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Interventions for treating amniotic fluid embolism: a systematic review with meta-analysis

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Summary

Purpose: Assessing to what extent the interventions for treating amniotic fluid embolism (AFE) are effective. *Materials and Methods:* A systematic review of cases of AFE available on PubMed, Scielo, Scopus, and AJOL databases from 1990 to 2015 was carried out. The perception of effectiveness of each kind of intervention on heart, lungs, coagulopathy, and the importance of immediate parturition was quantified semi-quantitatively, by scoring textual information (from 0 to 3). Scores 2 and 3 were considered positive scores (effective intervention), while 0 and 1 were considered negative scores (ineffective intervention). Rates of such scores were compared with a random distribution of scores from 0 to 3. Sub-groups analyses were carried out. *Results:* One hundred twenty-one typical AFE cases were assessed. Each intervention for supporting the heart and, predominantly, lung function is perceived as pivotal. *Conclusion:* The management of AFE should be focused on supporting the lung and the heart function.

Key words: Amniotic fluid embolism; Outcome; Treatments; Meta-analysis.

Introduction

Amniotic fluid embolism (AFE) is a rare and potentially catastrophic syndrome of pregnancy. It has been reported [1] that an estimated AFE rate of 1/15,200 deliveries is present in North America, and occurs at 1/53,800 deliveries in Europe. Additionally, the maternal mortality ratio for AFE ranges between 0.5 - 1.7 deaths per 100,000 live births. Due to its rarity and lack of unequivocal diagnostic criteria, AFE may have unknown true rates of occurrence, and data is lacking regarding clinical onset, outcomes, and the effectiveness of treatments provided [2]. As it has been reported that the survival rate is improving [1, 3], one could hypothesize that some interventions provided for managing AFE are effective for improving AFE outcome. To check that hypothesis, observational or randomized studies to prove the efficacy of treatments in AFE cases could be carried out. However, AFE is too rare to allow studies of large series. Therefore, all the evidence regarding AFE has been extracted from case reports or small series, with the best evidence available from national registries or population-based reviews. Therefore, the present authors assessed the effectiveness of intervention in cases of AFE by meta-analyzing the AFE case reports. They hypothesize that interventions provided in amniotic fluid embolism are effective, and to prove it, they quantified from textual information how much an intervention for AFE is perceived as effective by authors of the case reports. This meta-analysis has been registered on the International Prospective Register of Systematic Review (PROSPERO) site (number 34104).

Materials and Methods

On January 20th, 2016, the present authors performed a systematic review of the literature by introducing "amniotic" AND "fluid" AND "embolism" as key words in the PubMed, Scielo, AJOL (African Journal Online), and Scopus search engines. The time frame of the search was limited to run from 1990 to the present. This range was given because the care for AFE could have changed over the years. No languages limitations were set.

The PubMed search returned 607 references, Scopus returned 1,750 references, Scielo returned 16 references, and AJOL returned one reference. The whole body of references was checked for duplicates by both a manual check and the use of EndNote. After that, the authors read the titles and abstracts, checking for case reports, letters to the editors, and small series. They searched case descriptions in which the clinical picture of each case of AFE was reported. If titles and abstracts were not exhaustive, they read the full text article (if available) to understand if cases and small series of cases reported useful clinical information. They were able to read articles in Italian, English, French, Spanish, and Portuguese in their original languages, while other languages were translated into English or Italian.

Full texts were found on the "Sapienza" University of Rome electronic database, and by using the Italian interlibrary free exchange of full- text articles (NILDE tool) for obtaining full texts

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To the remaining 233 references, seven additional references incidentally found on Google Scholar during the full texts search process were added. The authors were unable to collect 20 full texts. Therefore, they were forced to discard 20 references.

To best assess the perception of effectiveness for interventions in AFE cases, the authors focused on the cases description and discussion. They chose to discard references in which the effectiveness of interventions for AFE was not reported or not discussed (51 references). Moreover, they discarded six references on small series not assessing the treatment of AFE, seven cases in which AFE was unlikely, one case in which an amniotic embolus was found and treated before it would have reached the heart, and one case reported in a retracted article.

Because some references reported more than one case, the authors thus collect a database of 181 cases of suspected AFE cases. However, they were forced to discard three cases due to insufficient information and one case where AFE seemed unlikely.

Figure 1 shows a flow-chart of phases for building the database of 177 presumed cases of AFE.

The interventions considered to be effective for managing AFE cases were: 1) pulmonary interventions (cardio-pulmonary resuscitation, extracorporeal membrane oxygenation, cardio-pulmonary by-pass, embolectomy), 2) cardiac interventions (cardio-pulmonary resuscitation, defibrillation, inotropic agents, fluid infusions, cardio-pulmonary by-pass, aortic balloon counterpulsation, open heart massage, aortic compression), 3) interventions on the coagulopathy (fresh frozen plasma infusion, cryoprecipitate, recombinant factor VIIa infusion, fibrinogen concentrate infusion, tranexamic acid, platelets infusion, antithrombin III infusion, desmopressin acetate therapy, aprotinin, C1 esterase inhibitor), and 4) immediate delivery (each operative intervention for delivery the baby or for interrupting the pregnancy and emptying the uterus).

The effect size to be meta-analysed is the perception of effectiveness of the interventions in AFE cases, as reported authors in their cases description and discussion. To provide an unequivocal measure of such effectiveness, the authors built a semi-quantitative score based on textual information. They assigned 0 if the interventions are not reported or if they were considered totally ineffective. They assigned 1 if the interventions were perceived to

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Table 3. — *Descriptive statistics with negative and positive scores.*

			Atypical AFE 16.4%	Atypical AFE + confirmations* 15.3%	Typical AFE 42.4%	Typical AFE + confirmations* 26%	Death 29.9%	Onset before delivery 59.9%
Pulmonary interventions	Negative scores	0	31%	22.2%	10.7%	15.2%	18.9%	14.2%
		1	41.4%	55.6%	30.7%	50%	50.9%	42.5%
	Positive scores	2	24.1%	14.8%	49.3%	21.7%	26.4%	36.8%
		3	3.4%	7.4%	9.3%	13%	3.8%	6.6%
Cardiac interventions	Negative scores	0	27.6%	29.6%	9.3%	17.4%	22.6%	14.2%
		1	41.4%	48.1%	33.3%	47.8%	50.9%	38.7%
	Positive scores	2	31%	7.4%	50.7%	13%	22.6%	39.6%
		3	0%	14.8%	6.7%	21.7%	3.8%	7.5%
Interventions on the coagulopathy	Negative scores	0	31%	51.9%	10.7%	13%	24.5%	20.8%
		1	31%	33.3%	26.7%	47.2%	47.2%	32.1%
	Positive scores	2	24.1%	7.4%	48%	19.6%	18.9%	34.9%
		3	13.8%	7.4%	14.7%	21.7%	9.4%	12.3%
Immediate delivery	Negative scores	0	69%	70.4%	50.7%	60.9%	60.4%	49.1%
		1	24.1%	14.8%	17.3%	23.9%	20.8%	25.5%
	Positive scores	2	3.4%	7.4%	24%	10.9%	15.1%	17%
		3	3.4%	7.4%	8%	4.3%	3.8%	8.5%

**Pathological or blood/serum confirmations (autopsy, pathological examination of specimens, bronco-alveolar lavage, blood keratinocytes, blood amniocytes, rise serum in IGF-BP1, and/or Syalil Tn, and/or Zn CP1, and/or tryptase).*

Table 4. — *Multivariate logistic regression analyses, cheeking for heterogeneity.*

	Pulmonary interventions OR for positive scores	Cardiac interventions OR for positive scores	Interventions on the coagulopathy OR for positive scores	Immediate delivery OR for positive scores
	Adjusted OR 95% CI *p*	Adjusted OR 95% CI *p*	Adjusted OR 95% CI *p*	Adjusted OR 95% CI *p*
AFE diagnosis	+	+	+	+
Atypical AFE	1	1	1	1
Atypical AFE + confirmations*	0.750 0.222-2.538 0.644	0.771 0.223-2.667 0.681	0.357 0.095-1.338 0.126	2.294 0.381-13.802 0.364
Typical AFE	3.726 1.463-9.491 **0.006**	3.240 1.273-8.244 **0.014**	2.874 1.174-7.035 **0.021**	6.582 1.433-30.227 **0.015**
Typical AFE + confirmations*	1.400 0.507-3.865 0.516	1.809 0.619-5.283 0.279	1.669 0.604-4.618 0.323	2.629 0.501-13.779 0.253
Death	0.598 0.281-1.275 0.183	0.428 0.195-0.939 **0.034**	0.399 0.184-0.866 **0.020**	1.037 0.416-2.584 0.938
Onset before delivery	1.215 0.635-2.327 0.556	1.913 0.984-3.720 0.056	1.244 0.645-2.402 0.515	2.149 0.944-4.894 0.069

**Pathological or blood/serum confirmations (autopsy, pathological examination of specimens, bronco-alveolar lavage, blood keratinocytes, blood amniocytes, rise serum in IGF-BP1, and/or Syalil Tn, and/or Zn CP1, and/or tryptase).*

be of some effectiveness, 2 if the interventions were perceived as effective, and 3 if the interventions were perceived to be very effective. Consensus among meta-analysts was used to carefully attribute those scores. Thus 0 and 1 were considered negative scores, while 2 and 3 were considered positive scores.

The AFE diagnosis is entirely clinical, basing on a typical triad of signs [4]. These are: cardiac arrest/ hypotension, respiratory failure, coagulopathy. Some additional information supporting a presumptive amniotic embolization can be provided pathologically or by checking for some component of the amniotic fluid [2, 5-8] in maternal blood. On the other hand, it has been reported that some cases of AFE are atypical [9], usually presenting with

Table 5. — *Analyses on the whole database.*

WHOLE DATABASE (177 cases; 53 died, 124 survived)		
Pulmonary interventions		
Scores	Given	Random
- 0	30 (16.9%)	34 (19.2%)
- 1	73 (41.2%)	53 (29.9%)
- 2	58 (32.8%)	56 (31.6%)
- 3	16 (9%)	34 (19.2%)
Chi square 9.94, $p = 0.01909$, 3 degrees of freedom.		
Cardiac interventions		
Scores	Given	Random
- 0	31 (17.5%)	32 (18.1%)
- 1	72 (40.7%)	56 (31.6%)
- 2	61 (34.5%)	57 (32.2%)
- 3	13 (7.3%)	32 (18.1%)
Chi square 10.17, $p = 0.01715$, 3 degrees of freedom.		
Interventions on the coagulopathy		
Scores	Given	Random
- 0	37(20.9%)	32 (18.1%)
- 1	59 (33.3%)	48 (27.1%)
- 2	54 (30.5%)	70 (39.5%)
- 3	27 (15.3%)	27 (15.3%)
Chi square 3.558, $p = 0.3134$, 3 degrees of freedom.		
Immediate birth		
Scores	Given	Random
- 0	105 (59.3%)	25 (14.1%)
- 1	35 (19.8%)	61 (34.5%)
- 2	26 (14.7%)	64 (36.2%)
- 3	11 (6.2%)	27 (15.3%)
Chi square 79.05, $p < 0.0001$, 3 degrees of freedom.		

signs and symptoms of a coagulopathy without other clinical manifestations. Therefore, the AFE diagnosis is elusive, and should be considered after the exclusion of other diseases mimicking an AFE.

By reviewing a database of cases reported as AFEs, the authors acknowledge that some cases are true and typical AFE cases and that other cases are atypical AFE cases or may not be AFE cases. They therefore were aware that they were analysing a heterogeneous database. The clinical picture of AFE along with the AFE outcome (death or survival) and its onset (before and after birth) could have conditioned the authors' perception of the effectiveness of their interventions. Therefore, they distinguished AFE cases as typical (cardiovascular collapse/hypotension, pulmonary failure, coagulopathy), or atypical (lack of one or more of the typical signs and symptoms), with or without pathological or blood confirmations. The pathological or laboratory confirmations were considered to be: autopsy findings of amniotic debris in the pulmonary bed, pathological examination of uterine specimens demonstrating amniotic debris in uterine vessels, bronco-alveolar lavage with amniocytes or keratinocytes, keratinocytes in maternal blood, amniocytes in maternal blood, rise in IGF-BP1 and/or Syalil Tn, and/or Zn CP1, and/or tryptase in maternal blood).

Logistic regression analyses were built to check the heterogeneity of the sample, assuming that the clinical picture of AFE (typical with pathological or laboratory confirmations, typical without any confirmation, atypical with pathological or laboratory confirmations, atypical without any confirmation), AFE outcome (death or alive), AFE onset (before and after birth) can have conditioned the positive scores.

To compare scores assigned to the interventions in AFE cases, the authors generated a random sequence of 177 numbers, from 0 to 3, by using Open.epi 3.03a, and they used the frequencies of such random distribution as a contrast. They checked the null hypothesis that the scores given from textual information were randomly distributed. Based on results of logistic regression analyses, they performed sub-groups analyses checking that, in the subgroups, the scores given from textual information were also randomly distributed. The Chi square test was used for inference and $p < 0.05$ was set for the level of significance.

Results

Table 1 lists the discarded references. Table 2 reports the list of 154 references used for meta-analysis. Table 3 reports the descriptive statistics, focusing on the rates of positive and negative scores.

Logistic regression analyses demonstrated that more positive scores were found in typical AFE cases, whereas obviously more negative scores were found if the patient died (Table 4). These results confirm heterogeneity. Therefore, the authors performed sub-group analyses on patients with

Table 6. — *Sub-group analyses: typical AFEs with or without pathological and/or lab confirmations of AFE.*

TYPICAL AFEs WITH OR WITHOUT AFE CONFIRMATIONS* (121 cases; died 37, survived 84)		
Pulmonary interventions		
Scores	Given	Random
- 0	15 (12.4%)	26 (21.4%)
- 1	46 (38%)	38 (31.4%)
- 2	47 (38.8%)	34 (28.1%)
- 3	13 (10.7%)	23 (19%)
Chi square 8.577, $p = 0.03547$, 3 degrees of freedom.		
Cardiac interventions		
Scores	Given	Random
0	15 (12.4%)	20 (16.5%)
- 1	47 (38.8%)	38 (31.4%)
- 2	50 (41.3%)	41 (33.9%)
- 3	9 (7.4%)	22 (18.2%)
Chi square 8.009, $p = 0.04583$, 3 degrees of freedom.		
Interventions on the coagulopathy		
Scores	Given	Random
- 0	14 (11.6%)	22 (18.2%)
- 1	41 (33.9%)	35 (28.9%)
- 2	45 (37.2%)	50 (41.3%)
- 3	21 (17.4%)	14 (11.6%)
Chi square 3.915, $p = 0.2708$, 3 degrees of freedom.		
Immediate birth		
Score	Given	Random
- 0	66 (54.5%)	16 (13.2%)
- 1	24 (19.8%)	41 (33.9%)
- 2	23 (19%)	49 (40.5%)
- 3	8 (6.6%)	15 (12.4%)
Chi square 46.45, $p < 0.00001$, 3 degrees of freedom.		

**Pathological or blood/serum confirmations (autopsy, pathological examination of specimens, bronco-alveolar lavage, blood keratinocytes, blood amniocytes, rise serum in IGF-BP1, and/or Syalil Tn, and/or Zn CP1, and/or tryptase).*

typical AFE (with and without pathological or laboratory confirmation), in patients with typical AFE (without any pathological or laboratory confirmation) and in patients who died.

Table 5 reports results for the whole database. Pulmonary interventions (Chi square 9.94, $p = 0.01909$) and cardiac interventions (Chi square 10.17, $p = 0.01715$) are perceived to be of some relevance in treating AFE cases (higher rates for score 1) while it is not perceived as pivotal (Chi square 79.05, $p < 0.0001$) to immediately giving birth (higher rate for score 0).

Table 6 reports results on typical AFE cases (with and without pathological and laboratory confirmation). Pulmonary interventions (Chi square 8.577, $p = 0.03547$) and cardiac interventions (Chi square 8.009, $p = 0.04583$) are perceived as effective in treating AFE cases (higher rates for score 2), while it is not perceived as pivotal (Chi square 46.45, $p < 0.00001$) to immediately giving birth (higher rate for score 0).

Table 7 reports results on typical AFE cases (without pathological and laboratory confirmation). Pulmonary interventions (Chi square 12.1, $p = 0.007035$) are perceived as effective in treating AFE cases (higher rate for score 2). Cardiac interventions fail to reach the significance level (Chi square 7.409, $p = 0.05995$), despite the higher rate for score 2). It is not perceived as pivotal (Chi square 30.89, $p < 0.00001$) to immediately giving birth (higher rate for score 0).

Table 8 reports results on cases of death for AFE. Pulmonary interventions (Chi square 14.59, $p = 0.002198$) and cardiac interventions (Chi square 9.667, $p = 0.02162$) are perceived of some relevance in treating AFE cases (higher rates for score 1) while it is not perceived as pivotal (Chi square 22.43, $p = 0.00005$) to immediately giving birth (higher rate for score 0). Interventions on the coagulopathy fail to reach significance ($p = 0.0522$) and do not seem pivotal.

Many authors of AFE case reports agree that immediate interventions should be provided and some reports show positive findings if extracorporeal membrane oxygenation is provided.

Discussion

The present meta-analysis is adapted to case reports, and aimed to synthesize the "*a priori*" perception of the effec-

Table 7. — *Sub-group analyses. Typical AFE cases without any pathological and/or lab confirmation of AFE.*

TYPICAL AFEs WITHOUT AFE CONFIRMATIONS* (75 cases: 12 died, survived 63)		
Pulmonary interventions		
Scores	Given	Random
- 0	8 (10.7%)	15 (20%)
- 1	23 (30.7%)	24 (32%)
- 2	37 (49.3%)	19 (25.3%)
- 3	7 (9.3%)	17 (22.7%)
Chi square 12.1, $p = 0.007035$, 3 degrees of freedom.		
Cardiac interventions		
Scores	Given	Random
- 0	7 (9.3%)	13 (17.3%)
- 1	25 (33.3%)	22 (29.3%)
- 2	38 (50.7%)	27 (36%)
- 3	5 (6.7%)	13 (17.3%)
Chi square 7.409, $p = 0.05995$, 3 degrees of freedom.		
Interventions on the coagulopathy		
Scores	Given	Random
- 0	8 (10.7%)	14 (18.7%)
- 1	20 (26.7%)	22 (29.3%)
- 2	36 (48%)	29 (38.7%)
- 3	11 (14.7%)	10 (13.3%)
Chi square 2.533, $p = 0.4693$, 3 degrees of freedom.		
Immediate birth		
Score	Given	Random
- 0	38 (50.7%)	7 (9.3%)
- 1	13 (17.3%)	28 (37.3%)
- 2	18 (24%)	31 (41.3%)
- 3	6 (8%)	9 (12%)
Chi square 30.89, $p < 0.00001$, 3 degrees of freedom.		

**Pathological or blood/serum confirmations (autopsy, pathological examination of specimens, bronco-alveolar lavage, blood keratinocytes, blood amniocytes, rise serum in IGF-BP1, and/or Syalil Tn, and/or Zn CP1, and/or tryptase).*

tiveness of interventions provided by authors who managed AFE cases and who wrote their case reports. Usually, in contrast, the traditional meta-analysis summarizes "*a posteriori*" results, by averaging an effect size, weighted for the inverse of the variance [10]. In very rare diseases, however, we cannot build large series to obtain data by observational or randomized studies, and, therefore, we cannot meta-analyse the data by averaging an effect size weighted for the inverse of the variance. The knowledge from the rarer diseases must be drawn from case reports or small series, which are written by authors focusing on their personal feelings, knowledge, and expertise. This subjective way to communicate information may be biased by personal opinions and produce evidence of limited quality. Therefore, readers may feel it is inappropriate to perform an analysis starting from subjective scores given from meta-analysts to the texts. It has been reported by some authors [11, 12] that semi-quantitative scores from textual information can summarize each personal feelings in a more objective way, allowing statistical inference and improving the level of evidence. This is what already happens when practice guidelines are issued by opinion leaders. Interestingly, findings from the current meta-analysis are reported in the same way in recent practice guidelines for the management of AFE [13].

The elusive diagnosis of AFE is always a concern. In national data sources or registries, stringent clinical criteria were adopted for indexing cases as AFE. This policy leads to the loss of atypical AFE cases, which could have a more favourable prognosis [9]. The present authors decided to perform sub-group analysis for assessing if some interventions are more effective in more likely cases of AFE (typical ones, with and without laboratory confirmation), thereby remedying the heterogeneity of the data. They found that each intervention aiming to support the heart and the lung was perceived as effective in treating typical AFEs. More pivotal seems to be support for the lung function. Typical AFE leads to cardiovascular and pulmonary failure: it is therefore logical to believe that supporting the heart and the lungs does improve AFE outcome. The body of evidence from case reports agrees that AFE requires immediate interventions. This is also in agreement with what was reported by Fitzpatrick *et al.* [14], who stated that the

Table 8. — *Sub-group analyses. Analyses of patients who died.*

DEATHS 53 cases		
Pulmonary interventions		
Scores	Given	Random
- 0	10 (18.9%)	13 (24.5%)
- 1	27 (50.9%)	10 (18.9%)
- 2	14 (26.4%)	20 (37.7%)
- 3	2 (3.8%)	10 (18.9%)
Chi square 14.59, $p = 0.002198$, 3 degrees of freedom.		
Cardiac interventions		
Scores	Given	Random
- 0	12 (22.6%)	11 (20.8%)
- 1	27 (50.9%)	15 (28.3%)
- 2	12 (22.6%)	17 (32.1%)
- 3	2 (3.8)	10 (18.9%)
Chi square 9.667, $p = 0.02162$, 3 degrees of freedom.		
Interventions on the coagulopathy		
Scores	Given	Random
- 0	13 (24.5%)	8 (15.1%)
- 1	25 (47.2%)	16 (30.2%)
- 2	10 (18.9%)	21 (39.6%)
- 3	5 (9.4%)	8 (15.1%)
Chi square 7.762, $p = 0.05120$, 3 degrees of freedom.		
Immediate birth		
Score	Given	Random
- 0	32 (60.4%)	9 (17%)
- 1	11 (20.1%)	16 (30.2%)
- 2	8 (15.1%)	21 (39.6%)
- 3	2 (3.8%)	7 (13.2%)
Chi square 22.43, $p = 0.00005$, 3 degrees of freedom.		

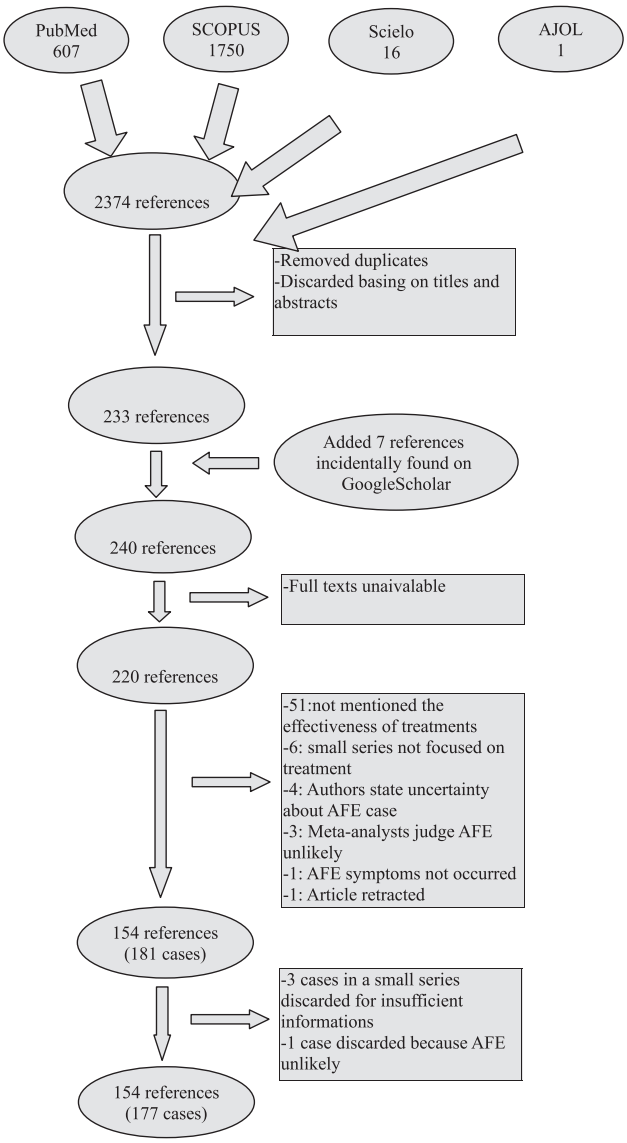

Figure 1. — Flow-chart of the systematic review.

AFE outcome can be improved if immediate interventions are provided. Each intervention for sustaining the heart and lungs is effective. From a practical point of view, after immediate resuscitation, it should be considered appropriate to perform a cardiopulmonary by-pass and extracorporeal membrane oxygenation, because this procedure also allows the purification of blood from amniotic debris, thereby avoiding worsening of the AFE [15]. The same concept was expressed by Ihara *et al.* [16] in a case of renal replacement therapy during AFE. However, it must be pointed out that the present authors were unable, from the available data, to establish if cardiopulmonary by-pass and extracorporeal membrane oxygenation can change the AFE outcome.

Interestingly, the efforts of treating the coagulopathy are not perceived as pivotal for the managing of AFE. Atypical cases of AFE are usually the ones presenting with the coagulopathy only. In such cases, authors have not highlighted the importance of the supportive treatment of the disseminated intravascular coagulation (DIC). This perception of authors could be explained because DIC has overall a standard treatment [17, 18], irrespective from the cause of DIC.

Finally, the immediate birth approach is rarely reported by authors as pivotal for managing AFE, despite it being acknowledged that it allows more effective resuscitation, improving both maternal and fetal survival chances [19]. This is due to the omission of authors of discussing and reporting the topic. As a result, the present authors found higher rates of the 0 score for the item "immediate birth". Maybe those authors have implied that their readers are well aware that successful resuscitation is more likely after giving immediate birth, though this is certain.

Further study and national data sources should assess which impact would have on the outcome of AFE each intervention able to filtrate and purify the blood from amniotic debris, and to what extent pulmonary and heart support along with blood purification are effective for improving the AFE outcome.

Conclusion

This meta-analysis provides "*a priori*" evidence that each immediate intervention for supporting the heart and, mostly, the lungs in AFE cases are perceived as effective for the management of AFE.

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