into Maternal Deaths (ENCMM).⁴ For each pregnancy-associated death identified, a team of assessors (an obstetrician or midwife, and an anaesthetist) conducts a confidential enquiry. Deaths are then anonymously reviewed by the national expert committee of the ENCMM, which reaches a unanimous determination of the underlying cause of death.

We retrospectively assessed this permanent nationwide database from 2001 to 2012 to identify maternal deaths related to anaphylaxis in order to estimate their frequency and identify the incriminated agent. Each case of possible anaphylaxis-related maternal death was reviewed by experts in anaphylaxis in order to confirm the diagnosis of anaphylaxis according to the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) and the French Society of Anaesthesia and Intensive Care.⁵ MMR and 95% CI were

calculated overall and specifically for anaphylaxis-related deaths using the number of live births as denominator and the number of corresponding maternal deaths as numerator.

Between 2001 and 2012, 973 maternal deaths and 9 779 756 live births were recorded in France for a total MMR of 9.95 per 100 000 live births (95% CI, 9.33–10.59). Five maternal deaths (0.5%) were attributed to anaphylaxis during this 12 yr period (Table 1). The ratio of anaphylaxis-related maternal mortality was estimated at 0.05 per 100 000 live births (95% CI, 0.02–0.19). In all patients, anaphylaxis occurred just after anaesthesia induction. In three patients (patients 1, 4, and 5), suxamethonium was highly suspected to be responsible for the reaction. Atracurium could also be involved in patient 1 as shown by the level of inhibition. In the two remaining patients (patients 3 and 4), the absence of specific IgE measurement did not allow certainty in identifying the culprit agent, but the assessors judged that suxamethonium was the most likely agent.

Data on anaphylaxis-related mortality during pregnancy are lacking, and only a few studies have tried to estimate its frequency. Although latex and antibiotics (penicillins or cephalosporins used for *Streptococcus B* infection prevention) are the most frequent allergens involved in peripartum anaphylaxis,^{3,6,7} our results clearly suggest that in France, fatal reactions are attributable to neuromuscular blocking agents (NMBAs). In this series of patients, because skin tests were impossible to perform, the diagnosis of anaphylaxis and identification of the triggering agent were based on a combination of a typical clinical history, increased tryptase values (4/4), and the presence of specific IgE against quaternary ammonium ions (3/3), when measured.

Table 1 Main characteristics of maternal anaphylaxis-related death. *Meningitis due to *Streptococcus pneumoniae*. †The hypnotic used for anaesthetic induction was not available. STP, sodium thiopental; SUX, suxamethonium; ATRA, atracurium; PRO, propofol; SUF, sufentanil; sIgE, anti-quaternary ammonium-specific IgE (positive threshold 2.3%); INH, specific inhibition (positive threshold 20%); NA, not available

Patient no.	Age (yr)	Weeks of gestation	Allergy history	Circumstances	Substances injected before anaphylaxis	Tryptase ($\mu\text{mol L}^{-1}$)	sIgE (%)	INH (%)	Suspected causal agent	Fetus survival
1	48	39	No	Elective Caesarean section	STP, SUX, ATR	12	2.4	SUX 76 ATR 77	SUX/ATR	No
2	33	39	No	Postpartum haemorrhage	PRO, SUX	49.4	NA	NA	SUX/PRO	Yes
3	30	33	No	Coma*	STP, SUX	NA	NA	NA	SUX/STP	Yes
4	39	39	No	Elective Caesarean section	STP, SUX, ATR, SUF	12	7.61	SUX 79	SUX	Yes
5	41	7	Atopic status	Ectopic pregnancy	SUX†	>200	9.32	SUX 42.9	SUX	No

Epidemiological studies have shown that, at the time of anaesthesia induction, clinical identification of an NMBA as the triggering agent was usually correct when a combination of a hypnotic and an NMBA were the only drugs administered.⁸ Although all injected drugs can be involved, NMBAs are by far the leading culprit in perioperative IgE-mediated hypersensitivity reactions,⁹ whereas reactions to hypnotics appear to be quite rare.¹⁰ Among NMBAs, suxamethonium, used for rapid sequence induction in all our patients, is associated with the highest risk of perioperative allergic reactions in many countries.^{9,11} NMBA-related anaphylactic reactions usually have symptoms occurring minutes after intravenous injection, which facilitates identification. In addition, increased tryptase levels have been demonstrated to be strong indicators of the allergic mechanism of the reaction⁸ especially in cases of fatal anaphylaxis, in the absence of another plausible cause.¹² Moreover, specific IgE measurements at the time of the reaction possess a high positive diagnostic value, making them helpful in identifying the culprit agent.¹³

Previous studies have focused mainly on non-fatal reactions. Anaphylaxis-related maternal deaths are rare, which probably explains why our incriminated drugs had not been reported earlier. NMBA-related anaphylactic shock is more severe and is associated with a higher risk of fatal reactions whereas latex-related reactions are generally delayed, occurring in the middle of the surgery, and are less severe.¹⁴

In conclusion, NMBAs appear to be the leading culprits in anaphylaxis-related maternal death. Fortunately, these reactions are rare and NMBAs should not be avoided when required. However, anaesthetists must be aware of this particular risk in order to ensure prompt recognition of these reactions and early intervention with the appropriate treatment. In case of a fatal reaction, tryptase measurement and specific IgE assays are helpful to identify the mechanism of the reaction.

Authors' contributions

Study conception and design: DC, CDT.

Acquisition of data: DC, CDT, MS, JMM.

Analysis and interpretation of data: CT, PMM.

Drafting of the article: CT, PMM.

Final approval of the version to be published: CT, PMM, DC, CDT, MS, JMM.

Agreement to be accountable for all aspects of the work: CT, PMM, DC, CDT, MS, JMM.

Critical revision of the article for important intellectual content: DC, CDT, MS, JMM.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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