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Original Research

Referral of Pregnant Women with Amniotic Fluid Embolism: A Retrospective, Descriptive Study

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Abstract

Background: Amniotic fluid embolism (AFE) is an urgent, catastrophic obstetric complication, but not all medical settings are equipped to manage AFE. The purpose of this study is to summarize the experience of referral of women with AFE in order to save the lives of women and improve the prognosis. **Methods**: We retrospectively collected the demographic characteristics, delivery process, symptoms and test indicators at the onset of AFE, as well as the treatment status and outcomes after referral of women with AFE who were treated at our hospital from January 2015 to November 2022. We descriptively summarized and analyzed these data. **Results**: A total of 13 women with AFE transferred to our hospital were included in the study. After referral, 3 women (23.08%) eventually died. One of the deceased women presented with hypothermia (34.5 °C) at the time of referral, and all 3 fatalities had lactic acidosis (pH $<$7.35 and lactic acid $\geq$5 mmol/L) and hypofibrinogenemia ($<$2 g/L). All 13 women were in shock after referral to our hospital and 92.31% (12/13) of the women were diagnosed with multiple organ dysfunction (MODS) when they were discharged. The markers of heart failure were abnormally elevated in the 3 deceased women. **Conclusions**: Referral should be considered as soon as possible in women with lactic acidosis, hypofibrinogenemia, and hypothermia with AFE.

Keywords: amniotic fluid embolism; pregnancy; referral; retrospective study

1. Introduction

Amniotic fluid embolism (AFE) is a rare and fatal obstetric complication with an incidence of approximately 2–8/100,000 [1]. The mortality rate of AFE varies widely among population-based and case-report studies, and the available evidence supports an overall mortality rate of 20.4% [2]. A local study in China reported a mortality rate of 53.69% (80/149) for AFE [3]. The high mortality rate of AFE is related to the severity and complexity of the disease itself, and the availability of multidisciplinary (obstetrics, intensive care, hematology, etc.) specialists experienced in the resuscitation of AFE along with a rapid response are the keys to patient survival [4].

In China, medical institutions are divided into three levels: primary, secondary, and tertiary [5]. While this health system hierarchy maximizes medical resources [6], it also means that some hospitals do not have the capacity to treat women with AFE. In addition to the lack of experience with AFE, there is a lack of advanced medical technologies such as veno-arterial-extracorporeal membrane oxygenation (VA-ECMO) [7] and plasma exchange at many institutions. Therefore, when conditions permit, patients should be transferred to hospitals with the capabilities of management of multi-organ dysfunction syndrome (MODS) caused by AFE [8].

Zhongda Hospital of Southeast University is a maternal critical care center in Jiangsu Province, China, where AFE patients are transferred from other hospitals. Even with extensive experience in AFE management and advanced technology, some patients have succumbed to AFE after being transferred to larger tertiary hospitals. There is limited experience about the state in which AFE patients can be considered for referral after successful resuscitation. Therefore, it is important to document the successful management of AFE patients at our facility and provide recommendations for the timing of patient transfer and appropriate management measures before transfer.

2. Materials and Methods

2.1 Diagnosis of AFE

There are no clear criteria for the diagnosis of AFE making it is a diagnosis of exclusion [9], with the diagnosis is based on clinical features [10]. The typical presentation of AFE includes sudden hypoxia, hypotension, and subsequent coagulation abnormalities [11]. AFE should be considered in any pregnant woman or in the postpartum period when she presents with cardiac arrest or sudden cardiovascular collapse, hypoxia, or severe dyspnea, especially if these symptoms are followed by unexplained coagulation

disorder [12]. There are no specific laboratory tests used to diagnose AFE. All women included in this study were diagnosed with AFE prior to referral to our hospital.

2.2 Study Subjects

This is a retrospective study in which we collected data from women with AFE treated in our hospital from January 2015 to December 2022. Participants included in this study were ranked and numbered according to whether they died and how early the AFE occurred.

Inclusion criteria: patients with AFE treated at our hospital.

Exclusion criteria: (1) patients with AFE that occurred in our hospital; (2) AFE patients with clinical data deficiencies.

2.3 Data Collection

We collected the following AFE women data from the electronic medical record system.

(1) Clinical and demographic characteristics of AFE patients, including age, pregnancy history, mode of delivery, and gestational week of delivery.

(2) Status at the onset of AFE, including clinical characteristics at onset, time to management and administration of treatment, markers of cardiovascular collapse, and coagulation status.

(3) Management and outcome after transfer to our hospital, including primary treatment, length of hospitalization, intensive care unit (ICU) stay, and maternal outcome.

3. Results

3.1 Basic Clinical and Demographic

By searching the electronic medical records, a total of 20 women with AFE treated at our hospital between 2015–2022 were identified. Seven women were excluded because 4 developed AFE in our hospital, and 3 women referred to our hospital had missing data. All 7 excluded women survived. Subsequently, 13 AFE patients were included in this study.

The 13 patients with AFE occurred during a period of six years from July 2016 to September 2022. The mortality rate was 23.08% (3/13) and 23.08% (3/13) of the women were primiparas. The mode of delivery was vaginal in 8 women (61.54%) and cesarean section occurred in 5 women (38.46%), of which 3 (No. 8, No. 9 and No. 10) underwent emergency cesarean section during vaginal delivery due to acute fetal distress and/or AFE. Five women (38.46%) experienced AFE during delivery, including 1 case that occurred during cesarean section. Eight women (61.54%) experienced AFE after delivery, including 1 woman (7.69%) after cesarean section. Oxytonic drugs used before labor are shown in Table 1.

3.2 Symptoms of AFE Women and Blood Coagulation Function

The AFE symptoms were varied at the time of occurrence. Symptoms included acute fetal distress in 46.15% (6/13); maternal cardiac arrest in 23.08% (3/13); cardiac arrhythmia in 38.46% (5/13); hypoxemia in 92.31% (12/13); hypotension, coagulopathy, and maternal hemorrhage were present in all women 100.00% (13/13) (Table 2).

Platelet counts were below the normal range in 75.00% (9/12) of the women; 92.31% (12/13) of the women had prothrombin time (PT) and/or activated partial thromboplastin time (APTT) outside the normal range or above the upper limit of the machine detection threshold; 91.67% (11/12) had fibrinogen (FIb) below the normal range or below the lower limit of the machine detection threshold.

3.3 Resuscitation and Management of AFE Women at the Time of AFE

23.08% (3/13) of the women experienced cardiac arrest and all received cardio-pulmonary resuscitation (CPR), with 1 woman eventually dying (No. 12). 23.08% (3/13) of the women underwent arterial ligation/embolization, of which 2 women eventually underwent an emergency hysterectomy. 38.46% (5/13) of the women had an intrauterine tamponade balloon inserted, but 4 of them eventually underwent an emergency hysterectomy. 38.46% (5/13) of the women underwent continuous renal replacement therapy (CRRT). A total of 10 (76.92%) women underwent an emergency hysterectomy after the onset of AFE, of whom 8 (80.00%) had an intraperitoneal gauze tamponade inserted.

Ten (76.92%) women received glucocorticoids, 4 (30.77%) women received tranexamic acid, and 11 (84.62%) women received norepinephrine.

In addition to these measures, all women were transfused. One woman (No. 11) was transfused with 4500 mL of whole blood but eventually died. 84.62% (11/13) of the women were transfused with packed red cells (13.0–55.5 U); 53.85% (7/13) were transfused with fibrinogen concentrate (3–12 g); 100.00% (13/13) were transfused with fresh frozen plasma (600–11,425 mL) and cryoprecipitate (4.00–120.00 U); 76.92% (10/13) were transfused with platelets (1–90 U); 30.77% (4/13) were given prothrombin complex concentrates; and 23.08% (3/13) of the women were given blood coagulation factor VII a (Table 3).

3.4 Referral Status and Post-Referral Management

The referred women were transferred to our hospital within 4 to 149 hours after the onset of AFE. One woman improved after treatment at a local hospital but was referred to our hospital 6 days later after her condition deteriorated (No. 9). Upon referral and admission to our hospital, vital signs (temperature, respiratory rate, heart rate, blood pressure) were recorded. Two women (15.38%) had significant hypothermia and 1 (7.69%) had a fever. Five women (38.46%) had a heart rate >100 beats/min; 3 women had a

Table 1. Basic clinical and demographic characteristics.

No.	Outcome	Year	Age (years)	Gestational age at delivery	Primiparous	VD/CS	Occurrence time
1	Survival	2018	36	38^{+6}		CS[a]	During CS
2	Survival	2019	28	39^{+5}		VD[c]	After VD
3	Survival	2020	39	40^{+2}		CS[b]	After CS
4	Survival	2021	27	40^{+2}		VD[c]	After VD
5	Survival	2021	32	38^{+6}	√	VD[c]	After VD
6	Survival	2021	33	40^{+4}		VD[d]	During VD
7	Survival	2021	28	39^{+6}	√	VD[e]	After VD
8	Survival	2021	32	40^{+5}		CS[b]	During VD
9	Survival	2022	33	39^{+5}		CS[b]	During VD
10	Survival	2022	29	40^{+4}		CS[b,d]	During VD
11	Death	2016	44	39^{+2}		VD[c]	After VD
12	Death	2018	43	39^{+1}		VD[c]	After VD
13	Death	2021	33	37^{+0}	√	VD[d]	After VD

VD, vaginal delivery; CS, cesarean section.

a, selective operation; b, emergency operation; c, spontaneous labour; d, oxytocin; e, misoprostol.

Table 2. Clinical characteristics and coagulation functions of AFE women.

	No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Acute fetal compromise		√	√			√	√	√			√		
Hypoxemia	√	√	√	√	√	√	√		√	√	√	√	√
Cardiac arrest									√	√		√	
Hypotension	√	√	√	√	√	√	√	√	√	√	√	√	√
Coagulopathy and maternal hemorrhage	√	√	√	√	√	√	√	√	√	√	√	√	√
Coagulation indicators													
Platelet count (10^9/L)	148	31	*	48	137	170	23	49	50	5	92	33	29
PT (s)	18.1	21.5	↑	17.6	↑	23.2	↑	↑	18.4	23.1	↑	46.2	↑
APTT (s)	62.1	125.5	↑	30.5	↑	47.2	105.80	↑	63.7	↑	↑	89.4	↑
FIb (g/L)	*	0.72	↓	2.10	↓	0.50	↓	↓	0.61	0.53	↓	1.77	↓

* Missing data; ↑ Exceeds the upper detection threshold; ↓ Exceeds the lower detection threshold. AFE, amniotic fluid embolism; PT, prothrombin time; APTT, activated partial thromboplastin time; FIb, fibrinogen.

respiratory rate >20 beats/min; and 7 women (53.85%) had abnormal blood pressure.

The AFE patient's platelet count, coagulation function (PT, APTT, FIb, D dimer), the pH, lactate dehydrogenase (LDH), and Ca^{2+} concentrations were re-determined after admission. Eight (61.54%) women had platelet counts lower than normal, 5 (38.46%) women had elevated PT, 3 (23.08%) women had elevated APTT, 4 (30.77%) had lower FIb than normal, and all 13 (100.00%) women had elevated LDH and D-dimer levels. Importantly, although all women were actively resuscitated and managed before referral, the 3 deceased women had lactic acidosis (pH <7.35 and lactic acid ≥5 mmol/L) and hypofibrinogenemia (<2 g/L) at the time of referral to our hospital. In contrast, the pH of the 10 surviving women was in the normal range or alkalotic, and the FIb was slightly lower than the minimum reference value. In addition, 4 women had Ca^{2+} concentrations below the reference range, but there did not appear to be significant differences in Ca^{2+} concentrations between the women who died and those who survived.

After referral to our hospital, 92.31% (12/13) of women received blood transfusion; 46.15% (6/13) underwent arterial embolization; 30.77% (4/13) had pulse indicator continuous cardiac output (PICCO) monitoring; 15.38% (2/13) had VA-ECMO applied; 53.85% (7/13) had CRRT; and 7.69% (1/13, No. 2) underwent multiple plasmapheresis.

Furthermore, 61.54% (8/13) of AFE women underwent laparotomy, 1 (No. 2) woman underwent craniotomy, and 1 (No. 12) woman underwent subtotal resection of the small intestine and colon due to vascular necrosis.

During treatment we measured creatine kinase MB isoenzyme (CKMB), N-terminal-probrain natriuretic peptide BNP (NT-proBNP), myoglobin (MYO) and troponin I (TnI) to analyze cardiovascular collapse. No significant differences were observed in the results of these 4 tests between those who expired and those who survived.

All the data is shown in Table 4.

Table 3. Resuscitation and management of AFE women.

	No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Cardiopulmonary resuscitation									√	√		√	
Operation		b, c, d	c, e	b, c, d	c, d, e	a, b, e	c, d, e	c, d	a, c	b, c, d	a, c, d, e	b, c, d	
Medicine	g, h	g	h	g	f, g, h	f, h	f, g, h	f, g, h	g, h	h	g, h	g, h	g, h
Blood transfusion													
Whole blood (mL)											4500		
Packed red cells (U)		46.0	55.5		47.5	13	34	14.5	22	15	18.5	17.5	19.5
Concentrated fibrinogen (g)			12	8		5		5		6		3	8
Fresh-frozen plasma (mL)	600	6625	11,425	1000	7525	1000	6950	5750	3275	1050	2950	1575	2900
Platelets (U)		3	9	1	6		90	1	3	2		3	5
Cryoprecipitate (U)	4.0	41.0	120.0	10.0	58.8	20.5	34.5	9.0	29.0	46.2	30.0	30.0	41.3
Prothrombin complex concentrates				√		√					√		√
Blood coagulation factor VII a	√						√						√

a, Vessel ligation/embolization; b, Intrauterine balloons; c, Hysterectomy; d, Intraperitoneal gauze tamponade; e, Continuous renal replacement therapy; f, Tranexamic acid; g, Glucocorticoid; h, Epinephrine.

Table 4. Referral status and management.

	No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Pre-referral time (hours)	24	48	37	47	10	4	19	9	149	13	26	17	24
Vital signs													
Body temperature (°C)	36.8	36.0	36.0	36.0	36.0	33.5	37.0	36.6	37.5	36.7	36.2	34.5	36.0
Heart rate (/min)	75	106	80	81	96	90	104	103	100	100	139	84	104
Breathing rate (/min)	33	16	11	15	18	20	22	27	18	18	20	18	12
Systolic pressure (mmHg)	108	120	130	152	107	90	123	124	150	130	117	84	140
Diastolic pressure (mmHg)	75	80	80	56	83	55	80	57	90	90	69	54	80
Coagulation indicators													
Platelet count (10^9/L)	243	55	87	32	92	117	56	42	173	130	43	68	190
PT (s)	11.6	18.4	14.9	21.6	13.9	13.5	17.1	12.6	10.4	12.3	35.1	11.1	15.5
APTT (s)	25.1	31.1	30.7	31.7	38.4	32.5	34.8	32	20.6	30.2	48.3	85.0	49.8
FIb (g/L)	4.28	2.91	2.40	2.10	2.60	2.40	2.90	1.3	4.30	3.00	0.94	1.77	1.30
D-Dimer (μg/L)	1008	16,369	3169	7617	5775	2147	11,120	138,853	12,692	133,489	3255	5015	26,299
pH	7.451	7.457	7.461	7.406	7.408	7.482	7.420	7.417	7.488	7.392	7.196	7.162	7.327
Lactic acid (mmol/L)	1.3	3.8	6.3	3.4	5.3	5.5	3.5	4.3	1.4	6.1	9.0	32.6	11.8
Ca^{2+} (mmol/L)	1.21	1.06	1.34	1.11	1.08	1.22	1.15	1.49	1.30	1.26	1.05	1.31	1.25
Myocardial injury markers													
CKMB isoenzyme	26.0	<2.0	23.0	19.0	9.9	32.0	55.0	4.0	6.8	84.0	>500	118.0	34.0
NT-proBNP	4560	3450	6260	4310	5340	5810	4860	270	2410	1260	3270	6160	5006
MYO	*	289	>900	>900	289	>900	>900	58	772	150	>900	>900	>900
TnI	3.66	0.35	1.40	0.91	0.77	1.70	1.20	10.17	0.06	0.87	4.20	2.20	24.50
Managements													
Operation	b	e	a, d	a, d	a, d	d	a, b, d	a		a	a, b, d	c	b, d
Blood transfusion													
Packed red cells (U)		56.5	39.5	20.0	4.0	6.0	3.0	6.0	3.0	10.0	10.5	36.5	
Fresh-frozen plasma (mL)		6175	9205	2900	400	1425	1400	400		1025	3170	8200	3800
Platelets (U)		6	19	11	4	3	2	2		1	10	6	
Cryoprecipitation (U)		15.80	69.50	6.50				8.75		9.50	9.00	49.00	25.00
Other managements		f, h	f	f						f	f	f, g	

CKMB, creatine kinase MB; NT-proBNP, N-Terminal Pro-Brain Natriuretic Peptide; MYO, myoglobin; TnI, Troponin I.

a, Vessel ligation/embolization; b, Pulse indicator continuous cardiac output; c, Extracorporeal membrane oxygenation; d, Continuous renal replacement therapy; e, Plasma exchange; f, Laparotomy; g, Enterectomy; h, Craniotomy.

* Missing data.

Table 5. Outcomes of AFE women.

	No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
Survival	√	√	√	√	√	√	√	√	√	√			
ICU (days)	2	89	55	10	8	11	6	3	30	7	3	2	4
Hospitalization (days)	13	89	55	26	28	25	28	13	30	15	3	2	4
Complications													
Infection		√	√	√	√			√	√				√
Shock	a	c, d, e	c	c	c	c	c	c	b	b	c	c	a, c
MODS	g, h	f, g, h, i, j, k	f, g, h, i, j, k	f, g, i, j, k	f, g, i, j, k	f, g, h, i, j, k	g, i, j, k		f, g, h, i, j	f, g, h, j	f, g, h, i, j, k	f, g, h, i, j, k	g, h, i, j

ICU, intensive care unit; MODS, multiple organ dysfunction syndrome.

a, Distributive shock; b, Cardiogenic shock; c, Hemorrhagic shock; d, Neurogenic shock; e, Septic shock; f, Brain; g, Heart; h, Lung; i, Renal; j, Liver; k, Intestine.

3.5 Maternal Outcomes of AFE

Maternal outcomes of AFE are shown in Table 5. Three (23.08%) women eventually died, and their length of stay in the ICU was 3, 2, and 4 days, respectively, which was shorter when compared to those who survived.

During hospitalization, 7 (53.85%) women developed infections, and all women had shock. The main types of shock were distributive shock (2/13), cardiogenic shock (2/13), hemorrhagic shock (10/13), neurogenic shock (1/13), and septic shock (1/13). 92.31% (12/13) of the women who developed MODS mostly involved the brain (9/12), heart (9/12), lung (9/12), liver (8/12), renal (8/12), and intestine (8/12).

4. Discussion

In this retrospective study, the overall AFE mortality rate was 15.00% (3/20) and the mortality rate among referred women was 18.75% (3/16). The mortality rate in this study was lower than that in some regions of China, such as 53.69% (80/149) in Zhejiang Province [3] and 32.00% (17/53) in Suzhou [13]. The appropriate procedure of rescue and management before referral as well as the timing of the referral need to be elucidated.

AFE is a catastrophic obstetric complication whose pathogenesis is unclear, and invasion of amniotic, fetal, or trophoblast components into the maternal circulation is a common feature. Recent studies have suggested that the placenta accreta spectrum (PAS) may be involved in the pathogenesis of AFE, which may mediate the entry of shaped components of amniotic fluid into the maternal circulation [14]. Exposure to fetal or trophoblast substances can prompt the production of inflammatory mediators in pregnant individuals, leading to severe acute reactions and subsequent AFE [15]. It is necessary to fully evaluate these risk factors for AFE before delivery and how to deal with AFE once it occurs. It is critical to elucidate the factors that should be considered when referring the patient to a higher-level hospital.

Studies have shown that AFE combined with coagulation dysfunction, shock, cardiac arrest, arrhythmia, and other factors can significantly increase the mortality of patients [14,16]. In our study, almost all the women had an increased mortality factor. Our low mortality rate may be attributed to the rapid insertion of uterine balloon tamponade, emergency laparotomy, hysterectomy, intraabdominal tamponade, CRRT, and other measures after the occurrence of AFE, as well as the timely use of anti-hemorrhagic and blood pressure raising medications. The purpose of CRRT is to replicate the purification function of the kidney, achieve continuous blood purification *in vitro*, correct body fluid overload, and expel excess toxins. For patients with massive hemorrhage or coagulopathy, a 1:1:1 infusion of packed red blood cells, fresh frozen plasma, and platelets are recommended. Cryoprecipitate and fibrinogen may be administered when appropriate [17]. Crystalloid and/or colloidal infusions should be avoided. When transfusions are performed to ameliorate coagulopathy, caution should be taken as unnecessary blood products may cause dilatation of the right ventricle.

Despite various treatments, AFE patients still have difficulty maintaining long-term physiological stability. At the time of referral to our hospital, 2 women had a body temperature below 35 °C, which may have been caused by severe hemorrhage and massive transfusion [18]. Hypothermia can lead to decreased thrombin activity, decreased platelet function, decreased fibrinogen synthesis, and increased fibrinolysis [19]. Clotting activity at 33 °C is 50% of that at 37 °C. Hypothermia can be reduced through measures such as pre-transfusion warming of the blood products and keeping the patient warm during resuscitation. In addition, the core temperature should be continuously monitored. One of the 2 women with hypothermia survived. This was possible because it took only 4 hours to transfer her to our hospital following the onset of AFE. The deceased patient underwent partial intestinal resection plus partial colectomy in our hospital. During the operation, the patient's intestines were found to be necrotic and mal-

odorous, suggesting that the patient's prognosis was already poor by the time she was referred to our hospital.

Significantly, we found that all 3 deceased women had lactic acidosis and hypofibrinogenemia at the time of referral to our hospital. These results seem to correlate with the "triad of death", a condition that involves hypothermia, acidosis, and coagulation dysfunction, with each additional element of the triad of death exacerbating the negative impact on survival [20]. The presence of the death triad in trauma patients has been recognized as a strong predictor of mortality [21]. Acidosis and hypothermia affect the metabolism and synthesis of fibrinogen [22]. Acidosis impairs the coagulation process in a progressive manner, and platelets may be lost from circulation at a reduced pH of 7.4 due to changes in internal structure and shape. In addition, bicarbonate is not the best choice for the treatment of acidic coagulation disorders and may interfere with clot formation [23]. Acidosis has a more significant effect on impaired coagulation than hypothermia [24], and the effects of acidosis and hypothermia on coagulation are synergistic [25]. Several studies have shown that the lack of improvement in coagulation impairment associated with acidosis after pH neutralization can be attributed to a decrease in fibrinogen levels and platelet counts [26]. Coagulation may not be restored by pH neutralization alone and other hemostatic factors (e.g., fibrinogen) may be important [23]. Fibrinogen plays an important role in coagulation disorders, especially in trauma patients. During hemorrhage, hemodilution, hyperfibrinolysis, acidosis, and hypothermia decrease plasma fibrinogen concentrations [27]. Current guidelines recommend that the threshold for plasma fibrinogen concentration should be 150–200 mg dL^{-1} and that fibrinogen replacement therapy should be triggered when the concentration falls below the minimum threshold.

A recent review documented the important role of calcium in normal hemostasis and suggested updating the "lethal triad" (hypothermia, acidosis, coagulation disorders) to "lethal diamond" to include hypocalcemia (hypocalcemia, hypothermia, acidosis, coagulation disorders). Hypocalcemia interferes with normal hemostasis and coagulation in bleeding patients [28]. Massive transfusion protocols (MTP) are effective for the rapid delivery of blood component therapy in women experiencing severe hemorrhage [29]. Whereas hypocalcemia is common in MTP and mortality is significantly higher in patients with severe hypocalcemia [30], there seems to be no clear trend between hypocalcemia and death in women with AFE in our study.

Furthermore, it is important to note that even though most of these referred women survived, MODS due to severe immune response and ischemia-hypoxia was not negligible. Dysfunction involving the brain and heart may be the most important reason for the poor prognosis of women with AFE. Although the heart failure markers of the 3 deceased women were not higher than those of the surviving women, 4 markers were far outside the reference range. Elevation of 4 myocardial markers at the same time may also be a factor for poor prognosis, and referral should also be considered when the patient is stable but all 4 myocardial markers are significantly abnormal.

Once AFE occurs, the patient's respiration and circulation should be maintained, and multidisciplinary consultations should be organized to save the lives of AFE patients. Some medical institutions need to consider whether to refer patients. Based on the results of our study, we have the following points to consider for referral (Fig. 1):

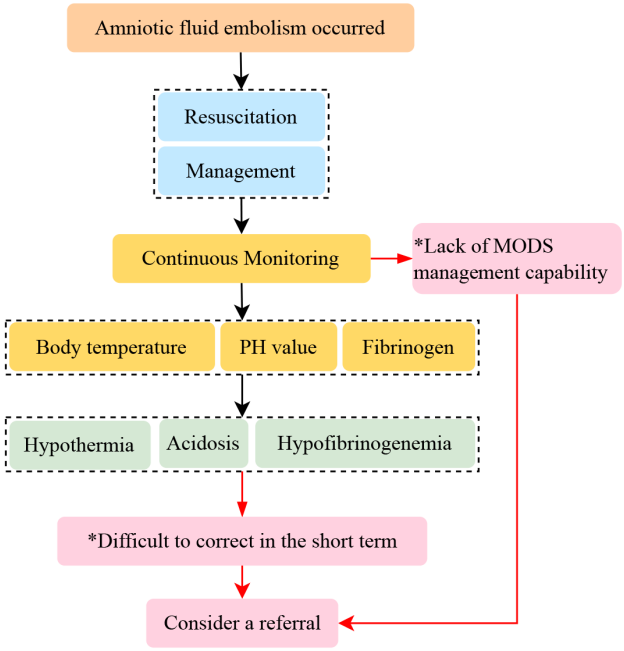

Fig. 1. Flow chart of AFE referral.

✓ Facilities that do not have the capacity to manage MODS should refer the patient as soon as possible while maintaining the patient's respiratory and circulatory systems.

✓ Transfusion therapy should be accompanied by vigilance for the occurrence of hypothermia, and women should be considered for referral.

✓ Continuous monitoring of pH, lactic acid and and FIb should be considered, and women should be referred as soon as lactic acidosis and hypofibrinogenemia appears.

In particular, our experience may not apply to the following situations:

✓ Vital signs of women with AFE remain unstable while on life support.

✓ Lack of transport vehicles with life support and monitoring systems.

✓ Areas where the overall medical conditions are not well developed.

5. Limitations

There are obvious limitations and deficiencies in this study. First of all, since our study only included 13 AFE women, we could only describe and attempt to interpret the data rather than analyze it. Secondly, some clinical data such as the presence of premature rupture of membranes, labor induction methods, labor analgesia, and other pre-referral data could not be obtained. Finally, records of patient management and monitoring during the referral process were missing, which is not conducive to continuous description and analysis of AFE management and referral.

6. Conclusions

AFE is a rare obstetric disaster, and suspected women should be treated promptly to maintain the patient's breathing and circulation. Hypothermia, lactic acidosis, and hypofibrinogenemia may be indicators of poor outcomes, and once present, a referral should be considered while these conditions are being corrected.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

HQ and WQ were responsible for the study design, data extraction and analysis, and article writing. YW, SL and YT were responsible for the study design, article writing, and revision. YL and CW were responsible for the study design and revision. NO was responsible for study design, revision, and polish. HY was responsible for study design and revision, paper review, and guidance. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Declaration of Helsinki was followed and the study was approved by the Ethics Committee of Zhongda Hospital affiliated with Southeast University (Approval No. 2023ZDSYLL023-P01). All participants' information was anonymized and their rights were protected. The ethics committee waived informed consent for this study due to its retrospective nature.

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Conflict of Interest

The authors declare no conflict of interest.

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