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ORIGINAL ARTICLE

Risk factors for fatality in amniotic fluid embolism: a systematic review and analysis of a data pool

Ugo Indraccolo[a], Caterina Battistoni[b], Irene Mastrantonio[b], Romolo Di Iorio[c], Pantaleo Greco[d] and Salvatore Renato Indraccolo[b]

[a]Complex Operative Unit of Obstetrics and Gynecology, "Alto Tevere" Hospital of Città di Castello, ASL 1 Umbria, Città di Castello, Italy; [b]Department of Gynecological, Obstetrical, and Urological Sciences, "Sapienza" University of Rome, Rome, Italy; [c]Department of Surgical and Clinical Sciences and Translational Medicine, "Sapienza" University of Rome, Rome, Italy; [d]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, Italy

ABSTRACT

Purpose: Investigating risk factors for amniotic fluid embolism (AFE)-induced fatality.

Methods: A systematic review of cases of AFE available on PubMed, Scielo, Scopus and AJOL databases that occurred from 1990 to 2015 was carried out. After careful reading of titles, abstracts and full texts, case reports of AFE were reviewed. Risk factors for AFE were considered as independent variables in logistic regression models. The first model was built on the whole data pool. The second model was built on typical cases of AFE, according to the classical triad of symptoms (heart, lungs, coagulopathy). The dependent variable was fatality in both models.

Results: 177 cases of AFE were assessed in the first model, while 121 typical cases of AFE were assessed in the second model. Among typical cases of AFE, only oxytocin infusion during labour increases the likelihood of death (odds ratio 2.890, 95% confidence interval 1.166–7.164, $p = 0.022$). No risk factors for fatality were found in the whole data pool.

Conclusions: Further research on national registries should focus on the behaviour of oxytocin infusion during labour in AFE cases.

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Amniotic fluid embolism; oxytocin infusion; labour induction; outcome; pregnancy complications; delivery

Introduction

Amniotic fluid embolism (AFE) is a catastrophic and uncommon complication of pregnancy [1,2]. Diagnostic criteria for defining AFE has been newly published by Clark et al. [3], for avoiding misdiagnoses of AFE and confusion about outcomes and management of such a rare disease. By assessing data sources from many countries, Knight et al. [4] extrapolated that maternal age greater than 35 years, placenta previa and placenta abruptio are risk factors for AFE, and also that a true association could be suspected between AFE and mode of delivery (caesarean section is more likely to be associated with AFE cases onsetting afterbirth). Due to the rarity of AFE and the different characteristics of the data sources, no clear associations were found by Knight et al. [4] between presumptive risk factors for AFE and fatality. More recently, Fitzpatrick et al. [5] reported an increase in odds ratios for AFE associated with age (equal to or greater than 35), multiple pregnancy, induction of labour (any method) and placenta previa. Again, Fitzpatrick et al. [5] did not find a significant association between any of those risk factors and fatality, which seems less likely if immediate intervention was provided [5].

By widely reviewing case reports of AFE in literature, we aim to test the hypothesis that, among the risk factors for AFE reported from recent population-based reviews [4,5], there are some factors related to fatality.

Materials and methods

On 20 January 2016, we performed a systematic review of the literature by introducing "amniotic" AND "fluid" AND "embolism" as keywords in the PubMed, Scielo, AJOL (African Journal Online) and Scopus search engines. The time frame of the search was limited from 1990 to present, without language limitation. The systematic review was the first step of a meta-analysis (registered in the PROSPERO database n° 34104) carried out for investigating which kind of intervention improves AFE outcome [6].

CONTACT Ugo Indraccolo ugo.indraccolo@libero.it Complex Operative Unit of Obstetrics and Gynecology, "Alto Tevere" Hospital of Città di Castello, ASL 1 Umbria, Città di Castello, Italy

The phases of the systematic review and studies selection were widely reported elsewhere [6]. By carefully checking the references and after discarding duplicates and inappropriate papers, we were able to built a data pool on AFE cases. From this data pool, we collected information about patient outcome (death or survival) and about several characteristics of patients and birth. The independent variables investigated for their possible associations with the death or survival of patients were those suggested by Fitzpatrick et al. [5] and Knight et al. [4] as risk factors for AFE: caesarean section (yes or no), placenta previa (yes or no), placenta abruptio (yes or no), multiple pregnancy (yes or no), preeclampsia and/or hypertensive disorders in pregnancy (yes or no), patient age ($\geq$35 years and $<$35 years), prostaglandin agonist use (yes or no) and oxytocin use during labour for inducing or augmenting labour (yes or no). We chose to match for oxytocin use in labour because Fitzpatrick et al. [5] did not specify which kind of induction increases the risk of AFE.

Because AFE may present atypical behaviour [3,7–9], it is possible that some authors suspected AFE despite the fact that the case is not typical. Therefore, we looked for typical cases of AFE based on the clinical triad of signs [10]: cardiac arrest/cardiovascular collapse, respiratory failure (dyspnea, cyanosis, severe desaturation), coagulopathy (both overt and non-overt disseminated intravascular coagulopathy). Those criteria were very similar to the ones reported more recently by Clark et al. [3], and were checked by carefully reading the case reports.

Based on the occurrence of signs and symptoms of cardiovascular, pulmonary and coagulative failure [10], authors have considered AFE cases as typical. The use of laboratory or pathological information in supporting AFE diagnosis, as reported in already-cited meta-analysis [6], was used as additional criterion for improving AFE diagnosis, allowing additional analysis on sub-group of patients with both typical signs and laboratory or pathological markers of amniotic embolisation.

The information collected was initially used for carrying out the above-mentioned meta-analysis [6]. However, the data also allowed the current post-hoc analyses. Therefore, we built three logistic regression models, the first one on the whole data pool (typical cases and atypical cases of AFE), the second one on the typical cases of AFE and the third one on the subgroup with typical AFE and some laboratory and/or pathological confirmation of amniotic fluid embolisation. Significance was set at $p < 0.05$, and SPSS 16.0 (SPSS Inc., Chicago, IL) was used for calculations.

Results

After the systematic review, we retrieved 2374 references. 2141 references were discarded either because they were duplicates or because they were not case reports, small series and letters (based on titles and abstracts). Seven more references were added, as they were incidentally found on Google Scholar during the full text search. 20 references were discarded because the full texts were unavailable. 66 references were discarded during the phase of quality assessment of the meta-analysis. 154 references involved 181 cases. We discarded 3 cases due to insufficient information and 1 case because AFE was unlikely (177 case reports of AFE available). Figure 1 shows the flow chart of the systematic review.

Table 1 reports the descriptive statistics, disaggregated for typical and atypical cases of AFE. Table 2

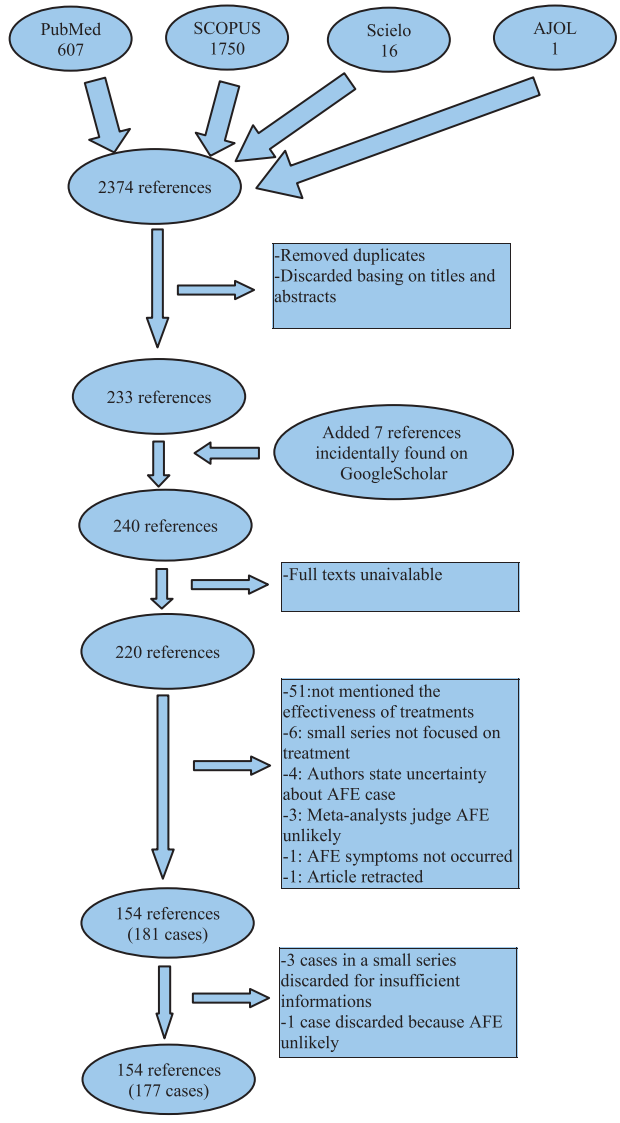

Figure 1. Flowchart of the systematic review (reproduced with permission).

Table 1. Clinical characteristics of patients with typical and atypical amniotic fluid embolism.

	Descriptive data	
Variables[a]	Atypical cases ($n = 56$)	Typical cases ($n = 121$)
Deaths	16 (28.6%)	37 (30.6%)
Age	Mean: 31.4 ages	Mean: 32.1 ages
	SD: ±6.66 ages	SD: ±6.22 ages
	Missing: 1 (1.2%)	Missing: 1 (0.8%)
	≥35 years: 17 (30.9%)	≥35 years: 46 (38.3%)
Multiparity	24 (48%)	68 (59.6%)%
	Missing: 6 (10.7%)	Missing: 7 (5.8%)
Over 30 weeks	44 (81.4%)	104 (87.4%)
	Missing: 2 (3.6%)	Missing: 2 (1.7%)
Caesarean section	37 (66.1%)	82 (67.8%)
Vaginal delivery	10 (17.9%)	15 (12.4%)
Operative vaginal birth	4 (7.1%)	20 (16.5%)
Miscarriage or pregnancy interruption	3 (5.4%)	6 (5%)
Blund trauma	2 (3.6%)	2 (1.7%)
Multiple pregnancy	5 (8.9%)	10 (8.3%)
Previous cesarean	2 (3.6%)	15 (12.4%)
Placenta previa	2 (3.6%)	15 (12.4%)
Placenta percreta	0	5 (4.1%)
Placenta abruptio	4 (7.1%)	1 (0.8%)
Premature rupture of membranes or amniotomy	25 (44.6%)	37 (30.6%)
Preeclampsia or hypertensive disorders of pregnancy	2 (3.6%)	6 (5%)
Prostaglandin agonists use	9 (16.1%)	28 (23.1%)
Oxytocin infusion during labour	10 (17.9%)	27 (22.3%)
Spinal anaesthesia/analgesia	17 (30.4%)	49 (40.5%)

[a]The rates of the above-mentioned variables were calculated on the total number of both atypical and typical AFE cases (descriptive statistics).

Table 2. Multivariable logistic regression analysis on the whole database (177 cases).

	Unadjusted odds ratio 95% confidence intervals *p*	Adjusted odds ratio 95% confidence intervals *p*
Placenta previa	1.347	1.323
	0.432–4.198	0.439–3.988
	0.608	0.619
Placenta abruptio	0.512	0.490
	0.054–4.829	0.052–4.589
	0.559	0.532
Age ≥35 years[a]	0.948	0.948
	0.470–1.915	0.470–1.913
	0.882	0.881
Cesarean section	0.815	0.845
	0.391–1.697	0.417–1.712
	0.584	0.639
Multiple pregnancy	0.984	0.984
	0.284–3.409	0.284–3.409
	0.980	0.980
Preeclampsia/hypertensive disorders of pregnancy	0.430	0.406
	0.050–3.727	0.048–3.457
	0.430	0.410
Prostaglandin agonists	0.544	0.531
	0.219–1.349	0.221–1.275
	0.189	0.157
Oxytocin infusion during labour	2.012	1.830
	0.909–4.454	0.861–3.892
	0.085	0.116

[a]As missing data are only two (1.1%), it was chosen to replace them with mean.

Table 3. Multivariable logistic regression analysis on the typical cases of AFE (121 cases).

	Unadjusted odds ratio 95% confidence intervals *p*	Adjusted odds ratio 95% confidence intervals *p*
Placenta previa	1.080	1.077
	0.306–3.810	0.314–3.690
	0.905	0.906
Placenta abruptio	115.145	120.331
	0–∞	0–∞
	1.000	1.000
Age ≥35 years[a]	1.010	1.010
	0.424–2.405	0.424–2.405
	0.983	0.983
Cesarean section	1.216	1.229
	0.484–3.058	0.499–3.025
	0.678	0.654
Multiple pregnancy	0.575	0.577
	0.106–3.132	0.112–2.959
	0.522	0.509
Preeclampsia/hypertensive disorders of pregnancy	0.848	0.841
	0.084–8.528	0.084–8.414
	0.889	0.883
Prostaglandin agonists	0.402	0.381
	0.127–1.271	0.129–1.129
	0.121	0.082
Oxytocin infusion during labour	2.521	2.890
	0.971–6.545	1.166–7.164
	0.057	0.022

[a]Missing case replaced with mean.

reports the unadjusted and adjusted odds ratios calculated after multivariable logistic regression analysis on the whole data pool (177 cases). No variable seems associated with death for AFE. Table 3 reports calculations on only typical cases of AFE (121 cases). Among the independent variables, only oxytocin infusion during labour increases the odds ratio of death in AFE cases (odds ratio 2.890, 95% confidence interval 1.166–7.164, $p = 0.022$). Among patients with both typical signs of AFE and some laboratory and/or pathological markers of amniotic embolisation (47 cases), none of the independent variables associate

with death, but the model overfits due to the paucity of data (results not shown).

Discussion

This in-depth analysis of AFE cases seems to suggest that, among the risk factors for AFE, the oxytocin use in labour (induction or augmentation) could associate with death if AFE onsets.

Caution in interpreting this result should be applied, because a post-hoc analysis of a data pool has some statistical flaws. The data pool is not the sample randomly extracted from a defined population, and the post-hoc analysis implies that cases were selected with another aim [6].

Moreover, as we do not know how much oxytocin was administered and how long the oxytocin administration lasted in labouring women, a drug-related effect cannot be speculated. Oxytocin during labour was adminisetred to 17.9% of atypical and to 22.3% of typical cases of AFE. Those rates were calculated on the whole groups of patients with AFE, thereby encompassing also patients not in labour (planned cesareans, abortions/pregnancy interruptions, blunt traumas: Table 1). Many population-based studies report heterogeneous rates of oxytocin augmentation, in relationship to obstetrical risk and obstetrical care [11–14], with a trend to reduction from 34.9% to 23.1% – for example – in Norway [14]. Therefore, it is difficult to compare rates of oxytocin administration reported in the present study to the various policy of oxytocin administration in labour worldwide.

Another point of caution in interpreting results is in relationship to the amount of the true cases of AFE in the series. The case definition of AFE remains challenging even after the publication of the article by Clark et al. [3]. Therefore, it is impossible to ascertain which case is not a true case of AFE. This kind of problem causes uncertainty also in interpreting population-based results among AFE cases. When stringent diagnostic criteria for AFE were used for finding sure AFE cases, information from non-typical cases of AFE was lost. We provided analysis on the whole data pool and on the typical AFE cases, finding that oxytocin in labour could be linked to fatality only in typical AFE cases. This behaviour cannot be exhaustively explained. A possible explanation could be that some atypical AFE cases were not true AFE cases in this data pool, leading to inconclusive results. However, Oi et al. [15] found an "abundance ratio" among the factors associated with fatality in AFE. Among these factors, there are the typical symptoms of AFE and the level of serum Syalil-Tn. The findings of Oi et al. [15] suggest that AFE has varying degrees of severity, the more severe is the disease (typical cases), the more severe is the outcome. Theoretically, this degree of severity should correlate with the amount of amniotic fluid embolisation. To have an amniotic fluid embolisation, two basic conditions are needed: the patency of vessels across the uterine wall and cervix, and a gradient of pressure from the amniotic cavity to the aforementioned vessels. Those conditions allow a flux of amniotic fluid, triggering AFE syndrome in predisposed patients [16]. Some risk factors for AFE could increase the amount of amniotic fluid embolisation [16], thereby worsening the outcome of AFE. Among those, the augmentation of labour with oxytocin could increase intra-uterine pressure, thereby realising the pressure gradient for amniotic fluid flow across the uterine vessels.

Fitzpatrick et al. [5] did not find that misoprostol (a prostaglandin agonist) increases the risk of AFE, thereby leading one to imagine that AFE should be related to other factors during labour induction. Moreover, the national-based survey of McDonnell et al. [17] highlights that some women with AFE and induction have also had labour augmentation with oxytocin; therefore, oxytocin augmentation of labour and labour induction could be at least inter-correlated. This inter-correlation could explain why induction is related to AFE [5,18] despite the fact that misoprostol use for induction is not related to AFE [5].

There are other side effects of oxytocin reported in the literature that could worsen the prognosis of AFE: during caesarean section, large doses of oxytocin cause a reduction of systolic blood pressure [19] and myocardial ischaemia [20]. It must be acknowledged that doses of oxytocin during labour augmentation or induction are lower than during caesarean section. However, as cardiac depression is involved in AFE pathophysiology [2], it should be proved if oxytocin infusion during labour can worsen AFE prognosis by acting on the cardiovascular system even at low doses.

The present study cannot determine if other conditions could be associated with fatality in AFE because some independent variables have a low rate of occurrence. We should consider that other clinical conditions could increase the amount of amniotic fluid embolisation. We hope that further case reports will describe the clinical picture of AFE in greater detail, allowing for a larger data pool. On the other hand, national registries and data sources should be checked to investigate the role of oxytocin infusion in labour in AFE cases.

In conclusion, this study would suggest that oxytocin use in labour associates with death if AFE onsets.

Other presumptive factors linked with fatality in AFE cases need a larger availability of data.

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Disclosure statement

The authors report no conflict of interest.

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