Original Article

Incidence of accidental awareness during general anaesthesia in obstetrics: a multicentre, prospective cohort study

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Summary

General anaesthesia for obstetric surgery has distinct characteristics that may contribute towards a higher risk of accidental awareness during general anaesthesia. The primary aim of this study was to investigate the incidence, experience and psychological implications of unintended conscious awareness during general anaesthesia in obstetric patients. From May 2017 to August 2018, 3115 consenting patients receiving general anaesthesia for obstetric surgery in 72 hospitals in England were recruited to the study. Patients received three repetitions of standardised questioning over 30 days, with responses indicating memories during general anaesthesia that were verified using interviews and record interrogation. A total of 12 patients had certain/probable or possible awareness, an incidence of 1 in 256 (95%CI 149–500) for all obstetric surgery. The incidence was 1 in 212 (95%CI 122–417) for caesarean section surgery. Distressing experiences were reported by seven (58.3%) patients, paralysis by five (41.7%) and paralysis with pain by two (16.7%). Accidental awareness occurred during induction and emergence in nine (75%) of the patients who reported awareness. Factors associated with accidental awareness during general anaesthesia were: high BMI (25–30 $kg.m^{-2}$); low BMI (<18.5 $kg.m^{-2}$); out-of-hours surgery; and use of ketamine or thiopental for induction. Standardised psychological impact scores at 30 days were significantly higher in awareness patients (median (IQR [range]) 15 (2.7–52.0 [2–56]) than in patients without awareness 3 (1–9 [0–64]), p = 0.010. Four patients had a provisional diagnosis of post-traumatic stress disorder. We conclude that direct postoperative questioning reveals high rates of accidental awareness during general anaesthesia for obstetric surgery, which has implications for anaesthetic practice, consent and follow-up.

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Accepted: 10 December 2020
Keywords: accidental awareness during general anaesthesia; anaesthesia; general; anaesthesia; obstetric; post-traumatic stress disorder; recall
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Introduction

The incidence of accidental awareness during general anaesthesia (AAGA) may be influenced by patient characteristics, but also by the methods used to ascertain it. At one extreme, studies based on spontaneous reporting by patients find a very low incidence [1]. The largest study using this methodology, the 5th National Audit Project in the UK and Ireland (NAP5) [2] reported an average incidence of 1 in 19,000, rising to 1 in 8000 when neuromuscular blocking (NMB) drugs were used. In contrast, studies that involved questioning patients directly about their memories of the intra-operative period, typically using a short series of questions termed the 'Brice' interview, which enquires about memories from immediately before, during and after general anaesthesia [3], consistently report incidences of 1–2 per 1000 (averaging 1 in 600) [4–10]. Direct questioning tends to identify the highest incidence when the Brice questions are repeated three times over a month [9, 11] (the 'thrice Brice' method).

The reasons for these differences in incidence are variously attributed. One interpretation is under-reporting, either because patients are distressed by AAGA and disinclined or not given the opportunity to make a report, or because patient reports are not considered credible and not escalated. Conversely, the Brice interview may not be precise enough to distinguish true AAGA from other memories. There is consensus that it is probably over-sensitive as a tool, and results require further consideration of the details of the case to establish whether a report represents AAGA or not [12].

One of the striking results of NAP5 was the relatively high incidence of AAGA in obstetric patients, 1 in 1200 or 1 in 670 for caesarean section delivery. This latter estimate is notable for being very similar to the incidences cited using Brice interviews for non-obstetric surgery. For obstetric surgery, the incidence of AAGA detected by Brice interviews is 1 in 110–152, but these estimates come from studies that are somewhat dated in terms of anaesthetic practice [13, 14] and have not triangulated Brice responses against anaesthetic records and detailed patient reports in the way NAP5 did. Obstetric general anaesthesia for caesarean section involves multiple risk-factors for AAGA, including the almost universal use of NMB drugs and rapid sequence induction alongside a high incidence of difficult airway management and emergency or out-of-hours surgery [15]. It is unclear whether estimated differences in AAGA incidences between obstetric and non-obstetric surgery can be accounted for solely by the combination of risk-factors, as is the impact of detection methodology [14]. It is also unclear if other pregnancy-specific characteristics further increase the risk.

The aim of the direct reporting of awareness in maternity patients (DREAMY) study was to describe the epidemiology of AAGA and its consequences in adult patients undergoing obstetric surgery. By direct questioning, the study aimed to describe the incidence, nature of experiences, risk-factors and psychological implications of AAGA. The specific hypothesis was that the incidence of AAGA detected with direct questioning would be higher in obstetric surgery compared with non-obstetric surgery, as was found with patient-initiated reporting in NAP5.

Methods

Full details of the study protocol are available separately [16], and we provide salient details in brief below.

Participants provided written informed consent for the study after their surgery. They were aged 18 years or older and underwent obstetric surgery under general anaesthesia in public healthcare sector hospitals in England. General anaesthesia was administered according to local institutional practice. Patients were not included if the date of surgery was < 24 weeks gestation or ≥ 48 h postpartum, or if surgery was for a non-obstetric indication during pregnancy. Only patients able to communicate in English were included.

A two-phase approach was initially used to assess whether AAGA had occurred. During the first phase, three repetitions of Brice screening interviews were conducted: within 24 h following extubation; within 24–48 h; and at 30 days after surgery. During the second phase, a verification semi-structured telephone interview was conducted by the study lead (PO) with all participants who indicated recall of events attributed to the period between 'going to sleep' and 'waking up'. This interview was conducted as soon as possible following patient reporting. Any specific description of events made in verification interviews, including the timing and nature of reported sensory perceptions was investigated with clinical teams and case records to establish corroboration or refutation.

Patients reporting suspected intra-operative recall were followed-up for 12 months, with further semi-structured telephone interviews and a self-report symptom measure for post-traumatic stress disorder (PTSD), the PTSD Checklist for DSM-5 (PCL-5) [17], administered at day 30, then at 3, 6, 9 and 12 months. In addition, patients were asked to report diagnoses and risk-factors associated with PTSD in the postnatal period, including postpartum depression [18]. A comparator sample of at least 300

patients with no intra-operative recall provided PCL-5 responses at day 30 only. All patients were offered best-practice supportive care in accordance with the NAP5 Anaesthesia Awareness Support Pack guidelines [19].

Researchers collected a detailed, standardised dataset from patients and their medical records that included characteristics of general anaesthesia and airway management, along with workforce, timing and surgical parameters [16].

After all participants had completed the study, a panel of five authors (PO, SB, NL, JA and JP) reviewed all participant reports, interview transcripts and anaesthetic data. Assessors were blinded to hospital site and patient identifiers. Panel members collectively discussed each case, and their adjudication decisions were assessed using Fleiss's κ statistic to measure agreement. Detail, plausibility and consistency of reported experiences with the intra-operative process were considered. All cases were then reviewed a second time by the same group of assessors on a different date to reach a final adjudication decision on each case, determined by majority. Reports were graded using the same system as for NAP5: 'certain/probable'; 'possible'; 'unlikely'; or 'none'. Reports were classified according to pre-declared structures, including sensory experience (the Michigan Awareness Classification Instrument); measure of psychological harm (a modified National Patient Safety Agency tool, revised for use in NAP5); and the phase of anaesthesia during which AAGA was judged likely to have occurred (i.e. induction, during maintenance of anaesthesia or emergence). Reports of dreaming during general anaesthesia (but with no evidence of AAGA) were graded according to whether specific memories of the dream content were present and whether such content was pleasant, neutral or unpleasant.

Primary outcome was the proportion of obstetric patients reporting a composite of certain/probable and possible AAGA. This composite outcome reflects patient-centric reporting considerations and provides consistency with NAP5 [20].

A minimum sample size of 2015 patients was estimated, based on an exact binomial test with power of 80% and α of 0.05 to detect an incidence of AAGA that was at least three times higher than a comparator baseline in non-obstetric surgical patients, taken as 0.15% [4, 5, 8, 9, 21]. Given expected imprecision in estimates for the binomial proportions with rare events, recruitment was planned to exceed this minimum estimate, thereby improving confidence intervals for estimation of prevalence. The Chi-square test, Fisher's exact test, unpaired t-test and unpaired Mann–Whitney test were used for other group comparisons.

As described, PTSD was evaluated using the PCL-5 instrument [17]. Any symptom rated as 'moderately' or higher was considered positive. Patients were considered to have screened positive for PTSD if responses from a single follow-up interval included at least: one 'positive' B item (intrusion symptoms, questions 1–5); one C item (avoidance symptoms, questions 6–7); two D items (negative alterations of cognitions and mood, questions 8–14); two E items (alterations in arousal and reactivity, questions 15–20).

Independent associations with AAGA and PTSD were explored using binary logistic regression and multiple imputation analyses. Suspected predictors of AAGA were: age; urgency of surgery; ASA physical status; BMI; and timing of surgery. These were entered into a stepwise regression model alongside variables for anaesthetic characteristics (induction drugs, seniority of attending anaesthetist). Post-traumatic stress disorder associations were entered as self-declared maternal mental health conditions that were defined as discrete binary variables (previous medical history of depression, anxiety disorder or PTSD). Ordinal variables were defined for neonate birth weight and Likert scale responses of maternal perceptions of support from healthcare providers or family members. Pre-term neonates were defined as those born at < 37 weeks gestation. The proportion of patients with missing data for any covariate included in the multivariable models ranged from 0.0% to 4.2%. Characteristics of the patients with full data were similar to those with missing data; hence a 'missing at random' assumption was used to impute missing data. The regression model results are presented with the imputed data and as adjusted odds ratios.

Results

Seventy-two hospitals in England recruited patients to the study between May 2017 and August 2018. A total of 3115 patients provided written informed consent for inclusion following eligibility screening of 4969 patients (Fig. 1). All patients completed at least one screening Brice interview and were included in the primary outcome analysis. A total of 2937 (94.3%) completed two interviews and 1808 (58.0%) completed all three interviews. Table 1 shows the baseline characteristics of participants.

During at least one screening Brice interview, 266 (8.5%) patients reported memories they attributed to the period between 'going to sleep' and 'waking up' at the end of surgery (Fig. 1; Table 2). All these patients underwent further verification or interviews. The most reported types of memories were: dreaming during anaesthesia by 167 (62.8%); hearing voices by 96 (36.1%); and anxiety by 31 (11.7%).

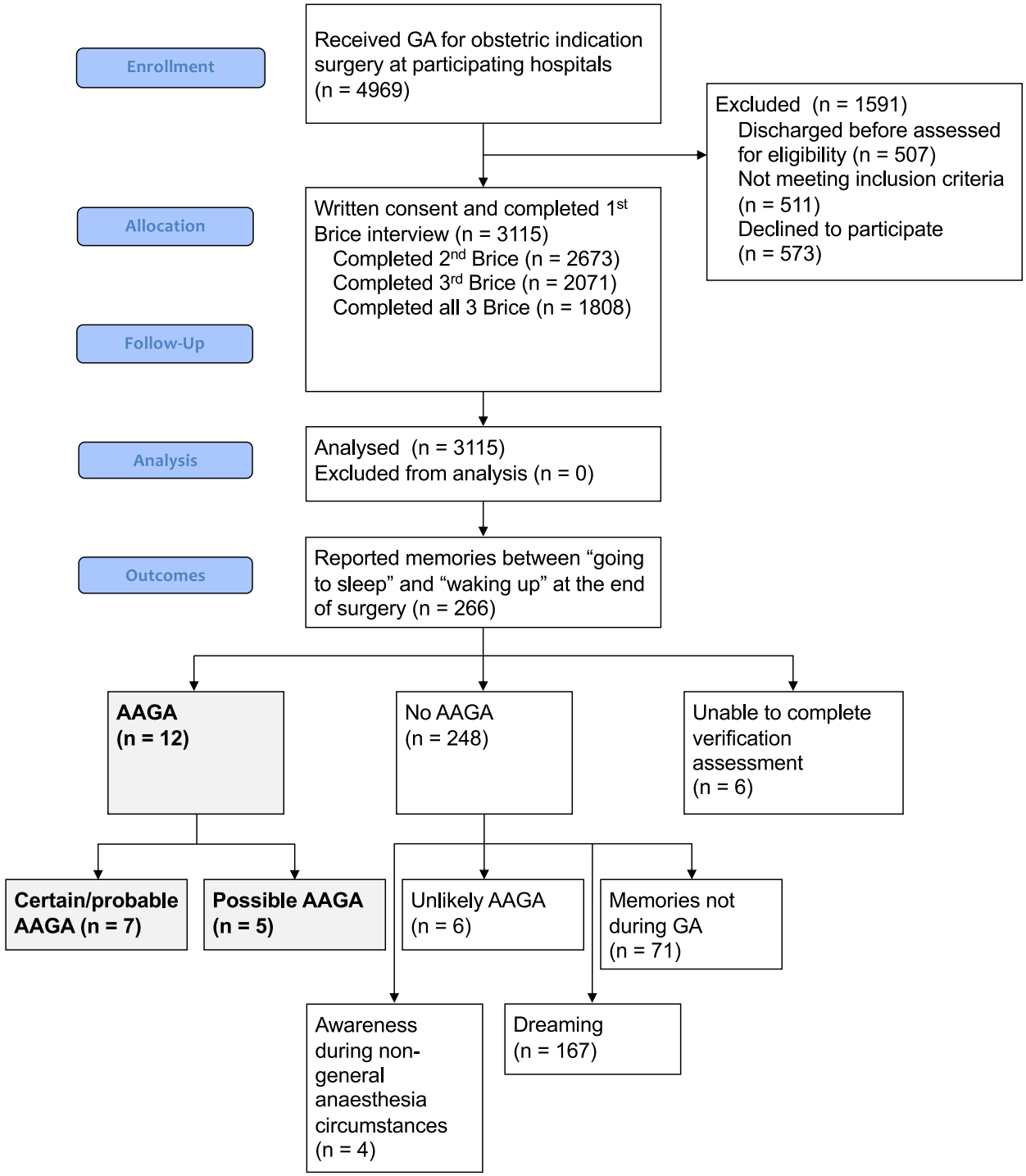

Figure 1 Study flowchart of participant recruitment and outcome adjudications. Outcomes are stratified as accidental awareness during general anaesthesia (AAGA) and 'No AAGA', with 'Unlikely AAGA' included in the latter category. A total of six patients had screening Brice interview responses indicating suspected awareness during general anaesthesia; however, verification assessment was not able to be completed, hence insufficient evidence was available to adjudicate these reports using equivalent criteria to the remaining cases.

Verification of initial responses demonstrated that the majority of memories, reported by 238 patients (89.4%), were evidently not AAGA events, instead representing memories of: an unrelated dream (that may have occurred during or after general anaesthesia); planned awake extubation; misunderstanding of the Brice questions (e.g.

Table 1 Baseline patient and surgical characteristics for all patients and only patients reporting certain/probable accidental awareness under general anaesthesia (AAGA). Values are mean (SD), median (IQR [range]) or number (proportion). For very low incidences, actual values are quoted. Weights were recorded at time of pregnancy booking appointment.

	All patients (n = 3115)	**Patients reporting AAGA (n = 12)**
Age; years	31.5 (6.1)	28.2 (5.7)
Weight; kg	70 (61–84 [38–188])	73 (64–78 [47–115])
BMI; $kg.m^{-2}$	26.3 (22.7–31.1 [14.4–80.4])	29.1 (25.7–30.4 [16.3–44.9])
BMI ≥ 30	737 (23.7%)	4 (25%)
ASA physical status ≥ 3	504 (16.6%)	0
Parity		
1	1842 (59.1%)	7 (58.3%)
2	724 (23.2%)	3 (25%)
3	290 (9.3%)	2 (16.7%)
≥ 4	214 (6.9%)	0
Unknown	45 (1.4%)	0
Intra-operative		
Duration; min	60 (45–75 [6–390])	65 (59–75 [55–105])
Start time		
08:00–19:59	1732 (55.6%)	2 (16.7%)
20:00–07:59	1383 (44.4%)	10 (83.3%)
Surgical procedures		
CS	2554 (81.9%)	12 (100%)
EUA	214 (6.4%)	0
MROP	202 (5.3%)	0
Other	23 (4.1%)	0
Unknown	101 (3.2%)	0
Urgency of surgery		
Emergency/category 1	1636 (52.5%)	3 (25.0%)
Urgent/category 2	815 (26.1%)	8 (66.7%)
Expedited/category 3	178 (5.7%)	0
Elective/category 4	387 (12.4%)	1 (8.3%)
Unknown	101 (3.2%)	0
Estimated blood loss; ml		
< 500	685 (22.0%)	4 (33.3%)
500–999	1192 (38.3%)	5 (41.7%)
1000–1999	740 (23.8%)	2 (16.7%)
≥ 2000	437 (14.0%)	1 (8.3%)
Unknown	61 (2.0%)	0
Experience of most senior attending anaesthetist		
Consultant	1216 (39.0%)	3 (25.0%)
Staff grade or Associate Specialist	670 (21.5%)	2 (16.7%)
Higher/advanced trainee (ST5-7)	501 (16.1%)	3 (25.0%)
Intermediate trainee (ST3-4)	494 (15.9%)	4 (33.3%)
Junior trainee (CT1-2)	105 (3.4%)	0
Unknown	129 (4.1%)	0

(continued)

Table 1 (*continued*)

	All patients (n = 3115)	Patients reporting AAGA (n = 12)
Induction drug incidence and dose; mg		
Thiopental	1649 (52.9%) 6.3 (5.2–7.3 [1.3–14.6])	9 (75.0%) 6.4 (5.1–8 [3.9–10.6]
Propofol	1419 (45.5%) 2.8 (2.3–3.3 [0.4–6.9])	2 (16.7%) 1.7, 2.0
Ketamine	28 (0.9%) 2.1 (1.7–3.2 [1.5–4])	1 (8.3%) 2.4

CS, caesarean section; EUA, exploration under anaesthesia; MROP, manual removal of placenta.

Table 2 Adjudication outcomes of the likelihood of accidental awareness during general anaesthesia (AAGA). A reported dream alone was not classified as awareness.

Adjudication panel outcome		n	Prevalence (95%CI)
AAGA	Total	12	1 in 256 (149–500)
	Certain/probable	7	1 in 455 (217–1111)
	Possible	5	1 in 625 (270–2000)
No AAGA	Unlikely	6	1 in 526 (238–1428)
	Awareness during non-GA circumstances	4	1 in 769 (303–3333)
	Awareness during total spinal anaesthesia	2	1 in 1666 (435–10,000)
	Awareness during postoperative sedation on intensive care unit	2	1 in 1666 (435–10,000)
	Dreaming	167	1 in 19 (16–22)
	With content recall:	71*	1 in 44 (35–56)
	Pleasant	20	28.2%
	Neutral	35	49.3%
	Unpleasant	8	11.2%
	Memories not during GA	71	n/a
Insufficient evidence	Unable to complete required verification assessment	6	n/a

*Eight patients reporting dreaming with content recall also described experiences consistent with AAGA; these patients were not included in the classification of dream emotional content.

reporting memories of the anaesthetist speaking during the initial process of induction of general anaesthesia); reports that clearly did not represent intra-operative events (e.g. feeling initial application of cricoid pressure, or being unable to move lower limbs after a spinal neuraxial block but before general anaesthesia).

Of the remaining 28 (0.8%) patients with suspected AAGA, six were determined by the adjudicating panel as being unlikely to have experienced AAGA. All these experiences consisted of reports that the patients considered to be intra-operative memories, but in which detail could not be established during verification interviews, or in which there was reasonable likelihood the episode occurred outside the period of anaesthesia. A further four patients described an awareness during non-general anaesthetic circumstances. Two experiences were associated with suspected total spinal anaesthesia and two patients reported wakefulness during sedation whilst on ICU postoperatively. Finally, a further six patients described responses lacking detail in the Brice interviews that might have represented AAGA, but further follow-up was declined or verification of the Brice responses was not possible.

The adjudication panel determined that a total of 12 patients had certain/probable AAGA (seven) or possible AAGA (five) (Table 2), an estimated prevalence of 0.39% (95%CI 0.20–0.67) or 1 in 256 (95%CI 149–500). Grading of the AAGA events according to the Michigan Awareness Classification Instrument is provided in Table 3, alongside characteristics of the surgical and general anaesthesia procedures undertaken for each participant. This estimated prevalence of AAGA is significantly higher than reported in previous large cohort studies of AAGA in non-obstetric

Table 3 Grading of accidental awareness during general anaesthesia events according to panel adjudication of likelihood and Michigan Awareness Classification Instrument. κ statistic indicates the measure of agreement of panel members on likelihood awareness classification, with a value of 1.0 representing unanimous agreement.

ID	Adjudication outcome	Michigan Awareness Classification instrument	Phase of anaesthesia	Surgery	Induction drug; dose ($mg.kg^{-1}$) Opioid for induction NMB drug for tracheal intubation	Maintenance drug Nitrous oxide for maintenance MAC; median [range] Additional NMB drug	NPSA	Summary of experience by the patient	κ
1	Certain/ probable	5D	Induction and maintenance	CS category 2	Thiopental (3.9) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 0.9 [0.7–1.0] No further NMB drug	3	Detailed recollection of the process of tracheal intubation and felt a painful initial surgical incision	1.00
2	Certain/ probable	4D	Emergence	CS category 1	Thiopental (6.7) No opioid Suxamethonium	Sevoflurane + nitrous oxide MAC 0.9 [0.8–1.2] No further NMB drug	3	Residual paralysis during emergence. Confirmed suxamethonium apnoea	1.00
3	Certain/ probable	5D	Maintenance	CS category 2	Thiopental (4.7) Alfentanil Suxamethonium	Sevoflurane + nitrous oxide MAC 1.4 [1.3–1.6] No further NMB drug	2	Felt surgical pain and hearing voices asking for surgical instruments	1.00
4	Certain/ probable	4D	Emergence	CS category 2	Thiopental (10.6) Fentanyl Rocuronium	Sevoflurane + nitrous oxide MAC 1.1 [1–1.2] No further NMB drug	2	Residual paralysis during emergence, secondary to incomplete reversal of rocuronium	1.00
5	Certain/ probable	2	Induction	CS category 1	Thiopental (8.0) No opioid Suxamethonium	Sevoflurane + nitrous oxide MAC 1.1 [1–1.2] Atracurium	0	Painless sensation of the initial surgical incision	1.00
6	Certain/ probable	4	Induction	CS category 2	Propofol (1.7) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 1.1 [1.2–1.5] No further NMB drug	2	Felt unable to move and heard multiple voices; likely occurred during management of difficult airway	1.00
7	Certain/ probable	4D	Induction	CS category 2	Thiopental (8.6) No opioid Suxamethonium	Isoflurane + nitrous oxide MAC 1.1 [0.9–1.2] Atracurium	1	Immediately after induction she experienced a dream-like sensation of falling into water, drowning and being unable to breath	0.33

(continued)

Table 3 (*continued*)

ID	Adjudication outcome	Michigan Awareness Classification instrument	Phase of anaesthesia	Surgery	Induction drug; dose ($mg.kg^{-1}$) Opioid for induction NMB drug for tracheal intubation	Maintenance drug Nitrous oxide for maintenance MAC; median [range] Additional NMB drug	NPSA	Summary of experience by the patient	κ
8	Possible	1	Other	CS category 4	Thiopental (5.9) No opioid Suxamethonium	Sevoflurane + nitrous oxide MAC 1.0 [0.8–1.2] Atracurium	0	Heard female voices holding a conversation, but unable to independently corroborate as occurring intra-operatively	1.00
9	Possible	3D	Maintenance	CS category 2	Thiopental (5.1) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 0.8 [0.6–0.9] No further NMB drug	n/a	Reported possible pain sensation whilst expecting to be unconscious, but inconsistent details	1.00
10	Possible	2	Emergence	CS category 1	Thiopental (6.4) No opioid Suxamethonium	Sevoflurane No nitrous oxide MAC 1.0 [0.4–1.5] No further NMB drug	0	Possible dissociative anaesthesia; reporting sensation of being out of her body	0.56
11	Possible	3D	Induction	CS category 2	Ketamine (2.4) Alfentanil Suxamethonium	Sevoflurane No nitrous oxide MAC 0.9 [0.7–1.0] No further NMB drug	n/a	Felt a sting at the back of her throat shortly after induction. Possible dissociative anaesthesia; felt asleep but aware of what was happening, like in a dream	0.56
12	Possible	1	Emergence	CS category 2	Propofol (2.0) Fentanyl Rocuronium	Sevoflurane No nitrous oxide MAC 1.2 [1.1–1.3] No further NMB drug	1	Hearing voices at an unspecified time point after induction, with little other detail	0.33

MAC, minimum alveolar concentration; NPSA, National Patient Safety Agency, CS, caesarean section.
Class 1 indicates isolated auditory perceptions; class 2, tactile perceptions (e.g. perception of surgical manipulation or endotracheal tube); class 3, pain; class 4, paralysis (e.g. a feeling that one cannot move, speak or breathe); and class 5, paralysis and pain. An additional designation of 'D' is applied where the report described distress during the experience (e.g. fear, suffocation, sense of impending death, etc.). Surgical and anaesthetic of participant surgical, anaesthetic and accidental awareness are summarised.
Modified NPSA classification summarises the psychological impact on the patient as: 0 = No harm occurred; 1 = Resolved (or likely to resolve) with no or minimal professional intervention, no consequences for daily living, minimal or no continuing anxiety about future healthcare; 2 = Moderate anxiety about future anaesthesia or related healthcare; symptoms may have some impact on daily living, patient has sought or would likely benefit from professional intervention; 3 = Striking or long-term psychological effects that have required, or might benefit from, professional intervention or treatment, severe anxiety about future healthcare and/or impact on daily living, recurrent nightmares or adverse thoughts or ideations about events; 4 = Caused death.

Table 4 Abbreviated narrative reports of accidental awareness during general anaesthesia experiences and postoperative follow-up psychological outcomes. Detailed reports of patient experiences are provided in online Supporting Information, Table S1.

ID	Narrative description
1	***Patient***: 32 years; BMI 27 $kg.m^{-2}$ ***Clinical scenario***: Failed epidural top-up for emergency CS. GA due to clinical urgency ***Induction***: Thiopental 3.9 $mg.kg^{-1}$ and suxamethonium ***AAGA experience***: Detailed, unpleasant memories of uncontrollable muscle spasm, intubation and pain of the first surgical incision ***Follow-up***: Anxiety and panic attacks several weeks later. High PTSD scores for 12 months. Required antidepressant therapy and community mental health team input
2	***Patient***: 30 years; BMI 28 $kg.m^{-2}$ ***Clinical scenario***: GA for fetal cord prolapse ***Induction***: Thiopental 6.7 $mg.kg^{-1}$ and suxamethonium ***AAGA experience***: Paralysis during emergence. Unable to breathe or move. Able to hear voices before being re-anaesthetised ***Follow-up***: Diagnosed with suxamethonium apnoea. PTSD scores initially low, rising at 6 months with anxiety symptoms. Patient required regular psychology consultations
3	***Patient***: 24 years; BMI 43 $kg.m^{-2}$ ***Clinical scenario***: GA for failed epidural top-up for emergency CS ***Induction***: Thiopental 4.7 $mg.kg^{-1}$, 1mg alfentanil and suxamethonium ***AAGA experience***: Detailed recall of voices and of sharp cutting pain across her abdomen. Unable to communicate ***Follow-up***: Low PTSD scores but required counselling after difficulty sleeping and nightmares of the experience
4	***Patient***: 29 years; BMI 16 $kg.m^{-2}$ ***Clinical scenario***: Intra-operative conversion to GA after inadequate neuraxial block ***Induction***: Thiopental 10.6 $mg.kg^{-1}$, fentanyl 100 μg and rocuronium ***AAGA experience***: Recall of profound paralysis and throat obstruction at emergence ***Follow-up***: High PTSD score, reducing at 6 months
5	***Patient***: 42 years; BMI 20 $kg.m^{-2}$ ***Clinical scenario***: De novo GA due to clinical urgency. Estimated blood loss > 2 l ***Induction***: Thiopental 8.0 $mg.kg^{-1}$ and suxamethonium ***AAGA experience***: Painless sensation of a cut across the abdomen, unable to communicate ***Follow-up***: Very low PTSD scores
6	***Patient***: 27 years; BMI 45 $kg.m^{-2}$ ***Clinical scenario***: GA following failed epidural top-up and unsuccessful spinal for emergency CS ***Induction***: Propofol 1.7 $mg.kg^{-1}$ with suxamethonium. Difficult airway management with additional 100 mg of propofol administered ***AAGA experience***: Recall of voices, but no distress or pain ***Follow-up:*** High PTSD scores and subsequent mental health review. Diagnosed with postpartum depression
7	***Patient***: 29 years; BMI 25 $kg.m^{-2}$ ***Clinical scenario***: GA following failed epidural top-up and unsuccessful spinal for emergency CS ***Induction***: Thiopental 8.6 $mg.kg^{-1}$ with suxamethonium ***AAGA experience***: Recall of a feeling of suffocation and inability to breathe, together with a drowning sensation on induction ***Follow-up***: Low PTSD scores
8	***Patient***: 31 years; BMI 30 $kg.m^{-2}$ ***Clinical scenario***: Elective GA ***Induction***: Thiopental 5.9 $mg.kg^{-1}$ with suxamethonium. Two attempts at intubation ***AAGA experience***: Recall of female voices and specific conversations ***Follow-up***: Very low PTSD scores
9	***Patient***: 19 years; BMI 29 $kg.m^{-2}$ ***Clinical scenario***: Intra-operative conversion to GA after inadequate neuraxial block ***Induction***: Thiopental 5.1 $mg.kg^{-1}$ with suxamethonium ***AAGA experience***: Recall of pain in vagina and lower abdomen. Reported that she was not fully asleep ***Follow-up***: Patient withdrew from follow-up
10	***Patient***: 29 years; BMI 27 $kg.m^{-2}$ ***Clinical scenario***: De novo GA due to clinical urgency ***Induction***: Thiopental 6.4 $mg.kg^{-1}$ with suxamethonium ***AAGA experience***: Describes a sensation of being out of her body, possible awareness during dissociative anaesthesia ***Follow-up***: Patient withdrew from follow-up

(continued)

Table 4 (*continued*)

ID	Narrative description
11	***Patient***: 23 years; BMI 31 $kg.m^{-2}$ ***Clinical scenario***: De novo GA due to clinical urgency ***Induction***: Ketamine 2.4 $mg.kg^{-1}$, 1 mg alfentanil and suxamethonium followed by 2 mg midazolam after 15 min ***AAGA experience***: Describes a disturbing sensation of a sting at the back of the throat accompanied by what she describes as a 'déjà vu' experience ***Follow-up***: Patient withdrew from follow-up
12	***Patient***: 32 years; BMI 30 $kg.m^{-2}$ ***Clinical scenario***: GA following failed epidural top-up ***Induction***: Propofol 2.0 $mg.kg^{-1}$, fentanyl 50 µg and suxamethonium ***AAGA experience***: The patient recalled hearing voices and felt that she was partly awake during surgery ***Follow-up***: High PTSD scores reducing over the course of 12 months

CS, caesarean section delivery, GA, general anaesthetic; PTSD, post-traumatic stress disorder.

surgical patients (p = 0.010) [4, 5] and is also higher than following spontaneous reporting by obstetric patients in NAP5 (p = 0.001) [2].

Awareness was first detected on the initial screening interview at < 24 h postoperatively for 11 patients and at the second interview (24–48 h postoperatively) for one patient. However, it was apparent during the verification interviews that this latter patient (ID 1) had recall of events following emergence, but chose not to share these during her first Brice interview (abbreviated details of which are provided in Table 4, full details are in online Supporting Information, Table S1). Of the 11 patients first detected at initial screening interview, two had already spontaneously made a report of AAGA to recovery nursing staff and a further five had spontaneously reported their experiences to relatives or partners. Seven of 12 (58.3%) made a spontaneous report and no additional patients were detected by repeating the Brice questionnaire. Nine patients completed 12 months of follow-up, two withdrew from the study follow-up at 30 days following surgery and one withdrew at 3 months.

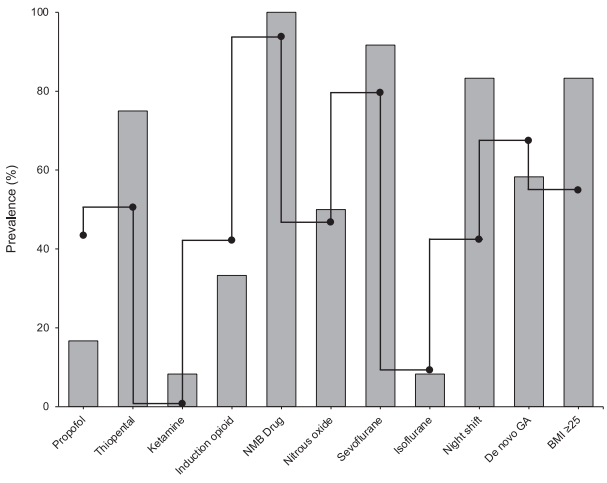

Figure 2 Comparison of the prevalence of characteristics in patients with certain/probable and possible accidental awareness during general anaesthesia (grey bars, n = 12) with baseline values for the whole cohort (dot and line, n = 3115). Thiopental use and general anaesthesia during the night shift (20:00–07:59) are over-represented in the accidental awareness group, whilst opioid use during induction of general anaesthesia is under-represented, for example. NMB drug = neuromuscular blocking drug. De-novo GA indication = general anaesthesia provided before the initial surgical incision (the remainder were conversions from neuraxial anaesthesia).

All patients with certain/probable or possible AAGA underwent caesarean section surgery, which represented 2554 (81.9%) of all surgical procedures and all received NMB drugs. The risk of AAGA after caesarean section in our study is therefore 0.47% (95%CI 0.24–0.82) or 1 in 212 (95%CI 122–417). The degree of surgical urgency was category 1 for only three (25.0%) patients, despite this category accounting for 52.0% of all caesarean section surgery. One participant reported AAGA during an elective caesarean section and the remainder were during category 2 caesarean section. Detailed analysis of baseline general anaesthesia characteristics and airway management techniques for the whole cohort are reported separately [15].

Awareness occurred during the dynamic phases of anaesthesia in nine (75%) patients, five at induction and four during emergence. Of the five patients reporting AAGA during induction, a potentially insufficient hypnotic drug dose, < 4.0 $mg.kg^{-1}$ thiopental or < 2.0$mg.kg^{-1}$ propofol, respectively, was administered to two patients, one of which also involved management of an unpredicted difficult tracheal intubation. The remaining three patients reported tactile sensations that may have occurred due to anaesthetic or surgical manipulation before adequate anaesthetic depth was achieved.

Two patients (16.7%) experienced residual paralysis during emergence. One instance was following

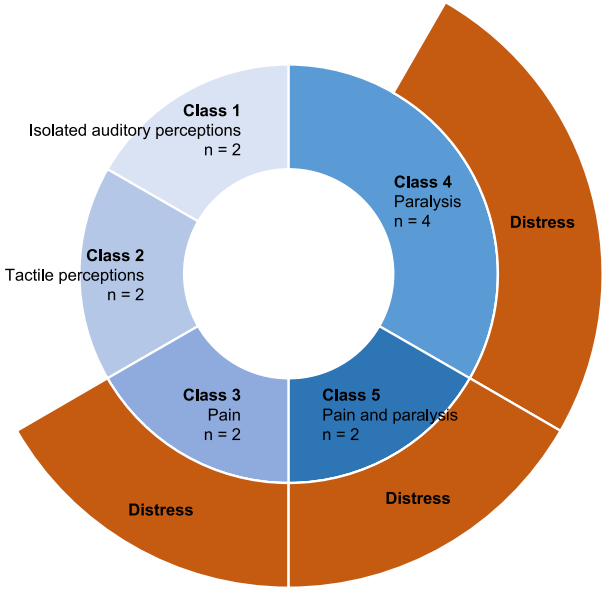

Figure 3 Hierarchical representation of Michigan Awareness Classifications for AAGA patients (n = 12), showing that immediate distress occurring exclusively in patients reporting pain and/or paralysis (affecting almost all patients reports those experiences). None of the four patients who reported auditory or tactile perceptions had distress.

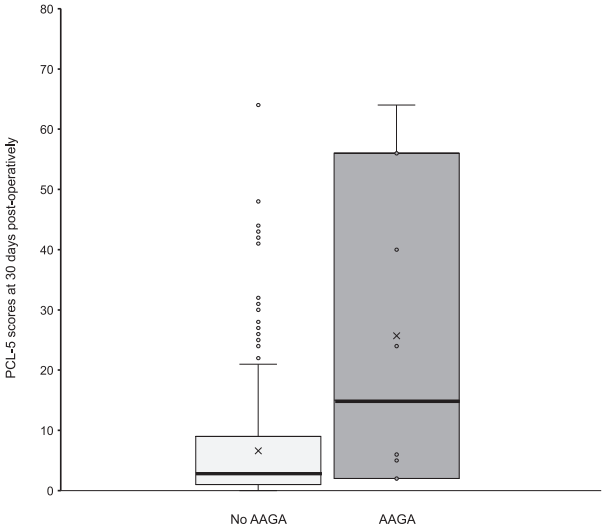

Figure 4 PCL-5 scores at 30 days postoperatively for patients with certain/probable and possible accidental awareness during general anaesthesia (n = 12), compared with baseline (n = 341). Solid line = median; box = IQR; whisker = upper and lower adjacent values.

administration of suxamethonium to a patient with previously undiagnosed abnormally reduced plasma cholinesterase function. The second was secondary to incompletely reversed neuromuscular blockade with rocuronium; neostigmine followed by sugammadex was administered sequentially during emergence. Neither patient received neuromuscular blockade monitoring before the AAGA event. The remaining two patients with emergence AAGA described less detailed accounts of events.

Two (16.7%) patients reported AAGA during the maintenance phase of anaesthesia. Both patients received suxamethonium to facilitate tracheal intubation but had no further doses of NMB drug. One of these had low end-tidal anaesthetic agent concentrations with no nitrous oxide during the maintenance phase; estimated age-adjusted minimum alveolar median concentration of 0.7, high of 0.8 and low of 0.5. The other had a high BMI (43 $kg.m^{-2}$).

Conduct of anaesthesia differed in several respects between patients reporting AAGA and those not reporting AAGA (Fig. 2). Propofol was under-represented in the AAGA group (p = 0.045), being used in only two patients (16.7%) compared with 1417 (45.5%) in the baseline group. Conversely, thiopental was used in nine patients (75.0%), compared with 1640 (52.9%) in the baseline group, p = 0.121. Opioid use during induction of general anaesthesia was lower in the AAGA group at four (33.3%) patients, but this was not statistically significant (p = 0.486) when compared with the 1347 (43.4%) patients in the baseline group who received opioids. All AAGA patients received NMB drugs. Non-depolarising NMB drug use was similar in the AAGA group to the baseline, received by 7 of 12 (58.3%) compared with 1620 of 3115 (52.0%), p = 0.661. Five of the AAGA patients received suxamethonium but no non-depolarising NMB drug (41.7%). Nerve stimulator use was influenced by the complications during emergence in the AAGA group, since monitoring was only applied after residual paralysis was clinically recognised and AAGA had already occurred in two patients. Four of the remaining 12 AAGA patients (33.3%) had nerve stimulator monitoring compared with 855 out of 3115 patients in the baseline cohort (27.4%). Use of nitrous oxide and sevoflurane was similar across the groups.

Ten patients with AAGA (83.3%) underwent surgery during the night shift (20:00–07:59), a far greater proportion compared with the non-AAGA cohort in which only 1373 (44.4%) patients had surgery at night, p = 0.007. Five (41.7%) patients with AAGA had general anaesthesia after failed or inadequate neuraxial anaesthesia. This was not significantly different from the 861 (27.6%) in the non-AAGA group, p = 0.278. Processed electroencephalogram monitoring was infrequent in the baseline cohort, used on only 148 (4.7%) patients across seven hospital sites. No AAGA patients received processed electroencephalogram monitoring. There were no cases of AAGA attributed to

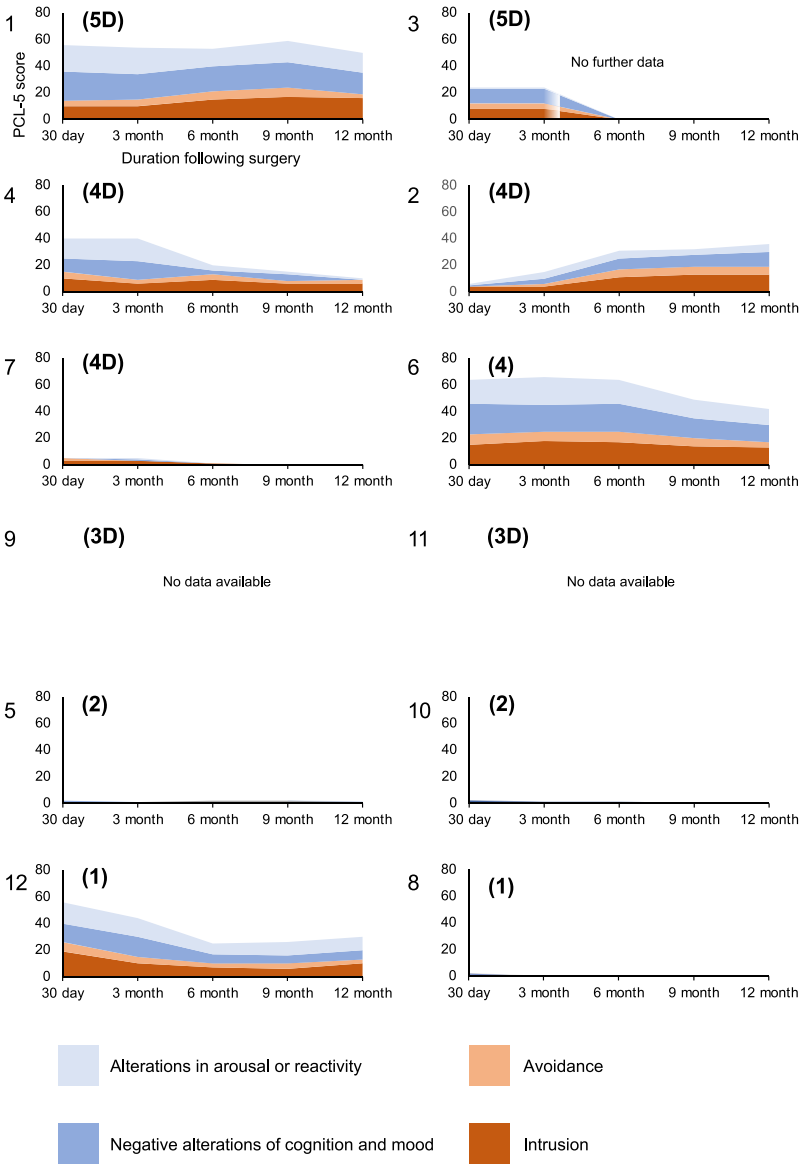

Figure 5 Psychological outcomes for each participant measured using PCL-5 scores. Each chart corresponds to a participant ID, with the Michigan Awareness Classification provided in parentheses ('D' designation is applied where the report described distress during the experience). The panels are arranged so that the higher Michigan classes are at the top, and the lower at the bottom. PCL-5 scores are grouped and labelled according to symptom clusters, as avoidance or intrusion symptoms etc. A PCL-5 score of between 31 and 33 is indicative of probable post-traumatic stress disorder.

wrong drug administration or syringe swap events. A consultant was the most senior anaesthetist present in theatre for only three (25.0%) of the AAGA patients, although one consultant attended only after the AAGA event had occurred. This was not significantly different to the proportion in the baseline cohort of 1216 (39.0%), p = 0.32.

In the binary regression model, deviation from a healthy reference BMI of 18.5–25 $kg.m^{-2}$ was significantly associated with AAGA, specifically, BMI < 18.5 (OR 18.1, 95%CI 1.0–318.9, p = 0.048) and BMI 25–30 (OR 10.8, 95% CI 1.23–93.8, p = 0.031). Although infrequently used as the primary induction drug, ketamine was over-represented in AAGA cases (OR 186, 95%CI 9.1–3824, p = 0.001). Thiopental use (OR 3.5; 95%CI 0.7–16.7) and start of general anaesthesia during a night shift (OR 3.3; 95%CI 0.61–18.2) were both significantly associated in univariate testing and had higher odds ratio of AAGA, but were not statistically significant; p = 0.122 and p = 0.163, respectively, in binary regression.

Table 4 provides abbreviated reports of each patient's experience of AAGA and a narrative description of individual psychological implications during the 12-month postoperative follow-up period (for detailed reports see online Supporting Information, Table S1). Distressing AAGA experiences in which fear, suffocation or a sense of impending death were reported occurred in seven (58.3%) patients (Fig. 3). Paralysis was reported by five (41.7%) patients, of whom two (16.7%) reported paralysis in conjunction with pain. A further two (16.7%) reported pain as the only feature of their AAGA experience. Four (33.3%) reported isolated auditory or tactile perceptions.

The PCL-5 scores during postoperative follow-up are provided in Figs 4 and 5. The PCL-5 scores at 30 days postoperatively were significantly higher in the 12 certain/probable and possible AAGA patients, (median (IQR [range]) 15 (2.7–52.0 [2–56]) than in the comparator cohort of 341 patients reporting no memories between 'going to sleep' and 'waking up' at the end of surgery; 3 (1–9 [0–64]), p = 0.010.

Four (33.3%) of the 12 AAGA patients met PCL-5 criteria, screening positive for PTSD (case IDs 1, 4, 6 and 12). All were referred for psychological support or mental health team review. A fifth participant (case ID 3) was marginally below the criteria, having only one, rather than the required two, significant symptom scores in the intrusion cluster, but scored a maximum total of 36 points at 12 months following her surgery, which is above the threshold of 31–33 points that is indicative of probable PTSD.

Accidental awareness under general anaesthesia was significantly associated with screening positive for PTSD (OR 32.4, 95%CI 1.6–662.0, p = 0.024), as was a diagnosis of postpartum depression (OR 25.4, 95%CI 2.4–274, p = 0.008). Other covariates in the regression model were not significant. These included: pre-term birth; history of depression; anxiety; PTSD; and low birth weight. Neither was self-perceived support from family or healthcare professionals, urgency of surgery or age. Four (1.17%) of the 341 patients in the non-AAGA comparator sample screened positive for PTSD compared with 4 out of 12 patients (33.3%) in the AAGA group. The odds ratio of developing PTSD following AAGA, compared with non-AAGA controls was 1 in 42.1 (95%CI 8.9–199.1).

Of the 12 patients with certain/probable or possible AAGA, seven (58.3%) were graded ≥ 1 on National Patient Safety Agency scores, indicating at least mild anxiety about future anaesthesia or intrusive psychological symptoms. Five (41.7%) patients were graded as 2 or 3, indicating moderate to severe anxiety about future anaesthesia or related healthcare, with symptoms having some impact on daily living. Due to withdrawal from follow-up, National Patient Safety Agency grades could not be allocated for two (16.7%) patients with possible AAGA.

Discussion

The main finding of the study is that the incidence of AAGA in obstetrics, assessed by using direct questioning, is almost three times higher than previously ascertained when relying on patient self-reports: 1 in 256 (95%CI 149–500) vs. 1 in 1200 (95%CI 714–2500) [2]. Both estimates are very much higher than the figure of 1 in 8000 reported for AAGA in the presence of NMB drugs for the general surgical population [2]. Almost two-thirds of the patients in our study described distressing experiences involving pain or paralysis during AAGA, and one-third of patients with AAGA met screening criteria for PTSD during 12 months of postoperative follow-up. The odds ratio of developing postnatal PTSD after AAGA was very high, at 1 in 42 compared with non-AAGA controls.

Previously, Paech et al., also using the Brice interview and similar adjudication criteria but without a detailed verification phase or any follow-up, reported an even higher incidence of 1 in 152 after caesarean section [14]. However, the use of thiopentone was very much higher in 2009 (83% in Paech et al. 's study vs. 52.9% in ours) and other changes in practice, perhaps informed by NAP5, may have reduced the incidence of obstetric AAGA somewhat. Intriguingly, the use of depth of anaesthesia monitors in the Paech et al. study was high (32% vs. 4.7% in our study), and this perhaps reflects its limited utility in preventing AAGA [22]. This limitation may also be because the majority of AAGA cases arise in the dynamic phases of anaesthesia (induction and emergence) when the interpretation of depth of anaesthesia monitors can be difficult, or they are not used during these phases.

Accidental awareness under general anaesthesia was a risk-factor for PTSD, with AAGA patients having a higher risk of developing PTSD and higher scores on the trauma symptomatology checklist. This finding extends previous research, where 9 out of 16 (56.3%) people who had experienced AAGA met criteria for PTSD compared with 0 out of 10 non-AAGA controls [23]. These participants were recruited retrospectively and AAGA occurred a mean of 17.9 years before, so it is plausible that people with distressing AAGA experiences were over-represented. However, data from the B-Aware randomised trial by Leslie et al. [24] showed comparable risks with prospective sampling. Accidental awareness during general anaesthesia cases were individually matched with non-AAGA controls. Five of seven AAGA cases (71%) met criteria

for PTSD compared with three (12%) of 25 controls. Our study confirms this serious risk of PTSD following AAGA in a prospective sample with a large control sample.

It is noteworthy that AAGA emerged as a strong additional risk, because childbirth is itself a risk-factor for PTSD [18]. Meta-analysis estimates that between 0.9 and 4.6% of women develop PTSD after childbirth [18]. Our figure of 1.17% for non-AAGA patients falls towards the lower end of this range, despite the additional complication of general anaesthesia and surgery occurring in our sample. Known predictors of PTSD, such as low social support, infant complications and history of mental health problems [18] were not significant covariates in our study, but there was an association between PTSD and postnatal depression [25, 26].

This study confirms the high incidence of AAGA in obstetrics, which was identified in NAP5 and persists despite putative changes in practice. Some patient risk-factors are immutable, such as the higher incidence of obesity and the difficult airway in obstetrics [15]. Some practices are constrained, such as the need to use NMB drugs, and we recently reported other practice changes [15]. The use of opioids appears to offer a little protection against AAGA (Fig. 2). It is plausible that opioids and prior neuraxial block attenuate pain responses. Even 'failed' neuraxial techniques may provide partial analgesia and obtund the arousal effects of higher intensity surgical pain that would otherwise lead to AAGA. Opioids have traditionally been avoided in obstetric general anaesthesia due to concerns about neonatal respiratory depression, although this rationale is not supported by current evidence [27].

The over-representation of thiopentone in the AAGA cases is striking (Fig. 2). Our data suggest that, compared with propofol, the risk of AAGA is increased four-fold when thiopentone is used for induction of anaesthesia and 26-fold when ketamine is used. It has recently been suggested that, based on EEG recordings, propofol induction maintains deeper anaesthesia than thiopental in pregnant women [28], so there may be a pharmacological basis to our observations. Regardless, it would now seem prudent to have a specific justification for the use of thiopentone or ketamine as induction agents in obstetrics, rather than consider these agents as default choices.

Our observation that night-shift operations with predominantly trainee-led anaesthesia were a risk-factor for AAGA suggests a complex problem that requires careful consideration. Working pattern changes take time to implement, and simply extending consultant hours or shifts may lead to other unintended consequences [29] or fail to improve outcomes.

We encountered two patients who reported AAGA but in fact had endured the complication of a total spinal (they were not included as part of the AAGA cohort). This highlights the reality that apparently unconscious patients can be fully aware of surroundings (akin to neuromuscular blockade without anaesthesia). While the focus of attention in this emergency scenario should be on cardiorespiratory resuscitation, it is also essential to ensure hypnosis to avoid potential psychological sequelae. Current recommendations are that hypnotic drugs should be given only when the clinical situation permits [30], but analysis of these patients' experiences suggests that the two interventions, resuscitation and anaesthesia, should go hand in hand.

Apart from practice issues, other factors could be contributing to the markedly increased incidence of AAGA in obstetrics. Childbirth is a time of heightened attention to surrounding events, such that brief episodes of AAGA may be magnified in recall, as are other details of the birthing experience [31]. Without the heightened attention, these experiences in the general surgical population, such as revealed using the isolated forearm technique [32], might be regarded as trivial and termed dysanaesthesia [33, 34]. This is a brain state in which uncoupling of perception from sensation results in a neutral experience, leaving patients unconcerned about potential awareness. In this regard, it is notable that the majority of our cases were also early self-reporters, and that repeated Brice interviewing did not yield a higher estimated incidence. In other words, obstetric patients are more likely to make a report of AAGA, perhaps due to their heightened attention.

Another possibility is that the hormonal changes associated with pregnancy influence memory, recall or even sensitivity to general anaesthesia and increase the likelihood of AAGA. Although the minimum alveolar concentration of volatile agents has been studied in animals and the first trimester of pregnancy in humans, and in both types of study has been shown to be reduced compared with non-pregnant women, it does not appear to have been studied in the third trimester. Uyema et al. [35] reported no effect of volatile anaesthetic sensitivity on electroencephalography in later stages of pregnancy compared with non-pregnant matched controls undergoing general anaesthesia.

As our study clearly shows, assessment of AAGA using a Brice questionnaire alone is inadequate, resulting in a misleadingly high incidence. The majority of 'positive Brice' responses were reports of dreaming or memories outside the period of anaesthesia, not AAGA. Therefore, at best, the Brice questionnaire should be viewed as a preliminary screening tool that could prompt recall in the patient's mind. Yet, given that the incidence we identified appears higher

than many other obstetric general anaesthetic complications [36], there is a case to suggest that a single screening assessment using Brice questions should become a routine follow-up procedure after general anaesthesia in obstetrics.

Our data also have implications for seeking consent for general anaesthesia. The Montgomery ruling by the UK Supreme Court in 2015 [37] concerned obstetric practice and a complication that arguably has a similar incidence (1 in 136 [38]) to the incidence of AAGA reported in our study (1 in 254). Logically, it would seem incumbent upon anaesthetists to cite this risk of AAGA within the consent process for obstetric general anaesthesia, as directed by the Supreme Court ruling.

Whilst some cases of AAGA may have been preventable by the practice changes discussed above, others occurred without any obvious deficiency in general anaesthetic drug delivery. A previously undiagnosed suxamethonium apnoea episode triggered one patient's AAGA experience. Plasma pseudocholinesterase activity is known to fall rapidly during the first trimester and remain reduced into the immediate postpartum period [39]. This is of particular concern, given that nerve stimulator monitoring use was suboptimal in the baseline group [15].

It is important to acknowledge some methodological limitations to this study, some of which we have discussed elsewhere [15, 16], and many of which are common to all studies using the Brice interview. Administering this process involved two key steps, the patient interview followed by an adjudication process. The details of the latter can vary across studies [40] and the rarity of AAGA events means that minor methodological inconsistencies within or between studies can influence the final result. We, therefore, employed the same adjudication structures as NAP5 and introduced the κ score, which at least confirmed consistency within our adjudication panel (Table 2).

Although 3115 patients completed the first Brice interview, only 1808 also completed the third and 42% were 'lost to follow-up'. However, we used as our denominator the original 3115; our estimate of incidence is very conservative and assumes that all these patients not followed-up did not have AAGA memories. This is a safe assumption since we detected no new cases of AAGA with repeated Brice questioning. If even a small proportion of those lost to follow-up experienced AAGA, then our estimate of incidence would be very much higher than we report. Therefore, although we were disappointed not to follow-up even more patients all the way to their third Brice interview, this does not affect our striking result of a very high incidence of AAGA in obstetrics. Action is needed to reduce this very high risk and national consensus guidelines would help to ensure consistency of anaesthesia practice. With the high incidence of AAGA and association with psychological harm, follow-up and support for patients and staff is also necessary. The NAP5 psychological support pathway is a useful guide [19], but may need refinement for the obstetric setting. Attention should also focus on the process of seeking consent from a pregnant patient receiving general anaesthesia.

Acknowledgements

Research Ethics Committee and Health Research Authority approvals were granted alongside prospective registration of the trial aims (ClinicalTrials.gov: NCT03100396). We wish to thank the allied trainee research networks that supported this study: South East Anaesthetics Research Chain (SEARCH); Oxford Critical Care and Anaesthetics Research Enterprise (OxCCARE); Southcoast Peri-operative Audit and Research Collaboration (SPARC); South Yorkshire Hospitals Audit and Research Collaboration (SHARC); and Midlands East Research by Critical Care and Anaesthetic Trainees (MERCAT). We also wish to thank K. Fox for her assistance with study co-ordination and patient follow-up. JP was the clinical lead for the 5th National Audit Project, is an elected Council member of the Royal College of Anaesthetists (RCOA) and Chair of the Safe Anaesthesia Liaison Group. DL chairs the OAA Education subcommittee and is a senior editor for the *International Journal of Obstetric Anesthesia*. RM holds senior and advisory positions in the Health Services Research Centre (RCOA) and NHS England. The views expressed are individual and not representative of those organisations. This work was supported by an Obstetric Anaesthetists' Association research grant. No other competing interests declared.

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Appendix 1

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Supporting Information

Additional supporting information may be found online via the journal website.

Table S1. Full narrative reports of accidental awareness during general anaesthesia experiences and postoperative follow-up psychological outcomes.