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Original Article

Anaphylaxis in pregnancy: a population-based multinational European study*

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Summary

Anaphylaxis in pregnancy is a rare but severe complication for both mother and infant. Population-based data on anaphylaxis in pregnancy are lacking from mainland European countries. This multinational study presents the incidence, causative agents, management and maternal and infant outcomes of anaphylaxis in pregnancy. This descriptive multinational study used a combination of retrospective (Finnish medical registries) and prospective population-based studies (UK, France, Belgium and the Netherlands) to identify cases of anaphylaxis. Sixty-five cases were identified among 4,446,120 maternities (1.5 per 100,000 maternities; 95%CI 1.1–1.9). The incidence did not vary between countries. Approximately three-quarters of reactions occurred at the time of delivery. The most common causes were antibiotics in 27 women (43%), and anaesthetic agents in 11 women (17%; including neuromuscular blocking drugs, 7), which varied between countries. Anaphylaxis had very poor outcomes for one in seven mothers and one in seven babies; the maternal case fatality rate was 3.2% (95%CI 0.4–11.0) and the neonatal encephalopathy rate was 14.3% (95%CI 4.8–30.3). Across Europe, anaphylaxis related to pregnancy is rare despite having a multitude of causative agents and different antibiotic prophylaxis protocols.

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Introduction

Anaphylaxis is a severe immune hypersensitivity disorder that is rapid in onset and occurs without premonitory signs. It often involves compromise to the cardiovascular, respiratory, cutaneous and gastro-intestinal systems, and in pregnancy can result in severe morbidity and mortality for both mother and infant [1].

The majority of the literature on anaphylaxis in pregnancy consists of case series and case reports, with limited high quality studies [1, 2]. To date, only two population-based studies have described anaphylaxis in pregnancy; a UK study showed an incidence of 1.6 per 100,000 maternities [3], while a national hospital database study in the USA identified an incidence of 3.8 per 100,000 pregnancy-related hospitalisations [4]. There are no population-based studies examining anaphylaxis in pregnancy in continental European countries.

As anaphylaxis in pregnancy is very rare, national studies from small populations may not accrue sufficient cases unless they are conducted for long periods; on the other hand, multinational studies are able to provide larger numbers that enable more precise estimates of incidence [5]. This study aimed to estimate the incidence, causative agents, management and outcomes of anaphylaxis in pregnancy across Europe using both prospective and retrospective data collection methods.

Methods

Anaphylaxis is defined as a severe, life-threatening generalised or systemic hypersensitivity reaction [6]. It is diagnosed by the presence of at least one of the following criteria: a life-threatening airway problem; life-threatening breathing problem; life-threatening circulatory problem (Fig. 1); in addition, there is sudden onset and rapid progression of symptoms. For inclusion in this study, such a reaction must have occurred at any point during pregnancy or up to 48 h after delivery. In addition, women were not included if the senior attending obstetrician or anaesthetist did not consider the case to be anaphylaxis on clinical grounds.

Women that had anaphylaxis during pregnancy were prospectively identified at a national level in the UK, Netherlands, France and Belgium. The UK data were collected using the UK Obstetric Surveillance System [7]; this study has been published previously [3]. In Belgium and the Netherlands, cases were notified through the respective Belgian Obstetric Surveillance System (B.OSS) and Netherlands Obstetric Surveillance System (NethOSS) [8, 9]. Women in Finland were retrospectively identified in the Finnish Medical Birth Registry linked to the Hospital Discharge Register [10]. A detailed description of data collection is presented in Table S1, and the methodology in each country is presented in Table S2.

The online data collection form used in France, Belgium, Finland and the Netherlands was a modified version of the UKOSS data collection form, with the majority of variables being the same. Identification of the study population is shown in Figure S1. Anonymised information on maternal characteristics, previous medical history, suspected causes and management of anaphylaxis, and maternal and perinatal outcomes of notified cases were entered. The online data collection used the OpenClinica system [11].

The incidence is presented as rate per 100,000 maternities, with the 95%CI estimated using the binomial distribution. Initially, the characteristics of women, management, causative agents and outcomes between the countries were checked to assess comparability. The Chi-squared test was used to assess statistical difference between categorical variables and countries; if there were no statistically significant differences between the countries, they are presented as a combined cohort. Management was different between the UK and mainland Europe, and as a consequence the results are presented separately. Women were categorised according to when the anaphylactic reaction occurred in relation to delivery. These groups included: antenatal (not in delivery suite or theatre); intrapartum (immediately before delivery); and post-delivery (up to 48 h after delivery). Women were categorised using the time of anaphylaxis and time of delivery, suspected causative agent and additional information included in the case notes. It is possible that management and causative agents may have changed over a 10-year period, so a sensitivity analysis was carried out in Finnish women who had anaphylaxis before 2012 to assess any difference in the management and causative agents. Analyses were completed using Stata version 13 (StataCorp LLC, College Station, TX, USA).

Results

There were 65 confirmed cases of anaphylaxis in 4,446,120 maternities, giving an estimated incidence of 1.5 per 100,000 maternities (95%CI 1.1–1.9; Table 1). The Netherlands was unable to collect data for its two reported cases due to changes in the General Data Protection Regulation guidance given to obstetricians in the Netherlands. Results are presented for the remaining 63 cases.

The characteristics of the women are given in Table 2. The majority of reactions, 35 (56%), occurred before delivery, with 16 (25%) reactions occurring in the antenatal

The presence of at least one of the following:
1. A life-threatening airway problem is taken to include:
- Laryngeal or pharyngeal oedema
- Hoarse voice
- Stridor

2. A life-threatening breathing problem is taken to include:
- Shortness of breath and raised respiratory rate
- Wheeze (laryngospasm or bronchospasm)
- Decreased oxygen saturations
- Confusion secondary to hypoxia
- Cyanosis
- Respiratory exhaustion or respiratory arrest

3. A life-threatening circulatory problem is taken to include:
- Signs of shock such as faintness, pallor or clammy skin
- Tachycardia > 100 beats min^{-1}
- Systolic pressure < 90 mmHg or diastolic pressure < 60 mmHg or measured hypotension
- Decreasing level of consciousness
- Signs of ischaemia on ECG
- Cardiac arrest

Figure 1 Clinical criteria for a diagnosis of anaphylaxis

period (not related to delivery), and 19 (30%) occurring immediately before delivery. Reactions immediately after delivery made up over a third of all reactions (Fig. 2). The timing of reactions according to country and mode of delivery is presented in Table S3. Three out of fourteen women who had a known penicillin allergy were given a penicillin-based antibiotic resulting in an anaphylactic reaction; two women with a known penicillin allergy had a reaction to a cephalosporin.

The majority of the reactions that occurred immediately before delivery, 18 (95%) occurred in women having a caesarean section. Four reactions occurred after administration of anaesthetic agents, three followed suxamethonium and one followed administration of spinal anaesthesia. Figure S2 and Table S4 show that there was only one reaction caused by prophylactic antibiotics before a caesarean section in France and Belgium, and there were no cases in Finland. Two of the three reactions that were the result of antibiotics given for the prophylaxis of Group B streptococcus occurred in France. In those who had reactions after delivery, 12 (43%) women had a reaction to an agent given for the management of a postpartum haemorrhage.

Reactions related to anaesthesia occurred in 11 (17%) women (Fig. 2). The suspected agents were: suxamethonium 6; suxamethonium or thiopental 1; lidocaine 1; sugammadex 1; unspecified agent but temporally related to anaesthesia 2.

IgE testing was completed in 9 (32%) women in mainland Europe (this question was not asked in the UK). Seven of nine women had a specified antigen identified; four had an anaesthetic agent confirmed (suxamethonium 3; sugammadex 1) and three had a penicillin-based agent

Table 1 Incidence of anaphylaxis in pregnancy across countries.

Country	Anaphylaxis in pregnancy	Maternities	Rate per 100,000 (95%CI)
UK	35	2,324,522	1.5 (1.1–2.1)
France	17	1,125,495	1.5 (0.9–2.4)
Finland	9	642,430	1.4 (0.6–2.7)
Netherlands[a]	2	173,013	1.2 (0.1–4.2)
Belgium	2	180,660	1.1 (0.1–4.0)
Combined	65	4,446,120	1.5 (1.1–1.9)

[a]Excluded from further analysis – see text.

Table 2 Characteristics of 63 women with anaphylaxis in pregnancy in the INOSS study. Values are mean (SD), number (proportion) or median (IQR [range]).

Physical characteristics		
Age[a]	31.7	(6.7)
Smoking status[b]		
Never/ex-smoker	45	(77.6%)
Smoked during pregnancy	13	(22.4%)
Gestational age at delivery[c]	39	(37–40 [27–41])
BMI[d]	26	(23–29 [18.5–44.6])
Obstetric characteristics		
Parity		
0	20	(31.7%)
≥ 1	43	(68.3%)
Previous pregnancy problem	20	(31.7%)
Multiple pregnancy	4	(6.3%)
Previous medical history		
Previous anaphylactic reaction	7	(11.1%)
Known drug allergy[a]	19	(30.6%)
Penicillin-based	14	(22.6%)
Other	5	(8.1%)
History of atopy[e]	20	(32.8%)
History of any allergic reaction	34	(54.0%)
History of any allergic reaction or atopy	38	(60.3%)

[a]n = 62.
[b]n = 58.
[c]n = 56.
[d]n = 59.
[e]n = 61.

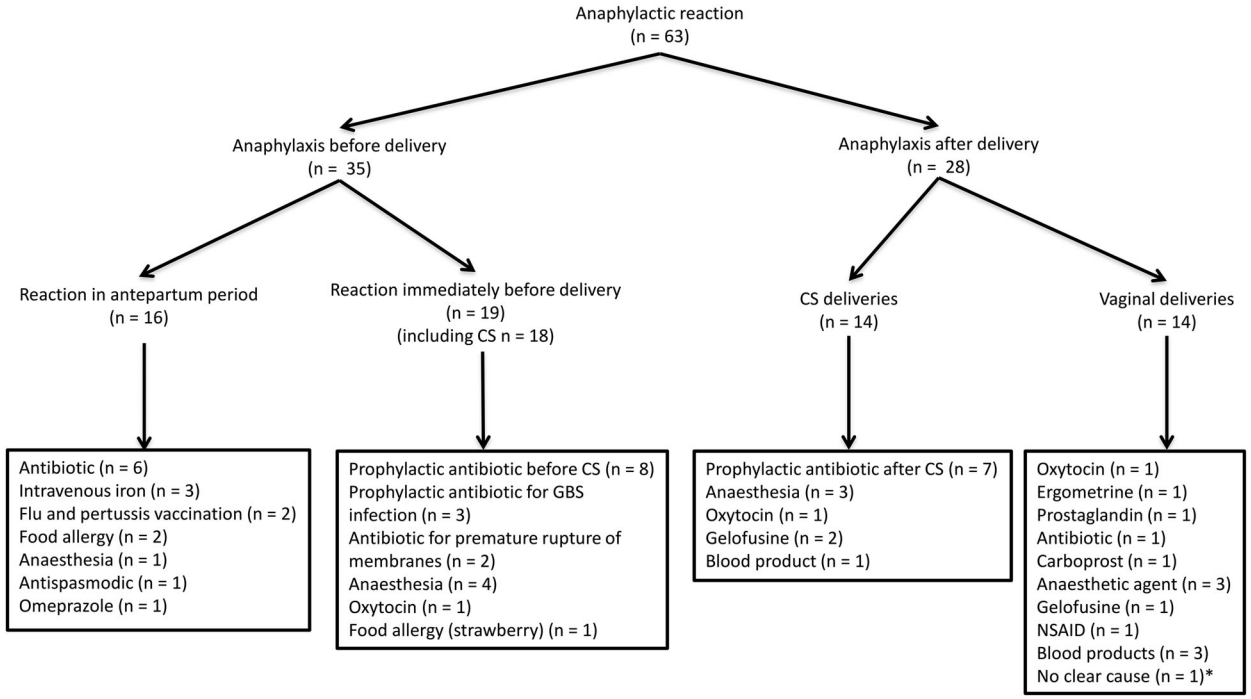

Figure 2 Timing of anaphylaxis in the INOSS study and suspected causative agents. * multiple agents including latex, penicillin, prostaglandin and temazepam. CS, caesarean section; GBS, Group B streptococcus; NSAID, non steroidal anti-inflammatory drug.

confirmed. Peri-operative anaphylaxis occurred in 36 (57%) women. The suspected causative agents for these women were as follows: 20 (56%) women had a reaction to an antibiotic; anaesthetic agents caused 11 (31%) reactions; and five (14%) reactions were the result of other agents. No anaesthetic-related reaction was associated with epidural analgesia during labour.

The UK and mainland European countries had similar proportions of women receiving oxygen and intravenous fluid to manage the reaction (Table 3). There was a difference in the proportion of women receiving adrenaline, 19 (68%) in Finland, Belgium and France combined vs. 27 (93%; $p = 0.016$) in the UK. A sensitivity analysis was performed without including the women from Finland who had a reaction before 2012. In this restricted cohort, 44 (85%) women received adrenaline, while 45 (88%) received corticosteroid and 29 (67%) received antihistamine.

Two women died giving a case fatality rate of 3.2% (95% CI 0.4–11.0), one from suxamethonium and one from amoxicillin combined with clavulanic acid (Co-amoxyclav; Table 4). There were no perinatal deaths or stillbirths to mothers who had anaphylaxis before delivery. The proportion affected by neonatal encephalopathy was 14.3% (95%CI: 4.8–30.3; Table 5).

Table 3 Management of anaphylaxis in pregnancy in UK compared with European nations. Values are number (proportion of those with information).

	France, Belgium and Finland (n = 28)	**UK (n = 35)**	**Combined (n = 63)**
High flow oxygen			
Yes	22 (88.0%)	27 (79.4%)	49 (83.1%)
No	3 (12.0%)	7 (20.6%)	10 (16.9%)
Intravenous fluid			
Yes	25 (92.6%)	30 (85.7%)	55 (88.7%)
No	2 (7.4%)	5 (14.3%)	7 (11.3%)
Epinephrine			
Yes	19 (67.9%)	27 (93.1%)	46 (80.7%)
No	9 (32.1%)	2 (6.9%)	11 (19.3%)
Antihistamine			
Yes	3 (20.0%)	26 (86.7%)	29 (64.4%)
No	12 (80.0%)	4 (13.3%)	16 (35.6%)
Corticosteroid			
Yes	17 (77.3%)	32 (97.0%)	49 (89.1%)
No	5 (22.7%)	1 (3.0%)	6 (10.9%)
Tryptase tested	14 (53.8%)	30 (85.7%)	44 (72.1%)
Tryptase raised	11 (84.6%)	8 (32.0%)	19 (50.0%)

Table 4 Severe maternal outcomes in 63 women with anaphylaxis. Values are number (proportion).

Death	2	(3.2%)
Severe morbidity including death	9	(14.3%)
Cardiac arrest	3	(4.8%)
Thrombotic event	2	(3.2%)
Other[a]	4	(6.3%)
ICU admission[b]	28	(45.2%)
Intubation required[c]	13	(48.1%)

[a]One each of: acute renal injury, acute cardiac failure and thrombocytopenia; respiratory distress or failure; stress cardiomyopathy; hypoxic brain injury.
[b]n = 62.
[c]Only collected in France, Belgium and Finland (n = 27).

Table 5 Perinatal outcome information available from 35 infants of women who had an anaphylactic reaction before delivery. Values are number (proportion).

Perinatal death[a]	0
Neonatal ICU admission[b]	12 (35.3%)
Neonatal encephalopathy	5 (14.3%)
Baby cooled	4 (11.4%)
Unknown	1 (2.9%)
Apgar ≤ 6 @ 5 min[c]	5 (16.1%)

N.B. four infants were included from two multiple pregnancies.
[a]n = 33.
[b]n = 34.
[c]n = 31.

Discussion

There appears to be a similar incidence of anaphylaxis in pregnancy across five European countries, affecting 1.5 per 100,000 women among almost 4.5 million births. Most reactions occurred at or around the time women gave birth. There was variation in the diagnosis and management of anaphylaxis between the UK and mainland Europe.

The main causative agents for anaphylaxis were antibiotics and anaesthetic agents, in particular neuromuscular blocking drugs [1, 2]. Similar to previous studies, the most commonly suspected causative agent was an antibiotic [2, 12], given either prophylactically for Group B streptococcus [12–14] or for surgical prophylaxis [2]. Three women had anaphylaxis following antibiotic administered for Group B streptococcus, including two in France and one in the UK. Over a fifth of reactions were found to be the direct result of prophylactic use of antibiotics at the time of caesarean section [15, 16]. Half of these reactions occurred once the caesarean section had been carried out. Importantly, had the antibiotics been administered before surgery, the burden of infant morbidity may have been higher. In Finland and France, prophylactic antibiotics were given at induction (before skin incision). The majority of women who had a peri-operative reaction did not receive an IgE specific test to confirm the causative agent involved, which would have important implications for future surgical procedures.

The findings from this study are similar to that of the 6th National Audit Project (NAP6); in particular, antibiotics and neuromuscular blocking drugs were the primary suspected causative agents [17]. It is interesting to note that suxamethonium was the only neuromuscular blocking agent used in this study, whereas rocuronium was the most common agent in NAP6 [17]. This may be explained by preferential use of suxamethonium during induction of general anaesthesia at caesarean section [18]. Furthermore, a previous study in France reported that neuromuscular blocking drugs were the main causes of maternal death from anaphylaxis [19]. It is important that allergy to neuromuscular blocking drugs is identified to guide management of future general anaesthesia.

Three women who had known penicillin allergies were administered the drug resulting in an anaphylactic reaction. This highlights that these cases were preventable, and indicates that a detailed drug allergy history must be taken at booking and immediately before administration of any antibiotics. Human factors have been demonstrated to play a role in medication errors [20]. The World Health Organization surgical checklist should be undertaken before caesarean section to reduce the risk of medical error [21], and we suggest that this concept might be extended to women having vaginal delivery.

The study findings show that an even lower proportion of women received adrenaline in mainland Europe compared with the UK. The NAP6 project stated that there was a low mortality rate from anaphylaxis, which was likely to be a consequence of the early detection and management of reactions [17]. Current guidelines recommend adrenaline as first line management of anaphylaxis, and timely use will prevent hypoxia and mortality [22–24]. In order to improve management, the anaphylaxis algorithm should be immediately available in operating theatres and delivery suites [6, 25].

This study has shown poor outcomes for women who have anaphylaxis, with a 3.5% case fatality rate and 11% of women suffering additional severe morbidity. The Confidential Enquiries into Maternal Deaths in the UK and France report a similar case fatality for anaphylaxis related to pregnancy [19, 26]. Furthermore, there were severe outcomes for infants, with a third of

infants admitted to neonatal ICU, one in six infants with abnormal Apgar scores, and one in seven with neonatal encephalopathy that required therapeutic cooling. This is consistent with previous case series and literature reviews [1, 2].

This multinational study, which included three countries with obstetric surveillance systems and two other countries using similar methodologies, has provided a large-scale study of a very rare complication of pregnancy. The prospective study design has the added advantage of being able to use a uniform case definition across nations. For the Finnish registry data, the method of case ascertainment allowed routinely identified cases of anaphylaxis to be validated against hospital records. This prevented false positives from being included in the study dataset.

Prospective studies have the same limitations as national surveillance systems, as they rely on reporters to identify cases within each maternity unit and are susceptible to under-ascertainment. In the case of the Netherlands, we had no reported cases entered into the data entry system; as a result, they were only included in the estimate of incidence. For the Finnish registry data, case notification relied on ICD-10 codes for the identification of cases with anaphylaxis. Consequently, the sample was still vulnerable to false negatives, and was reliant on the accuracy of the coding of clinical data for the identification of women with anaphylaxis. The validation of cases resulted in the removal of over half of the women identified using ICD-10 codes. In addition, as the sample was retrospective, it is possible that the management of anaphylaxis was historically different to that during the period of the prospective data collection for the rest of the study.

In conclusion, across five European countries, anaphylaxis related to pregnancy is similarly rare, despite having a multitude of causative agents and different prophylaxis protocols. It is imperative that current international management protocols are followed, which include immediate administration of adrenaline. Against the background of increased medicalisation of childbirth, an accurate drug allergy history and a visible signal of an allergy, for example, a coloured wristband, may prevent a medical error from causing a potentially fatal reaction.

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Supporting Information

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

Figure S1. Flow diagram of the study population: A registry-based study using Finnish registry data 2004-2014 and prospective studies in UK (2012-2015), Belgium, France and the Netherlands (2016-2018).

Figure S2. Suspected causes of anaphylaxis in pregnancy in Belgium, France and Finland. *indicates Finnish case **includes one Finnish case.

Table S1. Summary of the case identification from each country.

Table S2. Summary of data collection from each country.

Table S3. Timing of anaphylaxis by country and mode of delivery.

Table S4. Suspected cause of anaphylaxis by country.

