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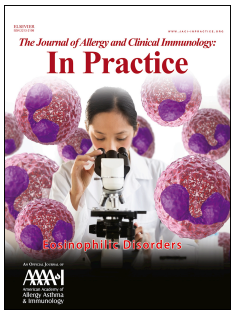

ANAPHYLAXIS AND PREGNANCY: A SYSTEMATIC REVIEW AND CALL FOR PUBLIC HEALTH ACTIONS

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ANAPHYLAXIS AND PREGNANCY: A SYSTEMATIC REVIEW AND CALL FOR PUBLIC HEALTH ACTIONS

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CONTRIBUTIONS:

The first and last authors contributed to the construction of the document (designed the study, including the questionnaire, analysed and interpreted the data, and wrote the manuscript). All the authors critically revised and approved the final version of the manuscript and agree to be accountable for all the aspects of the work.

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Highlight Box

1. **What is already known about this topic?** Although rare, anaphylaxis during pregnancy implies a risk to both mothers and newborns.
2. **What does this article add to our knowledge?** Risk factors for anaphylaxis during each trimester were identified, such as history of multiple cesareans/procedures, personal history of anaphylaxis and/or allergic reaction to medication without allergy work-up.
3. **How does this study impact current management guidelines?** Identification of patients at-risk and bilateral collaboration between different specialists involved in the care of pregnant women should be established in order to support preventive strategies.

ABSTRACT

Background: Although rare, anaphylaxis during pregnancy implies a risk to both mothers and newborns.

Objective: This systematic review is intended to identify key issues in the diagnosis and management of this condition in order to support prevention strategies and decrease the risk of death related to anaphylaxis during pregnancy.

Methods: We searched MEDLINE, Cochrane, Lilacs, Scielo and Science Direct databases for manuscripts concerning terms "anaphylaxis during pregnancy" without language restrictions. We screened studies, extracted data, and assessed risk of bias independently in duplicate.

Results: We selected 12 articles. Frequency of anaphylaxis during pregnancy is estimated between 1.5 to 3.8 per 100 000 maternities. Only one study provided anaphylaxis mortality data in pregnant women, and the rate of anaphylaxis-related maternal mortality is estimated at 0.05 per 100 000 live births. No standard definition of anaphylaxis severity has been utilized. Forty-nine percent to 74% of anaphylaxis cases were described during caesarean sections. Beta-lactam antibiotics (58%), latex (25%) and anaesthetic agents (17%) were the main culprits. In 17% of papers, causative agents were proven by allergy testing. Seventy two percent of articles proposed the same management and treatment for a clinical episode of anaphylaxis during pregnancy as in non-pregnant patients, and, use of epinephrine in the patient's care during anaphylaxis in pregnancy.

Conclusion: Few studies address anaphylaxis during pregnancy, and the majority have been produced by non-allergy specialists. Collaboration between different specialists involved in the care of pregnant women should be established in order to support preventive strategies and reduce avoidable deaths.

KEYWORDS: anaphylaxis, epidemiology, management, perioperative anaphylaxis, pregnancy, prevention

ABREVIATIONS

EAACI : European Academy of Allergy and Clinical Immunology

ENDA : European Network of Drug Allergy

ICD-9-CM : International classification of diseases, ninth revision, clinical modification

ICD-11 : International classification of diseases 11th Revision

NMBA : Neuromuscular blocking agents

NRL : Natural rubber latex

SPT : Skin prick test

UK : United Kingdom

USA : United States of America

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INTRODUCTION:

Anaphylaxis is a generalized hypersensitivity reaction with an acute onset after exposure (minutes to several hours) to a triggering factor [1, 2]. The lifetime prevalence of anaphylaxis is currently estimated at 0.05-2 % in the USA and about 3 % in Europe [3]. In fact, it can occur at any time of the life cycle, and it requires special attention when it happens in pregnant women because it implies a potential risk of fatality to both mother and fetus/newborn and can lead to sequelae in newborns related to brain anoxia and encephalopathies [4].

Although anaphylaxis during pregnancy is a known life-threatening reaction involving two lives at the same time, there are only a paucity of articles addressing this critical condition.

In pregnant women, clinical signs of anaphylaxis can be different from non-pregnant women, which may hinder the recognition of this condition [5]. For instance, blood pressure values in pregnant women tend to be lower than non-pregnant women, which could lead to the delayed diagnosis of an initial anaphylactic shock. Cutaneous signs could be absent in about 35% of cases [4]. These are reasons why clear definition of anaphylaxis during pregnancy and guidelines would be helpful to identify the reaction and avoid risk to two patients.

Management of anaphylaxis in pregnant women has been controversial over the past decades due to doubts regarding the safety of epinephrine use in pregnant women [6, 7]. Consensus guidelines among different specialists involved in the care of pregnant women, such as obstetricians, anesthetists, pediatricians, and allergists would harmonize the management of this health problem and facilitate optimal patient care. The lack of collaboration between specialties makes the identification of patients at-risk difficult and increases the risk for both the mother and the newborn.

This systematic review evaluates published data related to anaphylaxis during pregnancy and the potential risk factors in order to identify key issues in the diagnosis and management of this condition. Evidence-based data may support prevention strategies and certainly are the first step towards guidelines production.

METHODS

PROTOCOL AND ETHICS

This systematic review was performed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (PRISMA 15) [8].

No ethical approval was required for the performance of this work.

STRATEGY OF SEARCH

We searched for all published data to identify articles related to anaphylaxis during pregnancy in Pubmed, Science Direct, Cochrane, Scielo and Lilacs websites, with no language restrictions. The search was performed on the 1st of August 2020. The MeSH terms used were: “anaphylaxis” AND “pregnancy” or “anaphylaxis during pregnancy”. All the articles were screened in parallel by two independent authors. In all cases, disagreements were openly discussed among the co-authors. The Cohen's kappa coefficient demonstrated high agreement between the two reviewers (Kappa = 0.82).

Inclusion and exclusion criteria

As exclusion criteria we considered publications related to: in-vitro studies, animal studies, case reports, conference abstracts only, articles older than 1992, and articles without clear relation to our subject (Figure 1).

Studies were reviewed by two independent authors who screened full-text selected articles, and included studies were approved by all co-authors. In all cases, disagreements were openly discussed among the co-authors.

Data analysis and outcomes

Data abstracted from eligible studies were related to study design, population characteristics, rates of anaphylaxis morbidity (Table 1), triggers, clinical patterns, and management (Table 2). From a total of 733 initially identified articles, 12 reports describing epidemiological data, diagnostic features, triggers, and risk factors for anaphylaxis during pregnancy were selected to undergo the qualitative assessment of the study (Figure 1). Articles included in the final review are summarized in tables 1 and 2

RESULTS

Of the 12 articles, 5 (42%) are original articles, 4 (33%) are reviews, and the others are each of an editorial, case series, and correspondence. Only one original article is mentioned in 3 reviews, none of the others were cited in the reviews.

Six (50%) of these articles were published in anesthesia journals, 5 (42%) in allergy journals, and 1 (8%) in a gynecological journal. From overall 12 articles, 6 were published by anesthesiologists, 5 by allergists, 1 by gynecologists. Seven articles were studies focused on diagnosis and management of anaphylaxis during pregnancy (58%). Seventeen percent of articles (2) were written by anesthesiologists and allergists together but no international consensus between specialties about anaphylaxis in pregnant women is provided excepted for the French recommendations, endorsed by the European Network of Drug Allergy (ENDA) in 2011 [9].

Nine of the 12 articles were published after 2012 (75%), two articles between 2000 and 2006 (17%), and one in 1992 (8%). Half of the studies were carried out in Europe, 1 study including many European

countries (8%), 2 studies in the United Kingdom (16%), 2 studies in Italy (16%) and one in France (8%). 25% of studies were carried out in USA.

Most of articles (7/12, 58%) did not mentioned any definition of anaphylaxis. A definition of anaphylaxis was mentioned in 2 articles (16%) but did not provide the references. The Ring and Messmer anaphylaxis degree of severity was used in 3/12 articles, but the remainder of the publications simply described the clinical manifestations.

From the 4 epidemiological articles covering a total of 483 cases of anaphylaxis in pregnancy, three used national databases as the source of data, and two utilized the International Classification of Diseases (ICD)-9 CM to access the data. Three covered morbidity statistics (including the incidence, causative agents, frequency of triggers of anaphylaxis, management and associated outcomes of this condition) and one included mortality data.

Frequency of anaphylaxis during pregnancy was estimated to be 1.5 to 3.8 per 100 000 maternities, depending on the populations studied [4,10,11].

The mortality rate in pregnant women with anaphylaxis varied from 0% to 5% [4,10,11,12]. Forty-nine to 74% of anaphylaxis cases were described during caesarean sections [4,10,11]. In the only article reporting mortality of pregnant women due to anaphylaxis [13], all of the five deaths were during cesarean section. In 7 articles, differences regarding causative agents between vaginal versus cesarean delivery were not detailed. Four articles described detailed causative agents across terms of pregnancy and time in relation to delivery (pre, during and post), remaining articles covered broader list of possible triggers (Table 3). Among women presenting with anaphylaxis during pregnancy, 12% with a suspected or proven allergy prior to the pregnancy received the same molecule during the pregnancy, leading to a clinical allergic reaction (12.5% - 11.7%) [4,10].

The most common causative agent of anaphylaxis during pregnancy was not different across time in relation to delivery (pre, during and post).

Beta-lactam antibiotics (58%), latex (25%) and anaesthetic agents (17%) were the main culprit agents in the reviewed studies. In 2/12 studies an allergy work-up was performed, while in the remainder, no etiological investigation was performed. In the study focusing on mortality, the main causative agent was neuromuscular blocking agents.

For anaphylaxis occurring during a general anesthesia (usually used for emergency cesarean section or due to a suspicion of allergy to the local anesthetics) general anesthetics are by far the most frequently involved and the mortality rate is higher because they are often urgent cesarean sections. [13]

Frequent triggers and differential diagnosis according to the period of pregnancy (before or during/after the delivery) are shown in Table 3. In general, before labor and delivery, the causative agents and differential diagnosis of anaphylaxis are the same as in non-pregnant women. During labor

and delivery, the most frequent differential diagnoses are amniotic fluid embolism, preeclampsia/eclampsia-associated symptoms, laryngopathy gravidarum and seizures.

Although without proper statistical calculation, 1 article (16%) mentioned specific cofactors: cesarean delivery, clinical past history of allergic reaction, and black race. Five articles (42%) identified latex allergy or antecedent clinical reaction to latex as a risk factor for anaphylaxis during pregnancy.

Most of the articles (among articles proposing a management strategy, 71%) proposed the same management and treatment for a clinical episode of anaphylaxis during pregnancy as in non-pregnant patients, and, all of the articles in which management guidelines were available (n =7, 58%) recommend the use of epinephrine in the patient's care during anaphylaxis in pregnancy. However, no details regarding dose of epinephrine or position of the patient were detailed. No details regarding serum tryptase were available in any of the reports. Epinephrine has been administered in 125 (25.8%) cases of all 483 anaphylaxis reported in the selected articles.

DISCUSSION

We here present the first systematic review on the management of anaphylaxis during pregnancy. We were able to identify key issues related to this specific condition, and the outcomes of our manuscript supports the identification of potential phenotypes at risk for developing anaphylaxis, who should be the target for preventive measures. We could also highlight the need for strengthening the collaboration between specialists involved in the care of these patients, both during the acute phase and in the follow-up.

It is rather surprising to find so few articles specifically related to anaphylaxis during pregnancy, which is concerning, considering the potentially negative consequences of gestational anaphylaxis to both mothers and newborns. The majority of reports were descriptive and reviews. The restricted number of clinical trials in this population is expected due to logistical and ethical considerations [14]. However, epidemiological studies were also very limited, with only two populational-based studies. In the two manuscripts using national databases, the ICD-9 (or modifications) was the basis of the search. All of the guidelines were specialty-centered. Although it seems that anaphylaxis during pregnancy is a field of interest of many specialists, namely allergists, anesthesiologists, and gynecologists/obstetricians, there are very few manuscripts authored by different specialists in collaboration.

The frequency of anaphylaxis during pregnancy is estimated to be 1.5 to 3.8 per 100 000 maternities [10], depending on the populations studied. Although with limited epidemiological studies, the data may have been influenced by changes over the period of the study, such as the decline of latex allergy after 2000, the lack of availability of serum tryptase measurement in most areas prior to 2005-2010,

or the identification of Mast Cell Activation Syndrome (MCAS) only after 2010. Only one study included anaphylaxis mortality data in pregnant women, and the incidence of anaphylaxis-related maternal mortality is estimated at 0.05 per 100 000 live births [13]. Data show that the mortality is higher when a general anesthesia has to be used, most often for an emergency cesarean section. In this case, muscle relaxants are the substances most often involved [13].

Mortality rate in women experiencing anaphylaxis during pregnancy was estimated at 5% [4]. The mortality rate is low, and the morbidity data is in need of information regarding hospitalization duration, intensive care unit admissions and sequalae.

Only 25% of articles mentioned the negative impact in newborns, notably, encephalopathies, transfer to intensive care unit, and preterm births [4, 5]. Although two negative fatal outcomes of anaphylaxis (maternal deaths, newborn deaths) are possible, very few articles describe data related to the post-partum period [4,10,13].

Physiological characteristics of pregnancy such as the baseline blood pressure can delay the diagnosis of anaphylaxis. Lack of consensus regarding the definition of anaphylaxis in the studies may reflect the difficulties in clinical practice of the prompt recognition of anaphylaxis during pregnancy. In order to standardize the definition of anaphylaxis, allergy academies propose clear definitions of anaphylaxis, such as the WAO recent definition [1].

A broader method to increase the accuracy of anaphylaxis data is through international classifications. The WHO eleventh edition of international classification of diseases (ICD-11) could be used to determine uniform morbidity and mortality rates of anaphylaxis during pregnancy in different countries and by distinguished medical specialties. This classification is more precise, sensitive and accurate for anaphylaxis than the previous ICD editions [15].

Data from milder anaphylactic reactions are generally missing. Isolated cutaneous signs, itching in the valvular or vaginal areas, low back pain, fetal distress and preterm labor are specific manifestations of potential allergic reactions in this population [5]. Reminders for practitioners in the delivery room or operating room could be placed to red flag signs of a potential allergic reaction.

Although the majority of studies discuss possible culprit triggers for anaphylaxis, in only 17% of papers were causative agents proven by allergy testing [12,16]. In fact, "unknown cause" is considered a risk factor for severe anaphylaxis and biphasic anaphylaxis. In practice, the non-confirmed trigger increases the risk of developing another anaphylactic reaction in the future. Our data demonstrated that 12 % of women with a suspected or proven past allergy have been exposed to the same agent during the pregnancy, leading to a new reaction [4, 5]. The nature of the initial clinical reaction is not specified in the two of studies providing these data. Precise diagnosis, written recommendations, and correct label of allergy in electronic health records should be able to decrease this risk. After treating the acute

phase, we recommend that all cases of anaphylaxis should be referred to allergists for etiological confirmation, risk stratification and specific guidance in relation to the need of epinephrine auto-injectors or information regarding the possible cross-reactivity between allergens. This is the case, for example, of perioperative anaphylaxis (cesarean delivery) in which the patient is exposed to many agents simultaneously. Similar actions should be applied to cases of personal history of anaphylaxis seen by general practitioners, gynecologists, anesthesiologists. We emphasize that premedication with anti-histamine and/or systemic corticosteroids is insufficient to prevent immune-mediated anaphylaxis.

During the first trimester of pregnancy, the most frequent causes of anaphylaxis are the same as in non-pregnant women (food, venom, drugs) [5]. However, during the second and third trimesters, antibiotics are the most commonly reported cause of anaphylaxis, in particular beta-lactams used to prevent infection during cesarean section and to treat streptococcal B infections. The patterns of prescriptions for the treatment of Streptococcal B infections vary among countries. For instance, in USA, a routine bacteriological screening is performed before delivery [17], but in the UK the antibiotic is used as risk prevention strategy. Routine use of antibiotics can increase sensitization and antibiotic resistance [18, 19]. Currently there is an international effort by the allergy community to facilitate de-labelling of allergy to beta lactams [20-22]. Therefore, accurate diagnosis of drug allergy is key.

In general, pregnancy has been considered as a relative contraindication of allergy testing [23]. The indication has been restricted to cases in which the utilization of a molecule is absolutely necessary without any alternatives [24]. This is the case of suspected allergy to local anesthetics [9]. In order to minimize risks to both mother and fetus, allergy work-up should be performed in early pregnancy. We would also recommend routine surveillance at periodic pre-natal visits with a specific question about any noticed sign of reaction to latex during examination or with casual contacts.

The second most frequent cause of anaphylaxis during pregnancy is natural rubber latex, probably due to the frequent exposure of pregnant women to latex gloves during gynecological and/or obstetric procedures [25]. During delivery, causative agents are different between spontaneous or cesarean delivery [4, 5, 17].

During spontaneous delivery, the most common causative agents of anaphylaxis are anesthetic agents followed by antibiotics [4, 5]. Local anesthetics are used during spontaneous delivery in order to decrease pain of the mother as major components of an epidural/spinal anesthesia [26]. However, they are rarely implicated in true IgE-mediated anaphylaxis [27], and the rates observed in publications may probably be due to non-confirmed allergies. A study from the UK recently showed that the rate of proven allergy caused by local anesthetic agents is lower than 1% [28].

During cesarean delivery under local anesthesia, rates of causatives agents of anaphylaxis are relatively equally distributed between antibiotics and natural rubber latex. For cesarean deliveries under general anesthesia the main responsible agents are muscle relaxants [11].

This could be explained by the need for antibiotic therapy during surgical procedures and the utilization of sterile gloves composed of natural rubber latex. Latex allergy is mentioned as a risk factor for anaphylaxis during pregnancy [10]. Latex allergic clinical reactions occur usually less than one hour after contact [29]. Identifying latex allergy risk factors and history related to a possible latex allergy during the pregnancy is fundamental to prevention by advising a latex free environment [18, 29, 30]. Some countries are currently trying to reduce latex utilization for professional use. In some countries such as the UK and Germany, latex gloves have been replaced by synthetic ones, and in other countries such as in France, gloves are no longer powdered, which has been shown to substantially decrease the risk of latex sensitization and allergy [31].

Although a personal history of allergy or anaphylaxis is considered a risk factor for another episode during pregnancy [16], there are no data related to the increased risk of anaphylaxis according to the number of pregnancies. However, it is known that increased number of procedures can promote the sensitization to allergens [32]. Multiple pregnancies could be considered as a risk factor for anaphylaxis during pregnancy. Cesarean delivery and personal history of allergic reaction have been identified as two main co-factors for anaphylaxis during pregnancy [10].

With these cofactors clearly established, one could identify a phenotype at risk for anaphylaxis during pregnancy, represented by a second or third trimester pregnant woman with history of multiple pregnancies/cesareans/procedures, personal history of anaphylaxis and/or allergic reaction to medication without allergy work-up, with additional risk factors for natural rubber latex allergy and with indication to a new cesarean delivery. Risk factors for latex allergies include health care workers and others who frequently wear latex gloves, people who have had multiple surgeries (for example 10 or more) such as children with spina bifida, people who are often exposed to latex including rubber industry workers, and people with other allergies such as hay fever or allergy to certain foods [25,29,30]. Although decreased exposure to NRL has reduced the general risk of anaphylaxis and perioperative anaphylaxis overall, no decreased trends were observed specifically in anaphylaxis related to pregnancy over the time after the application of preventive measures for latex allergy in hospital, probably because of the rarity of this phenomena. Populations at-risk are the key target of prevention strategies aimed to decrease morbidity/mortality.

Two thirds of the selected articles propose clear management guidance for anaphylaxis during pregnancy.

The French recommendations, endorsed by the European Network of Drug Allergy (ENDA), insisted in 2011 on the need to use adrenaline and give precision about emergency treatment of pregnant women with anaphylaxis [33].

Fetal extraction should be done as soon as possible if the anaphylaxis occurs during labor, otherwise maternal resuscitation could fail due to compression of the vena cava by the fetus [9]. Conversely, in other situations in the operating room, the surgical procedure will not be undertaken in case of anaphylaxis at anesthetic induction [9].

Although recommended management measures are quite similar in the majority of articles, there is no mention of the dose of epinephrine to be used in the pregnant women, the position to place the woman in during the acute phase, nor the utility of evaluating blood tryptase levels.

If anaphylaxis during pregnancy is suspected, serum tryptase levels should be measured [34 , 35]. The serum tryptase level is a marker used to support the diagnosis of an anaphylactic episode in situations where clinical manifestations are not clear and made the diagnosis is uncertain, but no article in our review mentioned serum tryptase.

The presence of mast cell activation disorders, including mastocytosis, is one of the most important risk factors for anaphylaxis in pregnancy, but are not discussed in any of the articles.

In systemic mastocytosis, the pregnancy itself and/or delivery can be a trigger to mast cells degranulation, leading to significant maternal and fetal complications [36, 37]. Treatment with H1 blockers, and when indicated, steroids and epinephrine, can reduce these complications [38]. Ideally, the diagnosis of mast cell activation disorder should be made before the pregnancy and all health professionals involved should be aware to promptly recognize and treat anaphylactic manifestations and treat.

This study presents some limitations. Although with careful selection of the documents, we had a limited sample of articles probably due to the total number of publications in the field. Due to the limited epidemiological data, it was not possible to follow the changes overtime. Most of the studies were published by authors from Europe or USA; these data about anaphylaxis may reflect the situation in more wealthy countries, including the causative agents. Rather than common tendency for all medical publications having higher number of publications from higher incoming countries, these regions have easier access to investigations and treatments. Data from low-incoming countries are missing. It was also not possible to follow the differences in epidemiological trends due to the ICD editions cause only two articles were population-based studies based on ICD-9 (or modifications), in which anaphylaxis were under represented. Besides, the widespread availability of laboratory measurement of serum tryptase did not occur until the early 2000's in Europe and after 2010 in the US. This may have limited reporting in many of the studies. Similarly, MCAS was not really recognized

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widely or defined until about 2010. The risk factors mentioned have been identified from very limited available literature, and other yet unidentified factors may influence risks.

CONCLUSION

Anaphylaxis during pregnancy is still a rare but a life-threatening phenomenon for the mother and the newborn. This first systematic review focused on diagnosis and management of anaphylaxis during pregnancy identifies the main risk factors for anaphylaxis during each trimester, and during delivery or caesarean section, stressed specific gaps and reinforces future public health strategies. The evidence presented highlights the need for better investigation and risk stratification to avoid negative outcomes. A national or multi-national registry of anaphylaxis in pregnancy would begin to answer many questions despite some of the inherent reporting biases. Also a collaboration between different specialists involved in the care of pregnant women should be established in order to support preventive strategies and reduce avoidable deaths due to anaphylaxis during pregnancy.

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FIGURE LEGEND

Figure 1: Flow diagram showing the stages of selection for the systematic review analysis.

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Table 1. Summary of characteristics of the included publications regarding anaphylaxis during pregnancy.

Author, (year)	Region	Type of study	Database	Study aim	Specific population	Triggers	Number of women with anaphylaxis	Mortality rate	History of previous anaphylaxis	Severity of anaphylaxis	Risk factors/ co-factors
S. J. McCall et al. (2020) [10]	Europe	Descriptive multinational study: combination of retrospective and prospective population-based study	Data register: UK Obstetric Surveillance System / Netherlands Obstetric Surveillance System / Finnish Medical Birth Registry / UKOSS data collection	Estimation of the incidence, causative agents, management and outcomes of anaphylaxis in pregnancy across Europe.	51% had cesarean section Separation between antenatal / intrapartum / post - delivery anaphylaxis	The most common causes: -Antibiotics (43%) -Anesthetic agents (17%)	Sixty-five cases were identified among 4,446,120 maternities 1.5 per 100 000 maternities	Case/fatality rate: 3.2% (95% CI 0.4–11.0), 2 deaths: -one from suxamethonium and one from amoxicillin / clavulanic acid	7 cases (11.1%)	No data available	Multiple pregnancy 4 cases (6.3%) Drug allergy known 19 cases (30.6%) -14 cases allergy to penicillin (22.6%) Atopic status 20 cases (32.3%) Clinical history of allergy 34 cases (54.1%) Clinical history of allergy or atopy

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											38 cases (60.3%)
Zuber D. Mulla (2010) [12]	Texas	Retrospective study	ICD-9	Identify the epidemiologic features of anaphylaxis in women who delivered a neonate in Texas during a 2-year period	75% had cesarean section	-Antibiotics (usually Beta-lactam), -Latex -Succinylcholine	Nineteen maternal anaphylaxis cases 2.7 per 100 000 maternities	None of the patients died	No data available	No data available	14 cases of caesarean section (74%) 2 cases of cutaneous allergic symptoms related to drug intake (10.5%)
SJ McCall (2018) [4]	UK	Prospective case notification	Data register UKOSS	Estimate the incidence of anaphylaxis in pregnancy and describe the management and outcomes in the United Kingdom	21% had cesarean section <u>Reaction before delivery:</u> antepartum period / intrapartum	-Antibiotics	37 confirmed cases of anaphylaxis in pregnancy 1.6 per 100 000 maternities	Case/ fatality rate 5% (95% CI: 0.7–18.2%)	2 cases (5%)	2 deaths (5%) 7 cases of severe maternal morbidity (19%)	12 cases of drug allergy (32%) -10 cases allergy to penicillin (83%)

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					reaction of anaphylaxis <u>After delivery:</u> immediate reaction/ late post-partum period						20 cases of clinical history of allergic reaction (54%) 16 cases of atopic context (43%)
C. Tacquard (2019) [13]	France	Retrospective study	French database ENCMM	Retrospective assessment of permanent nationwide database to identify maternal deaths related to anaphylaxis in order to estimate their frequency and identify the incriminated agent		-Neuromuscular blocking agents appear to be the leading culprits in anaphylaxis-related maternal death -Latex -Antibiotics (penicillins or cephalosporins used for Streptococcus B infection prevention) are the most frequent allergens involved in peripartum anaphylaxis	Data available only for mortality due to anaphylaxis in pregnant women	The incidence of anaphylaxis-related maternal mortality was estimated at 0.05 per 100 000 live births (95% CI :0.02-0.19)	No data available	No data available	1 case of atopic context (25%)

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SJ.McCall (2019) [11]	USA	Original article	International Classification of Diseases, Ninth Revision Clinical Modification codes from the National Inpatient Sample, United States, over the period 2004 to 2014.	Describe the incidence and temporal trends and identify potential risk factors for anaphylaxis-related hospitalizations during pregnancy in the United States		-antibiotics -anaesthetic 3 factors that increased the odds of anaphylaxis during pregnancy: -caesarean delivery - history of a past allergic reaction -Black race and other race compared with white race.	358 cases of anaphylaxis in pregnancy, 126 in non-caesarean section, 228 in caesarean section 3.8 (95% CI, 3.4-4.2) per 100 000 hospitalizations while pregnant	No data available	No data available	No data available	28 cases of clinical history of allergy (7.9%) 228 of caesarean section (64.4%)

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Draisci (2006) (16)	Italy	Case series	Institutional database (Catholic University Medical School)	Analysed all the cases of anaphylactic reactions in women who underwent caesarean section in 2004.	1240 caesarean sections/year	!00% proven latex allergy	4 cases/1240 caesarean sections, data reported only due to latex allergy	None	No personal history of anaphylaxis in any of the 4 cases	3 cases (75%) grade 2, 1 case (25%) grade 3	3 cases (75%) with history of atopic disease, 100% with more than 6 vaginal examinations with latex gloves during pregnancy, 2 cases (50%) with personal history of contact dermatitis to natural latex rubber components

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Table 2. Anaphylaxis during obstetrics: causative agent and differential diagnosis (4,5,10-13,17,39-43)

	Pregnancy			Delivery		Post delivery
Stage r of the pregnancy	Trimester 1	Trimester 2	Trimester 3	Spontaneous delivery	Cesarean section	
Global triggers of anaphylaxis	General population: food, venom, drugs, biological agents such as immunotherapy, natural rubber latex	1)Antibiotics (58%) 2)Natural rubber latex (43%) 3)Anesthetic agents (14%)		1)Anesthetics (43%) 2)Antibiotics (14%)	1)Antibiotics (50%) 2)Latex (50%)	1 article: hormonal sensitivity 1 article: blood products
Risk factor for anaphylaxis	clinical past history of allergic reaction; risk factors for latex allergy (health care workers and other people frequently wearing latex gloves, people who have had multiple surgeries (10 or more) such as children with spina bifida, people who are often exposed to natural rubber latex (including rubber industry workers) and people with other allergies such as hay fever or allergy to certain foods)				Cesarean section	

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Table 3. Differential diagnosis for anaphylaxis during obstetrics. (5)

	Before Labor and Delivery	Labor and Delivery	
Differential diagnosis	Common diagnostic dilemmas: -acute asthma -acute generalized urticaria -acute angioedema -syncope/fainting -panic attack Postprandial syndromes: -scrombroid -pollen-food allergy syndrome (oral allergy syndrome) -monosodium glutamate reaction -sulfite reaction -food poisoning Upper airway obstruction (other forms): -nonallergic angioedema including hereditary angioedema types I, II and III Shock (other forms): -hypovolemic -septic -cardiogenic Nonorganic diseases: -vocal cord dysfunction -hyperventilation -psychosomatic episode -Munchausen stridor Common diagnostic: -excess endogenous histamine: mastocytosis/clonal mast cell disorder -flush syndromes -carcinoid syndrome -certain tumors -systemic capillary leak syndrome	Pulmonary embolism (thrombotic) and pulmonary edema Cardiac conditions (acquired and congenital) Hypotension caused by spinal block, local anesthetic, or hemorrhage, secondary to abruptio placentae or uterine rupture Cerebrovascular accident Amniotic embolism fluid Preeclampsia/eclampsia-associated symptoms, such as laryngopathia gravidarum and seizures	

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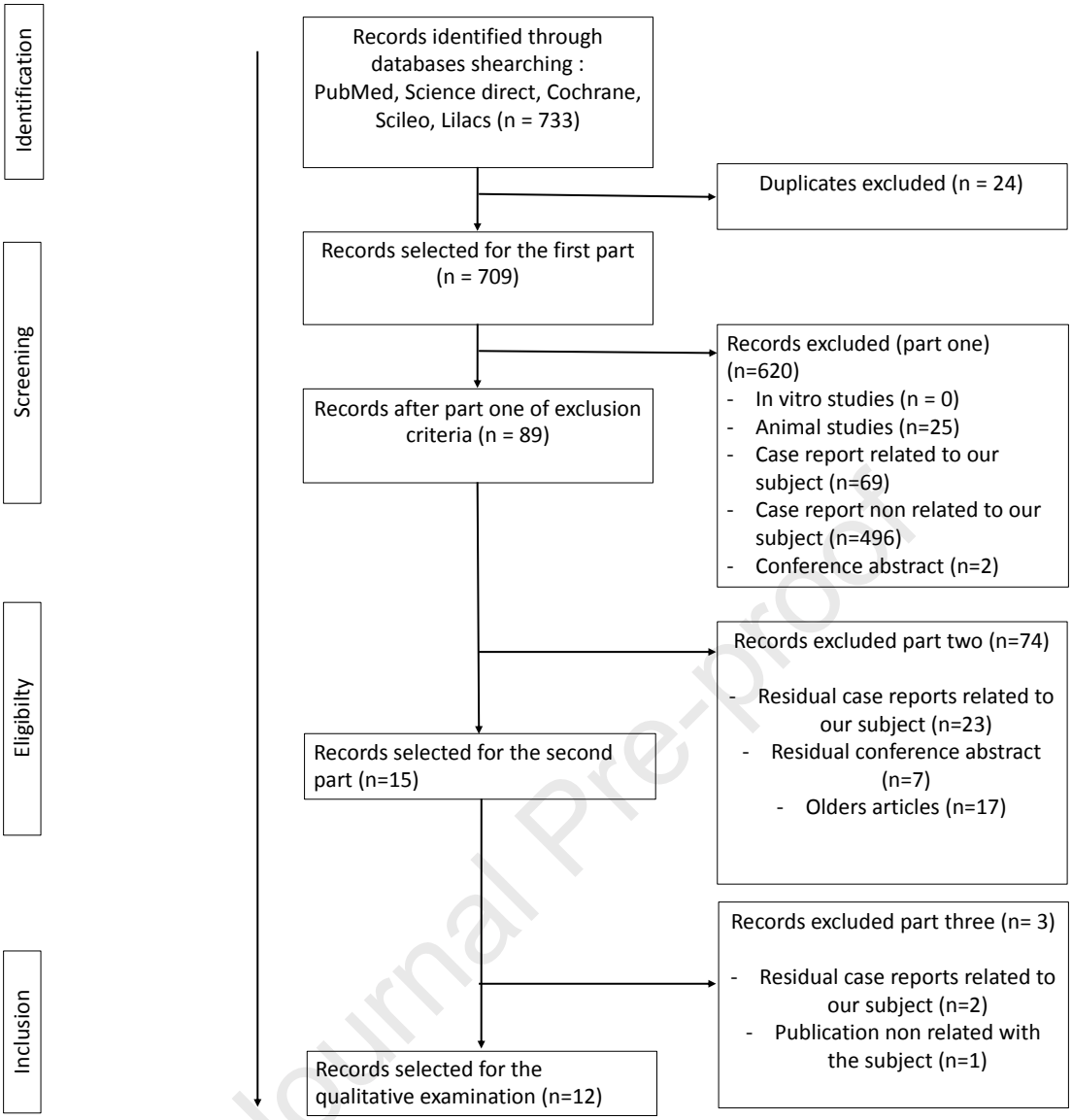

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