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Reproductive decisions after the diagnosis of amniotic fluid embolism

Amirhossein Moaddab[a], Miranda Klassen[b], Cynthia D. Priester[a], Elvira H. Munoz[a], Michael A. Belfort[a], Steven L. Clark[a], Gary A. Dildy[a,*]

[a] Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, TX, United States
[b] Amniotic Fluid Embolism Foundation, Vista, CA, United States

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ABSTRACT

Objective: This study aims to describe the subsequent reproductive outcomes in women who either correctly or incorrectly were diagnosed with amniotic fluid embolism (AFE).
Study design: Medical records were obtained, abstracted and reviewed by authors with extensive experience in critical care obstetrics. Telephone interviews of all survivors were conducted to determine obstetrical and contraceptive history. A subgroup underwent further telephone interview to address subsequent reproductive decisions.
Results: By November 2015, 116 medical records of patients diagnosed with AFE were reviewed. Patients who had undergone hysterectomy (n = 26), died (n = 9), or developed Sheehan's syndrome (n = 1) at the time of the original event were excluded from the present analysis. Of the remaining 80 women, 30% (24/80) had subsequently conceived and 32.5% (26/80) patients or their partners had undergone permanent sterilization. At the time of this report, 66% (21/32) of registry participants were categorized to have had AFE and 34% (11/32) as not likely AFE or indeterminate.
Conclusions: The syndrome of AFE is over-diagnosed. Women diagnosed with AFE who survive conceive another pregnancy less frequently than US women over similar time intervals and often choose a permanent sterilization method, whether or not they actually had AFE, largely out of fear of AFE recurrence.

Introduction

Amniotic fluid embolism (AFE) remains one of the most enigmatic and devastating conditions in obstetrics [1]. In its classic form, AFE presents with the acute onset of hypoxia, cardiovascular collapse and coagulopathy, during labor or in the immediate postpartum period. In such cases, maternal mortality is high, with reported death rates exceeding 60% [2]. However, it is clear that some patients with AFE present with a modified form of the condition in which one or more of the classic triad of clinical signs may be absent. In such cases, mortality rates are lower.

Our understanding of this condition has been hindered by the absence of definitive, objective diagnostic criteria. AFE remains a clinical diagnosis, often subject to error, especially with less-than-classic presentations [3]. Further, the rate of AFE recurrence in subsequent pregnancies is unknown; the number of reported cases of pregnancy following AFE is small and limited to a dozen individual case reports. Hence there exists no reliable data to cite recurrence risks in counseling these women; this uncertainty may impact future reproductive decisions [4].

Because the treatment of AFE is non-specific and directed at the correction of presenting pathologic physiologic alterations, the over-diagnosis of AFE is uncommonly detrimental to the patient's ultimate recovery. However, less is known about the long-term psychological impact of over-diagnosis on future reproductive decisions. Of particular concern is the impact on future reproduction in women in whom AFE is over-diagnosed, a group comprising 30–60% of women with an AFE diagnosis in some series [2]. We sought to investigate this question.

Materials and methods

The Amniotic Fluid Embolism Registry is an international database established at Baylor College of Medicine (Houston, TX, United States) in partnership with the Amniotic Fluid Embolism Foundation (Vista, CA, United States), a non-profit organization dedicated to advancing research, promoting education and awareness, and supporting those affected by AFE. The AFE Registry was IRB-approved in May 2012 and the database opened for enrollment in August 2013. Cases were obtained via advertisement

* Corresponding author at: Texas Children's Pavilion for Women, 6651 Main St, 10th Floor, Suite F. 1096, Houston, TX 77030, United States.
E-mail address: gadildy@bcm.edu (G.A. Dildy).

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using social media through the AFE Foundation and Baylor College of Medicine websites. All cases submitted to the registry were accepted for review, regardless of year of occurrence, as long as medical records were recorded in the English language. Cases from the previously published US Registry [5] were not included here because all of the US Registry cases occurred prior to 1995 and the original medical records were no longer available.

Surviving patients and non-survivors' families were self-identified with AFE and contacted the investigators by email directly or through the AFE Foundation. Written informed consent was obtained from survivors of AFE or from relatives of non-survivors, who voluntarily released pertinent medical records to the Foundation and Registry. We requested pertinent medical records were then examined and abstracted by the investigators (AM & GAD).

Based upon medical records review, patients were categorized into 2 major groups: (1) Probable AFE and (2) Probably not AFE or diagnosis indeterminate, per criteria we have previously published [5]. The "Probably not AFE" group consisted of cases of maternal hemodynamic collapse deemed likely due to other causes, such as protracted uterine atony or anesthetic complications. The "Diagnosis indeterminate" category consisted of cases in which the records were complete but etiology was unclear following review, or in some cases available medical records were suspected to be incomplete. Completed case report forms were reviewed by two authors with extensive experience in AFE research and critical care obstetrics (GAD, SLC & MAB) and any differences in opinion arbitrated by a third author.

Telephone interviews using standardized questionnaires of all reported AFE survivors were conducted by two investigators (EHM & MK) to determine obstetric and contraceptive history subsequent to the diagnosis of AFE. Three contact attempts were made, after which we assumed the individual declined participation in follow-up interviews. A follow-up standardized questionnaire to address to what extent fear of repeat AFE impacted these decisions was conducted by one investigator (MK) for available participants. We examined subsequent reproductive decision making, specifically contraceptive use and permanent sterilization of the patient or her partner. We also determined whether fear of repeat AFE played a major role in these decisions, based upon the telephone interviews described above.

It should be noted that post-AFE medical consultations were performed by local health care providers and not by AFE Registry or Foundation personnel. All information regarding reproductive recommendations to these patients was obtained by patient telephone interview and not from chart review, so we were left with the patients' impressions and not documented conversations. Neither the AFE Registry nor the AFE Foundation provided recommendations about medical care or future family planning.

This project was approved by the Baylor College of Medicine Institutional Review Board (H-29335 and H-36129). Statistical analysis was performed on statistical software package SPSS 21.0 (SPSS Inc., Armonk, NY). Normally distributed data are reported as mean (standard deviation) and nonparametric data as median (range).

Results

By November 2015, medical records of 116 women diagnosed with AFE have been submitted to the Registry (Table 1). There were 103 cases from the US (representing 32 states), 7 from the UK, 3 from Australia, 3 from Canada and 1 from Switzerland. One of the patients had two pregnancies complicated with the diagnosis of AFE. At the time of the AFE diagnosis, the median (range) age of these patients was 32 (19–49) years, pre-delivery parity was 1 (0–11) and gestational age was 39 (24–42) weeks. There were 113 singleton pregnancies, 3 twin pregnancies and 1 triplet pregnancy.

Of these 116 women, 36 were excluded from analysis: 9 women who died after the AFE event, 26 who underwent hysterectomy, and 1 who developed Sheehan's syndrome in conjunction with the index diagnosis (Table 2). Of women with the diagnosis of AFE who had preserved fertility after delivery, 70% (56/80) had not had further children at a median (range) interval of 4 (1–18) years from the index delivery.

Contraceptive practices are summarized in Table 3. Of women diagnosed with AFE who did not suffer involuntary loss of fertility, 32.5% (26/80) of these women or their partners had chosen permanent sterilization.

We performed additional extended interviews with 65 women enrolled in the registry, according to availability. In this specific group of patients, the median (range) interval between the AFE event and interview was 6 (2.5–13) years. The reported desired number of children prior to and after the AFE event was 3 (2–3) and 2 (0–3), respectively which reflects a deficit of 1 (0–2) in the desired number. The diagnosis of AFE affected child bearing desire in 57% (37/65) of individuals while 43% (28/65) did not confirm such an impact.

These women reported that the primary delivering physician advised against future pregnancy in 52% (34/65) cases. The reported reasons that physicians recommended against future pregnancies were: chance for recurrence (n = 19), potential emotional distress (n = 7), non-gynecologic complications

Table 1
Characteristics of women with prior diagnosis of AFE. Data are reported as median (range) and as proportions.

Number of enrolled women	n = 116[a]
Maternal age (years)	32 (19–49)
Pre-delivery parity (term + preterm)	1 (0–11)
Gestational age at delivery (weeks)	39 (24–42)
Mode of delivery	Spontaneous vaginal delivery 12.7% (15/117) Operative vaginal delivery 10.2% (12/117) Cesarean delivery 75.1% (88/117) Dilatation and evacuation 1% (1/117) Unknown 1% (1/117)
Fetal gender	Male 40% (48/122) Female 60% (74/122)
Neonatal outcome	Liveborn 93% (113/122) Neonatal Death 4% (5/122) Stillborn 3% (3/122)

[a] One woman had two suspected pregnancies.

Table 2
Subsequent pregnancies in patients with a prior diagnosis of AFE who survived with preserved fertility. Data are reported as median (range) and as proportions.

Women with preserved fertility	n = 80
Interval between AFE event and interview (years)	4.0 (0.2–36.7)
Maternal age at AFE event (years)	31 (19–49)
Gravidity at AFE event	2 (1–12)
Pre-delivery parity (term + preterm) at AFE event	0 (0–11)
Living children at time of AFE event	0 (0–11)
Women with subsequent pregnancy	30% (24/80)
Women without subsequent pregnancy	70% (56/80)
Interval to subsequent pregnancy (years)	3 (1–18)
Pregnancies following AFE event (n = 34)	1 subsequent pregnancy (n = 17) 2 subsequent pregnancies (n = 5) 3 subsequent pregnancies (n = 1) 4 subsequent pregnancies (n = 1)
Outcome of subsequent pregnancies (n = 34)	Ongoing (n = 2) Spontaneous abortion (n = 7) Elective abortion (n = 1) Spontaneous vaginal delivery (n = 8) Cesarean delivery (n = 16)

Table 3
Contraceptive method use among U.S. women age 15–44 years (6) and same-aged women with preserved fertility in AFE Registry. The category "Other methods" includes emergency contraception, female condom, spermicides, diaphragm, and contraceptive sponge. The "No method" group includes, no method, withdrawal, and fertility awareness based-method.

Method	U.S. women n = 61,750 (in 000s)	AFE Registry n = 80[a]
Pill	10,540 (17.1%)	6 (7.5%)
Tubal sterilization	10,200 (16.5%)	16 (20%)
Male condom	6280 (10.2%)	6 (7.5%)
Vasectomy	3860 (6.2%)	10 (12.5%)
Intrauterine device	2140 (3.5%)	9 (11.3%)
Injectable	1450 (2.4%)	0
Vaginal ring	830 (1.3%)	1 (1.3%)
Patch	290 (0.5%)	0
Implant	180 (0.3%)	1 (1.3%)
Other methods	200 (0.3%)	0
No method	23,360 (41.7%)	26 (38.6%)

[a] Loss to follow-up in 5 cases.

secondary to AFE (n = 7), advanced age (n = 5), gynecologic complications secondary to AFE (n = 4), no specific reason (n = 5).

Among all with preserved fertility, 90% (55/61) women sought further medical opinion with local consultants to discuss future pregnancies and 41% (25/61) had 2 or more consultation sessions with different consultants (not involved with the AFE Foundation or Registry, except in 1 case). General obstetrician/gynecologists (n = 51), maternal-fetal medicine specialists (n = 18), primary care physicians (n = 10), midwives (n = 4) and registered nurses/assistant physicians (n = 3) were among health care professionals who performed consultations with respect to subsequent pregnancies. During these consultations, 41% (25/61) patients were specifically advised not to get pregnant. The reasons against future pregnancy that consultants provided to patients were: chance for recurrence (n = 20), emotional distress (n = 8), non-gynecologic complications secondary to AFE (n = 8), advanced age (n = 3), gynecologic complications secondary to AFE (n = 3), no specific reason (n = 4).

Our data showed that 30% (24/80) of survivors achieved subsequent pregnancy. According to U.S. census data, among all women aged 15–44 years who gave birth to their first child in the United States during the years 2006–2010, 70.1% gave birth to a second child during the period of study and 49.5% gave birth to a second child within 4 years [7]. In our study population, among the same population of enrolled primigravida women (n = 51), 41 women survived with preserved fertility, 6 women died, and 4 patients underwent peripartum hysterectomy. Among these women, just 36.6% (15/41) gave birth to a second child within 4 years.

At the time of this report, 32 participants had submitted medical records substantial enough to judge the accuracy of the original AFE diagnosis, as outlined above. Of these registry participants 66% (21/32) were categorized to have had AFE and 34% (11/32) as not likely AFE or indeterminate.

Comment

The aim of this study is to determine the distribution of reproductive decisions in women who were diagnosed with AFE at the time of delivery, regardless of whether they were believed by the AFE Registry reviewers to have actually had an AFE, versus some other obstetrical event. The AFE Registry does not contain a sufficient number of closed cases categorized as "AFE" in order to describe risk factors and characteristics of AFE at this time.

Regarding AFE, in 1948 Eastman [6] cautioned "let us be careful not to make it a waste-basket for all cases of unexplained death in labor." While improvement in our diagnostic capabilities for other conditions has probably led to a reduction in the misdiagnosis of AFE in more recent years, overdiagnosis remains relatively common; published series based upon administrative/coding data generally report a higher rate of AFE with a lower mortality, compared to series involving expert review of individual medical records [2]. Extensive searches for reliable, objective serum markers of AFE have to date proven futile.

Women who suffer a classic case of AFE have a high incidence of death or major neurologic morbidity [2]. We should point out one potential limitation to our study: that the majority of participants in the AFE Registry are survivors without known significant neurologic morbidity (however we have not to date been able to objectively measure long-term neurologic and cognitive function). Thus our cohort may tend to over-represent less severe cases, as we have relatively few cases of lethal AFE or permanent major neurologic impairment submitted by survivors or non-survivors' family members. If we were able to capture these cases, we would expect our findings to be more concerning for women who survive with a diagnosis of AFE.

Our data suggest that the diagnosis of AFE has major impact upon further reproductive decisions of affected women and their partners, with 30% (24/80) of survivors achieving subsequent pregnancy. Among all women aged 15–44 years who gave birth to

their first child in the United States during the years 2006–2010, 70.1% gave birth to a second child during the period of study and 49.5% gave birth to a second child within 4 years [7]. In our study population, among the same population of enrolled primigravida women (n = 51), 41 women survived with preserved fertility, 6 women died, and 4 patients underwent peripartum hysterectomy. Among these women, just 36.6% (15/41) gave birth to a second child within 4 years. Such decisions are probably reasonable in women with AFE, given the often devastating nature of this condition and a paucity of reliable data regarding recurrence risks. However for a woman to limit childbearing out of fear of recurrent AFE with a misdiagnosis of this condition is tragic.

Our Registry data, through in-patient medical record review, demonstrated that few affected individuals received psychiatric/psychological consultations during their initial course of hospitalization. Previous studies have shown a reduction in subsequent reproductive capacity in women who have experienced a maternal near-miss during pregnancy [8]. Such events may severely impact psychological desire to conceive despite preservation of fertility [9]. Such considerations necessitate that the multidisciplinary approach to the optimum management of AFE includes psychological counseling. We would propose that the optimum management includes psychological counseling in a multidisciplinary approach.

Treatment of AFE is non-specific; if the patient is hypoxic, provide oxygen and ventilator support, if the patient is hypotensive, optimize cardiac preload and provide pressor support if necessary, if disseminated intravascular coagulopathy follows the initial cardiovascular collapse, blood and component replacement is the mainstay of therapy. Advanced cardiac life support is provided for women undergoing cardiac arrest, without regard to a specific diagnosis. Overdiagnosis of AFE is principally dangerous if conditions potentially treatable with disease-specific therapy are missed; septic shock would be one such example. Our data demonstrates an additional, undescribed hazard of the overdiagnosis of AFE. While not life-threatening, such overdiagnosis may certainly be life–altering and unethical. This overdiagnosis violates physicians' beneficence-based obligation to avoid unnecessary harm to their patients [10].

Unfortunately, AFE may mimic conditions such as sepsis, anaphylaxis, hemorrhage or anesthetic accident, particularly when presenting in a less-than-classic form. Our data suggest that in non-classic cases involving maternal survival, the clinical diagnosis of AFE should be considered tentative. Such women may benefit from formal post-hospitalization consultation with record review by a physician with more extensive experience in such cases, prior to committing to the initial clinical impression of AFE; in order to avoid erroneously impacting future reproductive decisions.

The obstetrician/gynecologist may be consulted by a woman with a history of suspected AFE, seeking advice about the probability of AFE recurrence and the risk of future pregnancy. To date, no case of verified AFE recurrence has been published, but the number of reported cases of subsequent pregnancy is small. Considering the rarity of AFE, we should be aware that with a limited sample size, zero numerators do not imply "no risk" [11]. Future study of additional verified cases of AFE and subsequent pregnancy outcomes will provide more meaningful data in order to advise women regarding this important question.

Previous studies demonstrated that women experienced near to death events like severe postpartum hemorrhage suffer from long-term psychological and emotional complications especially due to the pervasive uncertainty and realization that childbearing may contains potentially life threatening consequences [12]. Moreover, a pregnancy complicated by a condition such as preeclampsia reduces the chance of conceiving a second pregnancy by 11% compared to women without this condition [13]. In our Registry, 70% of women diagnosed with AFE with preserved fertility did not conceive a subsequent pregnancy.

The high rate of AFE misdiagnosis previously described in the literature and confirmed by our current data adversely impacts the quality of published administrative and case report data, and hinders advances in understanding of this condition since a large number of reported patients with AFE did not actually have the disease. Our current data suggests an additional adverse impact upon future reproductive decisions of women so misdiagnosed. These observations add to the urgency to adopt uniform criteria for the diagnosis of AFE [14].

Conflict of interest

The authors report no conflicts of interest.

Authorship

All authors contributed to the present study.

Presentation at conference

This study has been presented as a poster at the 36th Annual Meeting of Society for Maternal-Fetal medicine (SMFM) (Pregnancy Meeting™) Atlanta, Georgia, U.S.A.

Condensation

Amniotic fluid embolism is over-diagnosed and women diagnosed with this condition less frequently conceive another pregnancy, whether or not the diagnosis was confirmed.

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