REVIEW ARTICLE/BRIEF REVIEW

Echocardiography findings in amniotic fluid embolism: a systematic review of the literature

Observations échocardiographiques lors d'une embolie de liquide amniotique : une revue systématique de la littérature

Daniel Wiseman, MD · Camille Simard, MD · Stephen S. Yang, MD, MSc · Maral Koolian, MD, MSc · Haim A. Abenhaim, MD, MPH · Jed Lipes, MD ⓘ

Abstract

Purpose *Amniotic fluid embolism (AFE) is a leading cause of obstetrical cardiac arrest and maternal morbidity. The pathogenesis of hemodynamic collapse is thought to be from right ventricular (RV) failure; however, there is a paucity of data documenting echocardiography findings in this population. We undertook a systematic review of the literature to evaluate the echocardiography findings in patients with AFE.*

Sources *We retrieved all case reports and case series reporting AFE in Embase and MEDLINE from inception to 20 November 2021. Studies reporting AFE diagnosed by fulfilling at least one of three different proposed AFE criteria and echocardiography findings during hospitalization were included. Patient and echocardiographic data were retrieved, and univariate logistic regression analysis was performed for outcomes of interest. Bias was assessed using the Joanna Briggs Institute clinical appraisal tool for case series.*

Principal findings *Eighty publications reporting on 84 patients were included in the final review. Fifty-five out of 82 patients with data (67%) showed RV dysfunction, including 11/82 (13%) with biventricular dysfunction; 14/82 (17%) had normal systolic function. No data on RV or left ventricular function were reported for two patients. The presence of RV dysfunction on echocardiography was associated with cardiac arrest (odds ratio [OR], 3.66; 95% confidence interval [CI], 1.39 to 9.67; P = 0.009), and a composite risk of cardiac arrest, maternal death or use of extracorporeal membrane*

D. Wiseman, MD
Department of Medicine, McGill University, Montreal, QC, Canada

C. Simard, MD · M. Koolian, MD, MSc
Division of General Internal Medicine, Jewish General Hospital, McGill University, Montreal, QC, Canada

S. S. Yang, MD, MSc
Department of Anesthesia, Jewish General Hospital, McGill University, Montreal, QC, Canada

Division of Critical Care, Jewish General Hospital, McGill University, Montréal, QC, Canada

H. A. Abenhaim, MD, MPH
Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Jewish General Hospital, McGill University, Montreal, QC, Canada

J. Lipes, MD (✉)
Division of General Internal Medicine, Jewish General Hospital, McGill University, Montreal, QC, Canada
e-mail: jed.lipes@mcgill.ca

Division of Critical Care, Jewish General Hospital, McGill University, Montréal, QC, Canada

oxygenation (OR, 3.86; 95% CI, 1.43 to 10.4; P = 0.007). A low risk of bias was observed in 15/84 (18%) cases.

Conclusions *Right ventricular dysfunction on echocardiography is a common finding in AFE and is associated with a high risk of cardiac arrest. The finding of RV dysfunction on echocardiography may help diagnose AFE and help triage the highest risk patients with AFE.*

Study registration *PROSPERO (CRD42021271323); registered 1 September 2021.*

Résumé

Objectif *L'embolie amniotique (EA) est l'une des principales causes d'arrêt cardiaque obstétrical et de morbidité maternelle. Il est présumé que la pathogenèse du choc hémodynamique provient d'une défaillance ventriculaire droite (VD). Cependant, il y a peu de données documentant les constatations de l'examen échocardiographique dans cette population. Nous avons effectué une revue systématique des données probantes visant à évaluer l'utilité de l'échocardiographie chez les patientes atteintes d'embolie amniotique.*

Sources *Nous avons évalué tous les rapports de cas et séries de cas rapportant une EA dans les bases de données Embase et MEDLINE de leur création jusqu'au 20 novembre 2021. Les études rapportant une EA diagnostiquée en remplissant au moins l'un des trois critères d'EA proposés et les résultats échocardiographiques pendant l'hospitalisation ont été inclus. Les données sur les patientes et échocardiographiques ont été colligées, et une analyse de régression logistique univariée a été effectuée pour les issues cliniques d'intérêt. Le risque de biais a été évalué à l'aide de l'outil d'évaluation clinique de l'Institut Joanna Briggs pour les séries de cas.*

Constatations principales *Quatre-vingts publications incluant 84 patientes ont été incluses dans la revue finale. Cinquante-cinq des 82 patientes présentant des données (67 %) avaient une dysfonction du VD incluant 11/82 (13 %) avec une dysfonction biventriculaire. Quatorze patientes sur 82 (17 %) avaient une fonction systolique normale. Aucune donnée sur la fonction du ventricule droit ou gauche n'a été rapportée pour deux patientes. La présence d'une dysfonction du VD à l'échocardiographie était associée à un arrêt cardiaque (rapport de cotes [RC], 3,66; intervalle de confiance à 95 % [IC], 1,39 à 9,67; P = 0,009), et à un risque composite d'arrêt cardiaque, de décès maternel ou d'utilisation de l'oxygénation par membrane extracorporelle (ECMO) (RC, 3,86; IC 95 %, 1,43 à 10,4; P = 0,007). Un faible risque de biais a été observé dans 15/84 (18 %) des cas.*

Conclusion *La dysfonction ventriculaire droite à l'échocardiographie est une constatation courante dans l'embolie amniotique et est associée à un risque élevé d'arrêt cardiaque. La découverte d'une dysfonction du VD à l'échocardiographie peut aider à diagnostiquer l'embolie amniotique et à identifier les patientes atteintes d'embolie amniotique les plus à risque.*

Enregistrement de l'étud *PROSPERO (CRD42021271323); enregistrée le 1er septembre 2021.*

Amniotic fluid embolism (AFE) is a rare clinical syndrome reported to complicate one to eight per 100,000 pregnancies with a mortality rate between 20% and 60%.[1,2] Clinical features consist of profound maternal hypotension with or without respiratory distress and severe coagulopathy, often progressing to maternal cardiac arrest.[2] Amniotic fluid embolism remains one of the leading causes of maternal death in high-income countries.[3] The pathophysiology of this condition is incompletely understood. It is thought to occur following maternal exposure to amniotic fluid or fetal debris, causing either an anaphylactoid or immune-mediated cardiovascular collapse with acute right ventricular (RV) failure.[4] Rarely, actual maternal vascular obstruction with subsequent cardiogenic shock can occur.[4]

Different criteria for the diagnosis of AFE have been proposed.[5–7] The USA diagnostic criteria were created to establish uniform criteria for research purposes and have been recently validated.[8] Other criteria have been shown to have only modest agreement.[9,10] The diagnosis remains clinical, without specific diagnostic tests or biomarkers, and there is considerable overlap with other etiologies of maternal collapse.[4,11] Moreover, because of the fulminant clinical presentation and rarity of the condition, the study of AFE is challenging.[12]

Point-of-care echocardiography has emerged as a valuable tool in the diagnostic algorithm of patients with hemodynamic instability or cardiac arrest, and several reports have suggested using echocardiography to both help identify and promptly manage AFE.[13,14] The aim of the current systematic review was to describe echocardiographic findings in patients with AFE who fulfilled established diagnostic criteria.

Methods

Protocol and registration

The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[15] The

protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021271323) on 1 September 2021. Review objectives, criteria for article selection, and bias assessment method were defined *a priori*.

Data sources and search strategy

A search strategy was developed in conjunction with a medical librarian. An electronic search was conducted from database inception to 20 November 2021 in Medical Literature Analysis and Retrieval System (MEDLINE) and Excerpta Medica Database (Embase). We used a combination of keywords and database-specific medical subject heading terms to describe AFE and anaphylactoid syndrome of pregnancy. Our detailed search strategy is presented in the Electronic Supplementary Material (ESM), eAppendix 1. The search strategy was adapted for each database based on its specific nomenclature. The search was restricted to articles written in English. There was no geographic location restriction. All results were imported into an EndNote X9 library (Clarivate Analytics, London, UK) to remove duplicates and then transferred into Rayyan (Qatar Computing Research Institute, Hamad Bin Khalifa University, Ar-Rayyan, Qatar) to ensure rigorous methodology and reporting.

Article selection and eligibility criteria

All case series or case reports of patients suspected of having AFE were initially screened. Screening forms were developed with inclusion and exclusion criteria. Title and abstracts were screened by two independent reviewers (C. S., D. W.). Disagreements were first resolved by discussion. If disagreement persisted, a third author (J. L.) was asked to independently review to achieve consensus. Full-text manuscripts were independently reviewed by two independent authors (D. W., C. S.) and disagreement was resolved by consensus.

All publications reporting AFE diagnosed by the United Kingdom Obstetrical Surveillance System (UKOSS), Japan, or USA criteria, and reporting echocardiography findings were included for analysis.[5–7] The UKOSS criteria include either 1) acute maternal collapse with one or more of the following features: acute fetal compromise, cardiac arrhythmias or arrest, coagulopathy, convulsion, hypotension, maternal hemorrhage, premonitory symptoms (such as restlessness, numbness, agitation, tingling), shortness of breath, and excluding women with maternal hemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardiorespiratory compromise or 2) women in whom the diagnosis was made at post mortem examination based on fetal squames or hair in the lungs.[7] The Japan diagnostic criteria for AFE include patients requiring any intensive medical intervention to treat either 1) cardiac arrest, 2) severe bleeding ($\geq$ 1,500 mL) of unknown origin within two hours of delivery, 3) disseminated intravascular coagulation (DIC), or 4) respiratory failure if symptoms appeared during pregnancy or within 12 hr of delivery and the findings cannot be explained by other diseases.[6] The USA criteria consist of 1) sudden onset of cardiorespiratory arrest, or both hypotension (systolic blood pressure < 90 mm Hg) and respiratory compromise (dyspnea, cyanosis, or hypoxia [oxygen saturation $< 90\%$]), 2) DIC, 3) clinical onset during labor or within 30 min of delivery, and 4) the absence of fever (temperature $< 38.0°C$) during labor.[5]

Data extraction

Data pertaining to study characteristics, maternal demographics, medical history, and obstetrical history were collected in an electronic data extraction spreadsheet. The individual components of the three aforementioned AFE diagnostic criteria were recorded.[5–7] The timing of echocardiography following AFE, the type of echocardiogram (transthoracic or transesophageal), and all qualitative and quantitative measures of ventricular structure and function were recorded. Clinical outcomes including the incidence of cardiac arrest, maternal and fetal mortality, perimortem Cesarean delivery, the use of extracorporeal membrane oxygenation (ECMO), and length of stay were also recorded.

Risk of bias assessment

We evaluated the risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal tool for assessing bias in case series on all included studies.[16] As individual patient data from case series provided the best available evidence for our study question, this validated tool was used to assess the internal validity and the risk of bias. The JBI checklist was modified for our study population using standard questions. Four questions from the JBI checklist were not applicable to our study and were not scored. The critical appraisal of included publications is available in ESM eAppendix 2. Studies obtaining a "yes" for all questions were deemed to be of low risk of bias; if they obtained one "unclear," they were considered to be of moderate risk of bias; if they obtained one "no" or two "unclear" responses, they were considered at high risk of bias (ESM eAppendix 2). Two independent assessments of bias were done by study authors (D. W., C. S.) and disagreement was resolved by consensus.

Data synthesis and analysis

Maternal characteristics and echocardiography findings in AFE are summarized using descriptive statistics. Data from

each individual participant were retrieved from the articles and analyzed. As cardiac function can be affected by cardiac arrest, we compared echocardiography findings between patients with and without cardiac arrest using Chi square statistics. Significance was defined as $P < 0.05$ and all tests were two-sided. As AFE may present with a wide spectrum of clinical phenotypes, from isolated bleeding to hemodynamic collapse, we sought to investigate whether echocardiographic findings may be associated with important clinical outcomes. Univariate logistic regression analyses were performed to determine association between predefined risk factors and cardiac arrest, as well as a composite outcome of cardiac arrest, maternal death, and use of ECMO. Independent variables included age, delivery type, placental abnormalities (abruption or previa), DIC, left ventricular (LV) dysfunction, RV dysfunction, biventricular dysfunction, and normal function. Disseminated intravascular coagulation was defined as $\geq$ 26 points on the International Society of Thrombosis and Hemostasis DIC score modified for pregnancy.[17] Rotational thromboelastometry was accepted if used as a surrogate for other markers of coagulation.

Ventricular dysfunction was defined as any abnormal quantitative or qualitative assessment of structure or function of the right or left ventricle. We extracted quantitative LV ejection fraction assessment with dysfunction defined as an LV ejection fraction less than 50%, LV myocardial performance index, or qualitative description of regional all motion abnormalities, dyskinetic or visually reduced LV contraction or author described LV failure on echo. Right ventricular dysfunction was defined quantitatively if tricuspid annular plan systolic excursion (TAPSE) was below 17 mm, or fractional area change (FAC) was less than 35%. Qualitatively, RV dysfunction was defined as any mention of a dilated, dyskinetic RV, including the presence of D-shaped septum or McConnel sign, or when the authors explicitly described RV dysfunction on echocardiography. Biventricular dysfunction was defined as having at least one of each RV or LV dysfunction features listed above. For missing data related to echocardiography reports, if the function of only one ventricle (LV or RV) was reported, we imputed the data for the other ventricle as normal. Stata/MP version 15 (College Station, TX, USA) was used for all statistical analysis.

Results

A total of 2,636 publications were identified from MEDLINE and Embase. We assessed 426 publications for full-text review, with 91 reporting both AFE and echocardiography findings; 11 articles were ultimately excluded (ESM eAppendix 3). Eighty-four cases from 80 publications were found to satisfy all inclusion and exclusion criteria. The PRISMA flow diagram is presented in the Figure.

Quality assessment using the JBI checklist for case series revealed that 15/84 (18%) of cases were considered to have a low risk of bias, whereas 24/84 (29%) and 45/84 (54%) had an intermediate and high risk of bias, respectively (ESM eAppendix 2).

All patients (100%) met AFE criteria as defined by UKOSS, with 50/84 (60%) patients meeting the Japan criteria, and 36/84 (43%) meeting the USA criteria. Seven (9%) patients died, and 54/84 (64%) patients had a cardiac arrest. Perimortem Cesarean delivery was performed in 14 (17%) patients, and 18/84 (21%) required ECMO. Demographics, clinical characteristics, and outcomes are shown in Table 1.

Most patients (55/82 with data, 67%) showed signs of RV involvement, including 11/82 (13%) patients who had biventricular failure. Left ventricular dysfunction was reported in 24/82 (29%) of patients, while 14/82 (17%) had normal function (Table 2). Only four publications reported detailed quantitative measures of RV function with TAPSE or FAC;[13,18–20] 19 publications (23%) reported quantitative assessments of ejection fraction. No data on RV or left ventricular function were reported for two patients.

The echocardiography findings were not dependent on meeting one proposed AFE criteria over another (Table 2). Moreover, when comparing patients who did not meet Japan or USA criteria with the patients meeting UKOSS criteria, there was no difference in the presence of RV dysfunction ($P = 0.08$), LV dysfunction ($P = 0.69$), or biventricular dysfunction ($P = 0.96$).

Right ventricular dysfunction was more frequent in patients who had a cardiac arrest ($P = 0.03$) (Table 3), and the presence of RV failure on univariate logistic regression was associated with both cardiac arrest (odds ratio [OR], 3.66; 95% confidence interval [CI], 1.39 to 9.7; $P = 0.009$), and a composite outcome of cardiac arrest, maternal mortality, and the use of ECMO (OR, 3.86; 95% CI, 1.43 to 10.4; $P = 0.007$) (Table 4). Normal ventricular function was associated with a lower incidence of cardiac arrest (OR, 0.16; 95% CI, 0.04 to 0.55; $P = 0.004$) (Table 4).

Only 23/84 (27%) cases reported pulmonary pressure assessments of which 20/23 (87%) had pulmonary hypertension; 9/23 (39%) consisted of the authors declaring the presence of pulmonary hypertension without providing any quantitative assessment, while 14/23 (61%) provided quantitative assessments, including three with normal values. Of the 14 that provided quantitative data, three specified that pulmonary pressures

Identification of studies via databases and registers
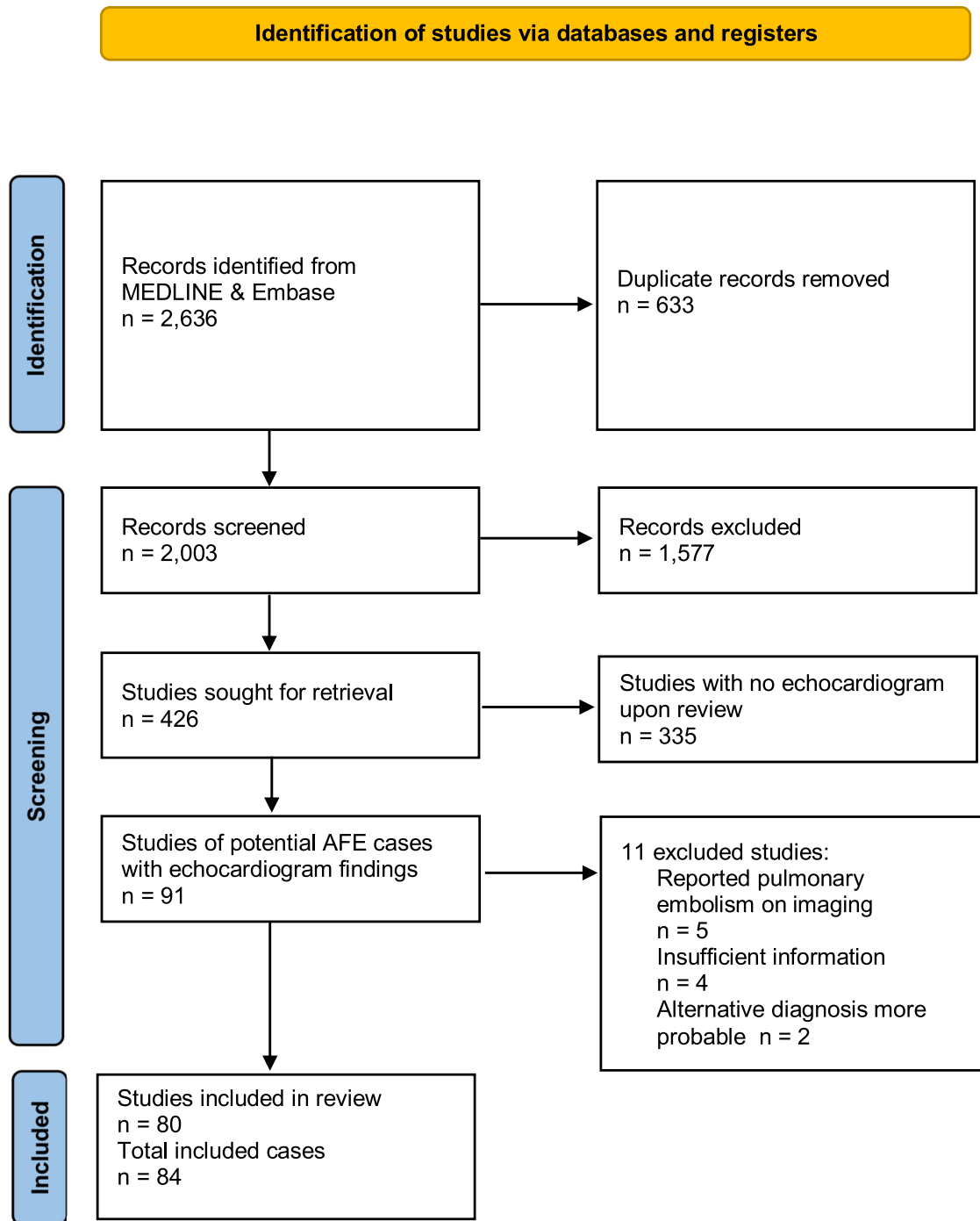
AFE=amniotic fluid embolism

Figure PRISMA flow diagram for the systematic review detailing the database searches, the number of abstracts screened, and the full texts retrieved

were calculated using continuous wave Doppler through a tricuspid regurgitation jet.

Table 1 Characteristics and outcomes of patients with amniotic fluid embolism

Variables	N = 84
Age (yr), mean (SD) (N = 82)	32.8 (6.2)
Age categories (yr) (N = 82)	
18–24	9/82 (11%)
25–29	14/82 (17%)
30–34	26/82 (32%)
35–39	21/82 (26%)
≥ 40	12/82 (15%)
AFE UKOSS criteria	84/84 (100%)
AFE Japan criteria	50/84 (60%)
AFE USA criteria	36/84 (43%)
Cesarean delivery (N = 81)	59/81 (73%)
Instrumental delivery (N = 64)	14/64 (22%)
Placental pathology (N = 50)	
Abruption	4/50 (8%)
Previa	11/50 (22%)
Normal	35/50 (70%)
Transesophageal echocardiography (N = 62)	32/62 (52%)
Disseminated intravascular coagulation (N = 54)	49/54 (91%)
Major bleeding (N = 66)	58/66 (88%)
Perimortem Cesarean delivery (N = 83)	14/83 (17%)
Extracorporeal membrane oxygenation (N = 83)	18/83 (22%)
Cardiac arrest	54/84 (64%)
Maternal mortality (N = 82)	7/82 (9%)
Fetal mortality (N = 41)	9/41 (22%)
ICU LOS, mean (SD) (N = 35)	7.9 (11%)
Hospital LOS, mean (SD) (N = 60)	15.3 (18)

Numbers are n/total N with data (%) unless otherwise specified

AFE = amniotic fluid embolism; ICU = intensive care unit; LOS = length of stay; SD = standard deviation; UKOSS = United Kingdom Obstetric Surveillance System

Twelve cases described intracardiac lesions, 3/84 (4%) described debris, 4/84 (5%) described thrombus or clot, and 5/84 (6%) described a mass. In 26 cases, pulmonary embolism (PE) was formally excluded as a potential alternative diagnosis with either computed tomography scanning or ventilation perfusion imaging.

Approximately, half (40/84, 48%) of echocardiograms were performed periresuscitation, defined as within one hour of the event; 5/84 (6%) were performed between one and six hours after the event, 11/84 (13%) occurred between six and 24 hr after the event, and 3/84 (4%) occurred at least 24 hr after the event. In nearly one third of cases (25/84, 29%), the timing of the echocardiogram was not specified. When compared with the 40 echocardiography examinations that were performed within one hour of an AFE, 19 that were performed > one hour after the AFE had no significantly different RV ($P = 0.23$), LV ($P = 0.42$), or biventricular dysfunction ($P = 0.90$).

Of the 26 patients who had a follow-up echocardiogram following clinical resolution of acute illness, 23 (88%) had resolution of ventricular dysfunction.

Table 3 Echocardiography findings stratified according to the occurrence of cardiac arrest

Echocardiography findings	Cardiac arrest N = 53*	No cardiac arrest N = 29*	P value
Normal systolic ventricular function	4/53 (8%)	10/29 (35%)	0.002
Right ventricular dysfunction	41/53 (77%)	14/29 (48%)	0.03
Left ventricular dysfunction	18/53 (34%)	6/29 (21%)	0.41
Biventricular dysfunction	10/53 (19%)	1/29 (3%)	0.05

All numbers are n/total N (%)

*One patient in each group had unknown ventricular function and was excluded

Table 2 Echocardiography findings according to UKOSS, Japan, or USA criteria for amniotic fluid embolism

Echocardiography findings	UKOSS N = 82*	Japan N = 48*	USA N = 36
Normal systolic ventricular function	14/82 (17%)	4/48 (8%)	2/36 (6%)
Right ventricular dysfunction	55/82 (67%)	36/48 (75%)	28/36 (78%)
Left ventricular dysfunction	24/82 (29%)	14/48 (29%)	12/36 (33%)
Biventricular dysfunction	11/82 (13%)	6/48 (13%)	6/36 (17%)

All numbers are n/total N (%)

*Two patients in the UKOSS and Japan cohorts had unknown ventricular function and were excluded

UKOSS = United Kingdom Obstetric Surveillance System

Table 4 Univariate analysis for the risk of cardiac arrest and a composite risk of arrest, death, or need for ECMO

Variable	Odds ratio for cardiac arrest (95% CI)	P value	Odds ratio for cardiac arrest, maternal death, or ECMO (95% CI)	P value
Age	1.05 (0.97 to 1.13)	0.21	1.07 (0.99 to 1.16)	0.09
Cesarean delivery	1.90 (0.69 to 5.19)	0.21	1.86 (0.67 to 5.19)	0.24
Placental abnormality	1.19 (0.44 to 3.23)	0.73	1.82 (0.55 to 6.07)	0.33
DIC	1.05 (0.16 to 6.89)	0.96	1.38 (0.21 to 9.07)	0.74
Normal ventricular function	0.16 (0.04 to 0.55)	0.004	0.12 (0.03 to 0.45)	0.001
Right ventricular dysfunction	3.66 (1.39 to 9.67)	0.009	3.86 (1.43 to 10.38)	0.007
Left ventricular dysfunction	1.97 (0.68 to 5.71)	0.21	2.16 (0.70 to 6.62)	0.18
Biventricular dysfunction	6.5 (0.79 to 53.71)	0.08	5.4 (0.66 to 44.94)	0.12

CI = confidence interval; DIC = disseminated intravascular coagulation; ECMO = extracorporeal membrane oxygenation

Discussion

In this systematic review of case reports and case series on echocardiography findings in patients with AFE, most patients showed RV dysfunction, including RV dilatation or abnormal systolic wall motion. Although the mechanism of disease remains incompletely understood, hypothesis with regard to the pathophysiology of AFE has evolved and is now thought to include acute pulmonary vasospasm causing pulmonary hypertension, ultimately leading to RV dysfunction.[2,21] Our findings are consistent with this contemporary understanding of AFE pathophysiology.[21] Right ventricular pressure overload on echocardiography is often seen as RV dilatation with a diameter of > 43 mm in females in the basal segment on an apical four-chamber RV focused view, an increased RV to LV ratio > 1 at end-diastole in the apical four-chamber view, or as a D-shaped septum in the short-axis view.[22] These are all rapidly obtained on point-of-care echocardiography.[23] Measurement of TAPSE, RV FAC, tissue Doppler-derived tricuspid lateral annular systolic velocity, free wall longitudinal strain, and RV index of myocardial performance are additional measurements that can help quantify RV dysfunction, and when time permits should be obtained for a more complete RV assessment.[22] Unfortunately, likely owing to the hemodynamic instability of the patients undergoing an echocardiogram in our review, only four publications reported detailed quantitative measures of RV function with TAPSE or FAC.[13,18–20]

Right ventricular dysfunction was associated with an increased risk of cardiac arrest and a composite outcome of severe maternal complications (cardiac arrest, death, and use of ECMO). Our findings further strengthen the hypothesis that the pathophysiology of AFE results from transient acute pulmonary hypertension and acute RV failure. Indeed, of those patients for whom pulmonary pressures were reported, 87% had pulmonary hypertension. The presence of RV dysfunction in patients with AFE should be considered an ominous sign, and urgent transfer to a critical care unit with the ability to provide hemodynamic support and possible ECMO should be considered.[24]

Our review found that most echocardiograms were done in the immediate (< one hour) periresuscitation period; however, some were performed well after cardiac arrest and/or after medical treatments were initiated. It is possible that findings found on more delayed echocardiograms represent sequelae of AFE and not diagnostic AFE findings. Ongoing shock and medical therapies (e.g., vasopressors or volume resuscitation) have been found to alter echocardiography findings.[25] Nevertheless, when comparing echo findings in studies with echocardiograms performed within one hour of the AFE to those performed > one hour following AFE, we found no statistical difference in reported RV or LV dysfunction. Moreover, ventricular dysfunction described in AFE is thought to occur in a biphasic fashion, with early RV dysfunction related directly to the proposed pathophysiology of AFE, and a second phase where LV failure occurs related to ongoing shock.[21,26] Importantly, post return of spontaneous circulation echocardiograms from cardiac arrest often shows specific patterns in line with the underlying diagnosis and can be used to elucidate the etiology of arrest.[27,28]

The most common causes of cardiac arrest in pregnancy include hemorrhagic shock, anesthetic complications, left heart failure, thromboembolic disease, and AFE.[3,29] Echocardiography can help classify obstetrical patients who are in shock into distinct hemodynamic categories with either a hyperdynamic profile, LV hypokinesis/dilation, or RV hypokinesis/dilation.[13] The presence of acute RV dysfunction on echocardiography can rapidly help narrow the differential diagnosis and facilitate patient

management. Nevertheless, RV failure is not pathognomonic for AFE, and PE may present with similar clinical and echocardiographic findings.[23] We attempted to mitigate the risk of misclassification in our review by only including cases that met currently accepted definitions for AFE, and excluded cases that had a clear alternative diagnosis. It, however, remains possible that some of the echocardiography findings described may have been caused by other conditions. Twelve percent of cases reported a clot or mass on echocardiography; despite fulfilling criteria for AFE and although vascular occlusion from large fetal material has been reported in AFE, this is thought to be an unlikely mechanism of disease.[4,20] When intracardiac masses are detected on echocardiography in the peripartum period, PE with a clot in transit remains an alternative diagnosis.[30] Interestingly, in our systematic review, only one third of the cases formally excluded PE. As AFE presents with acute cardiorespiratory collapse and signs of RV dysfunction, there is no reliable way at the bedside to exclude PE. For this reason, we recommend that, when feasible, all suspected cases of AFE undergo a formal PE study, or if unstable, a point-of-care ultrasound (POCUS) to rule out deep vein thrombosis.

No significant differences were found when comparing echocardiography findings across three different AFE criteria. Past studies have shown only modest agreement between the different proposed criteria for AFE with the understanding that each definition may identify different AFE subgroups.[9] The Japan criteria include a timeframe of up to 12 hr postpartum and allow for inclusion of isolated unexplained DIC or bleeding without hemodynamic compromise or so-called "atypical AFE."[31] In comparison, the USA criteria only allow AFE to be defined if occurring within 30 min postpartum and require the presence of hemodynamic instability.[9] The findings of similar echocardiography characteristics across the different AFE criteria found in our review could be attributed to the fact that AFE patients who had an urgent echocardiogram were more likely to be hemodynamically unstable, and likely represent similar clinical phenotypes.

Limitations

This study has limitations. The data were extracted from case series and case reports, and most studies had an intermediate or high risk of bias. Because of the rarity of this diagnosis, prospective observational evidence is not available for this population. This review represents the best available evidence and the risk of bias was assessed with a validated critical appraisal tool to help assess methodological quality in case series.[16] Moreover, there is likely publication bias, as evidenced by a very low reported mortality in the included publications; however, despite

mortality being potentially underestimated, this should not affect the descriptive echocardiographic findings. The echocardiograms were performed on selected patients who were clinically ill enough to warrant rapid diagnostic imaging, and survived long enough to undergo this test, raising the question of an immortal-time bias. Although only patients who are hemodynamically unstable may have had urgent echocardiograms, it makes physiologic sense that patients with hemodynamically significant AFE leading to instability would show RV failure. Another important consideration is the timing of the echocardiogram in relation to the AFE. The delay to echocardiography may have important consequences on its results given that some findings may be transient, and others may be affected by ongoing treatment, or other physiologic changes. We aimed to report all described findings in the literature and not restrict to a particular timeframe because it is not clear how long certain echocardiographic findings may remain after the event. Eliminating some studies based on timing of echo might have introduced bias. Nonetheless, given the small numbers of studies reported, and the challenge in determining if the AFE or concurrent treatments affected the echo findings, the timing of echocardiogram remains a significant limitation.

Additionally, many studies only reported findings of one ventricle being abnormal, and we chose to impute the data for the other ventricle as normal. This may have introduced bias into our findings and is an important methodologic limitation. Finally, most studies provided only qualitative descriptions of LV and RV function, frequently reporting only abnormal findings, and did not mention the operator's training in echocardiography, which may decrease the accuracy of the findings. Nevertheless, POCUS studies performed by relatively less experienced operators compared with fully trained cardiologists have been reported to maintain diagnostic accuracy in the critically ill.[32]

Conclusion

Right ventricular dysfunction is the most common finding in acute AFE and is associated with an increased risk of cardiac arrest. These findings further support the contemporary view of acute pulmonary hypertension and RV failure as the cause of cardiorespiratory collapse in AFE. Echocardiography may be useful to narrow the differential diagnosis in obstetrical shock, and to triage the highest risk AFE patients who may require more advanced hemodynamic support. Given the limitations related to focused and qualitative echocardiographic reporting, and echocardiograms occurring at variable times post AFE, the

abovementioned findings are hypothesis-generating and require further study.

References

1. *Kramer MS, Berg C, Abenhaim H, et al*. Incidence, risk factors, and temporal trends in severe postpartum hemorrhage. Am J Obstet Gynecol 2013; 209: e1–7. https://doi.org/10.1016/j.ajog.2013.07.007

2. *Shamshirsaz AA, Clark SL*. Amniotic fluid embolism. Obstet Gynecol Clin North Am 2016; 43: 779–90. https://doi.org/10.1016/j.ogc.2016.07.001

3. *Mhyre JM*. Maternal mortality. Curr Opin Anaesthesiol 2012; 25: 277–85. https://doi.org/10.1097/aco.0b013e3283530580

4. *Ito F, Akasaka J, Koike N, Uekuri C, Shigemitsu A, Kobayashi H*. Incidence, diagnosis and pathophysiology of amniotic fluid embolism. J Obstet Gynaecol 2014; 34: 580–4. https://doi.org/10.3109/01443615.2014.919996

5. *Clark SL, Romero R, Dildy GA, et al*. Proposed diagnostic criteria for the case definition of amniotic fluid embolism in research studies. Am J Obstet Gynecol 2016; 215: 408–12. https://doi.org/10.1016/j.ajog.2016.06.037

6. *Kanayama N, Tamura N*. Amniotic fluid embolism: pathophysiology and new strategies for management. J Obstet Gynaecol Res 2014; 40: 1507–17. https://doi.org/10.1111/jog.12428

7. *Fitzpatrick KE, Tuffnell D, Kurinczuk JJ, Knight M*. Incidence, risk factors, management and outcomes of amniotic-fluid embolism: a population-based cohort and nested case-control study. BJOG 2016; 123: 100–9. https://doi.org/10.1111/1471-0528.13300

8. *Stafford IA, Moaddab A, Dildy GA, et al*. Evaluation of proposed criteria for research reporting of amniotic fluid embolism. Am J Obstet Gynecol 2019; 220: 285–7. https://doi.org/10.1016/j.ajog.2018.11.1099

9. *Kobayashi H, Akasaka J, Naruse K, et al*. Comparison of the different definition criteria for the diagnosis of amniotic fluid embolism. J Clin Diagn Res 2017; 11: QC18–21. https://doi.org/10.7860/jcdr/2017/26746.10283

10. *Ponzio-Klijanienko A, Vincent-Rohfritsch A, Girault A, Le Ray C, Goffinet F, Bonnet MP*. Evaluation of the 4 diagnosis criteria proposed by the SMFM and the AFE foundation for amniotic fluid embolism in a monocentric population. J Gynecol Obstet Hum Reprod 2020; 49: 101821. https://doi.org/10.1016/j.jogoh.2020.101821

11. *Thomson AJ, Greer IA*. Non-haemorrhagic obstetric shock. Baillieres Best Pract Res Clin Obstet Gynaecol 2000; 14: 19–41. https://doi.org/10.1053/beog.1999.0061

12. *Clark SL*. A biomarker for amniotic fluid embolism: the search continues. BJOG 2021; 128: 1974. https://doi.org/10.1111/1471-0528.16833

13. *Simard C, Yang S, Koolian M, Shear R, Rudski L, Lipes J*. The role of echocardiography in amniotic fluid embolism: a case series and review of the literature. Can J Anesth 2021; 68: 1541–8. https://doi.org/10.1007/s12630-021-02065-4

14. *Blanco P, Abdo-Cuza A*. Point-of-care ultrasound in the critically ill pregnant or postpartum patient: what every intensivist should know. Intensive Care Med 2019; 45: 1123–6. https://doi.org/10.1007/s00134-019-05682-2

15. *Page MJ, McKenzie JE, Bossuyt PM, et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71. https://doi.org/10.1136/bmj.n71

16. *Munn Z, Barker TH, Moola S, et al*. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. JBI Evid Synth 2020; 18: 2127–33. https://doi.org/10.11124/jbisrir-d-19-00099

17. *Erez O, Novack L, Beer-Weisel R, et al*. DIC score in pregnant women–a population based modification of the International Society on Thrombosis and Hemostasis score. PloS One 2014; 9: e93240. https://doi.org/10.1371/journal.pone.0093240

18. *Barriuso V, Pombar X, Bankowski HA*. The use of therapeutic hypothermia in the management of amniotic fluid embolism. Obstet Med 2013; 6: 92–3. https://doi.org/10.1258/om.2011.110069

19. *De Angelis E, Prota C, Matturro R, Citro R*. Amniotic fluid embolism in a grown-up congenital heart disease patient. J Cardiovasc Echogr 2019; 29: 20–2. https://doi.org/10.4103/jcecho.jcecho_64_18

20. *Maack KH, Munk K, Dahl K, Jørgensen HH, Christiansen A, Helmig RB*. Right heart masses demonstrated by echocardiography in a patient with amniotic fluid embolism during labour. Acta Anaesthesiol Scand 2018; 62: 134–7. https://doi.org/10.1111/aas.13006

21. *Bernstein SN, Cudemus-Deseda GA, Ortiz VE, Goodman A, Jassar AS*. Case 33-2019: a 35-year-old woman with cardiopulmonary arrest during cesarean section. N Engl J Med 2019; 381: 1664–73. https://doi.org/10.1056/nejmcpc1904046

22. *Zaidi A, Knight DS, Augustine DX, et al*. Echocardiographic assessment of the right heart in adults: a practical guideline from the British Society of Echocardiography. Echo Res Pract 2020; 7: G19–41. https://doi.org/10.1530/erp-19-0051

23. *Mandoli GE, Sciaccaluga C, Bandera F, et al*. Cor pulmonale: the role of traditional and advanced echocardiography in the acute and chronic settings. Heart Fail Rev 2021; 26: 263–75. https://doi.org/10.1007/s10741-020-10014-4

24. *Viau-Lapointe J, Filewod N*. Extracorporeal therapies for amniotic fluid embolism. Obstet Gynecol 2019; 134: 989–94. https://doi.org/10.1097/aog.0000000000003513

25. *Tabi M, Burstein BJ, Anavekar NS, Kashani KB, Jentzer JC*. Associations of vasopressor requirements with echocardiographic parameters after out-of-hospital cardiac arrest. J Intensive Care Med 2022; 37: 518–27. https://doi.org/10.1177/0885066621998936

26. *Conde-Agudelo A, Romero R*. Amniotic fluid embolism: an evidence-based review. Am J Obstet Gynecol 2009; 201: e1–13. https://doi.org/10.1016/j.ajog.2009.04.052

27. *Elfwén L, Hildebrand K, Schierbeck S, et al*. Focused cardiac ultrasound after return of spontaneous circulation in cardiac-arrest patients. Resuscitation 2019; 142: 16–22. https://doi.org/10.1016/j.resuscitation.2019.06.282

28. *Zengin S, Yavuz E, Al B, et al*. Benefits of cardiac sonography performed by a non-expert sonographer in patients with non-traumatic cardiopulmonary arrest. Resuscitation 2016; 102: 105–9. https://doi.org/10.1016/j.resuscitation.2016.02.025

29. *Balki M, Liu S, León JA, Baghirzada L*. Epidemiology of cardiac arrest during hospitalization for delivery in canada: a nationwide study. Anesth Analg 2017; 124: 890–7. https://doi.org/10.1213/ane.0000000000001877

30. *O'Neill JO, Iqbal R, McGarry K*. "Thrombus in transit"–the role of echocardiography in the diagnosis of massive pulmonary embolism and a review of the literature. Acta Cardiol 2002; 57: 291–4. https://doi.org/10.2143/ac.57.4.2005429

31. *Shen F, Wang L, Yang W, Chen Y*. From appearance to essence: 10 years review of atypical amniotic fluid embolism. Arch Gynecol Obstet 2016; 293: 329–34. https://doi.org/10.1007/s00404-015-3785-z

32. *Albaroudi B, Haddad M, Albaroudi O, Abdel-Rahman ME, Jarman R, Harris T*. Assessing left ventricular systolic function by emergency physician using point of care echocardiography compared to expert: systematic review and meta-analysis. Eur J Emerg Med 2022; 29: 18–32. https://doi.org/10.1097/mej.0000000000000866