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Original Article

An investigation of the risk factors, an analysis of the cause of death, and the prevention strategies for amniotic fluid embolism

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Abstract: Objective: This study explores the major risk factors and analyzes the cause of death from amniotic fluid embolism (AFE), so as to provide prevention strategies for the disease. Methods: A total of 52 maternal women diagnosed with AFE who gave birth in our hospital were retrospectively reviewed (the AFE group). Another 52 maternal women without AFE symptoms who gave birth in our hospital were enrolled at the same time. The basic indicators, obstetric situations, and laboratory indexes between the two groups were compared and analyzed. Results: The results of the univariate and multivariate analyses indicated that a regular prenatal examination could be regarded as a protective factor against death caused by AFE, but the use of oxytocin and misoprostol, associated obstetric trauma, and high concentrations of IL-6 and IL-8 are the main risk factors. Conclusion: Our data demonstrate that the use of oxytocin and misoprostol, associated obstetric trauma, and high concentrations of IL-6 and IL-8 are the main risk factors for death caused by AFE.

Keywords: Amniotic fluid embolism, risk factors, interleukin-6, interleukin-8

Introduction

Amniotic fluid embolism (AFE) is a critical obstetric disease. In spite of its low incidence rate, the disease is characterized by acute onset, rapid progression, and an extremely high mortality rate. As early as 1926, Meyer reported for the first time that [1] the elements of amniotic fluid can enter the maternal circulation. In 1941, Steiner et al. [2] discovered fetal mucins and squamous epithelial cells in the pulmonary vessels of eight parturients who died suddenly and defined them as AFE, so increased attention has been paid to the disease. According to the report of Clark et al. [3], the incidence rate of AFE is 1:8000-1:80000 in the USA, but its fatality rate reaches as high as 80%. In addition, it has been revealed that 10.0% of the total deaths of maternal women are caused by AFE [4]. It is believed that AFE is triggered by a mechanical obstruction of formed elements in the amniotic fluid and stimulation to the pulmonary vasospasm [5, 6]. Furthermore, several studies have discovered that an allergic reaction plays an important role in the pathogenesis of AFE [7, 8]. So far, no laboratory examination or clinical manifestation can solely make a confirmatory diagnosis of AFE. Meanwhile, adverse symptoms are prone to being neglected in the early stages, so it is of great significance to analyze the risk factors and cause of death for the disease and take timely effective prevention and control measures. As a result, this paper aims to explore the major risk factors influencing AFE by retrospectively reviewing the clinical features and laboratory examinations of AFE, which may favor the early discovery and timely intervention for therapy against AFE.

Patients and methods

Research cases

A total of 52 maternal women diagnosed with AFE who gave birth in the Second Affiliated Hospital of Kunming Medical University from February 2002 to February 2017 were retro-

spectively reviewed (the AFE group). Another 52 maternal women without AFE symptoms who gave birth in our hospital at the same time period were enrolled as the healthy control group. All AFE patients met the diagnostic criteria of AFE formulated by the USA in 1998. Inclusion criteria: patients who did not have other medical explanations, patients who had any combination of acute hemodynamic collapse, respiratory distress/hypoxia, DIC, and/or mental status changes. Exclusion criteria: patients with the sudden onset of hypotension followed by a coagulopathy. On the premise of conforming to the medical record management regulations and the principle of confidentiality, the clinical features, laboratory examinations, and other data of the maternal women with AFE were collected by searching the electronic medical record library. There were two modes of conception among the parturients, including spontaneous conception and conception through assisted reproductive technology (ART) (such as artificial insemination, ovulation induction treatment, in-vitro fertilization-embryo transfer, and intra-cytoplasmic sperm injection). Two modes of delivery, namely spontaneous delivery and caesarean section, were adopted. The patients or their families were informed of and agreed with all the cases enrolled, and they signed the informed consent. This research was approved by Second Affiliated Hospital of Kunming Medical University Ethics Committee.

Research methods

The basic indicators in the AFE group and the healthy controls were compared, including regular prenatal examination, age, parity, gestational age, mode of conception, and mode of delivery of the gravidae.

The obstetric situations in the AFE and healthy control groups were also compared, including hypertensive disorders complicating pregnancy, placental abruption, placenta praevia, and precipitate delivery. The diagnostic criteria of relevant diseases were in line with those in *Beckmann's Obstetrics and Gynecology (Seventh edition).*

The prodromal symptoms of onset in the AFE group were recorded.

The concentrations of interleukin-6 (IL-6) and IL-8 in the amniotic fluid in the AFE and healthy control groups were measured and compared. The concentrations of IL-6 and IL-8 in the amniotic fluid of the parturients were evaluated by using an enzyme-linked immunosorbent assay (ELISA). All the operations were conducted by professionals in strict accordance with the corresponding instructions.

A univariate analysis was performed to determine whether the AFE resulted in death or not, and then a binary logistic regression model was applied to analyze the major risk factors of death from AFE.

Statistical methods

Statistical Product and Service Solutions (SPSS) 18.0 software (SPSS Inc., Chicago, IL, USA) was utilized. The enumeration data were presented as the mean ± standard deviation (mean ± SD), and a *t*-test was performed. The constituent ratios and rates were compared using an exact probability of contingency table (χ^2 test). The risk factors and independent risk factors of death from AFE were analyzed using univariate and multivariate logistic regression analyses. $P<0.05$ indicated that the difference was statistically significant.

Results

Comparisons of basic indicators of the two groups of pregnant women

The differences in the regular prenatal examinations and parity between the two groups of pregnant women were statistically significant (all $P<0.05$). There was a lower rate of regular prenatal examination and more multiparae in the AFE group compared to the control group. However, the differences in age, gestational age, modes of conception, and delivery were insignificant ($P>0.05$) (**Table 1**).

Comparisons of the obstetric situations of the two groups of pregnant women

We compared the obstetric situations and found that there were significant differences in hypertensive disorders complicating pregnancy, placental abruption, placenta praevia, the use of oxytocin and misoprostol, artificial rupture of the membrane, amniotic opacity, precipitate delivery, and associated obstetric

Table 1. Comparison of basic data of the pregnant women in the AFE group and the healthy controls

Observation index	AFE group (n=52)	Control group (n=52)	t/χ^2	*P*
Regular prenatal examination				
Yes	11	28	11.375	0.000
No	41	24		
Age (years old)	28.61±4.58	27.24±5.03	1.156	0.206
Parity (time)				
1	20	35	8.764	0.004
>1	32	17		
Gestational age (week)	37.81±0.45	37.79±0.56	1.124	0.241
Mode of conception				
Spontaneous	48	47	0.594	1.023
ART	4	5		
Mode of delivery				
Spontaneous delivery	36	38	0.685	0.917
Caesarean section	16	14		

trauma between the two groups of pregnant women (P<0.05) (**Table 2**).

Occurrence of prodromal symptoms in the AFE group

The occurrence of prodromal symptoms in the 52 maternal women with AFE was recorded. Of note, there were 6 cases of postpartum hemorrhage (11.54%), 4 cases of errhysis in the wound (7.69%), 3 cases of dysphoria (5.77%), 2 cases of coagulation disorder (3.85%), 2 cases of shivering (3.85%), 1 case of coughing (1.92%), and 34 cases of atypical clinical symptoms (65.38%) (**Figure 1**).

Comparisons of the inflammatory indexes between the two groups of pregnant women

The IL-6 concentrations (μg/mL) in the AFE group (31.02±4.32) were significantly higher than those in the control group (0.02±0.03) (P<0.05). The IL-8 concentrations (μg/mL) in the AFE group (24.05±5.81) were also statistically elevated compared to that the concentrations in the control group (0.18±0.15) (P<0.05) (**Table 3**).

Univariate and multivariate analyses of AFE resulting in death

Univariate analysis of AFE resulting in death: In the AFE group, 32 patients died and 20 patients survived, a mortality rate of 61.54%. The results of the univariate analysis showed a significant difference between the death and survival subgroups regarding regular prenatal examinations, multiparity, hypertensive disorders complicating pregnancy, placental abruption, placenta praevia, the use of oxytocin and misoprostol, artificial rupture of the membrane, amniotic opacity, precipitate delivery, associated obstetric trauma, IL-6, and IL-8 levels (P< 0.05). However, the differences in age, modes of conception, delivery, and gestational age were not statistically significant (P> 0.05) (**Table 4**).

Multivariate analysis of AFE resulting in death: The binary logistic regression model analysis indicated that the indexes which were statistically different in the univariate analysis were taken as independent variables, and AFE resulting in death was regarded as an outcome variable. Our result showed that regular prenatal examinations could be regarded as a protective factor for AFE resulting death, and the use of oxytocin and misoprostol, associated obstetric trauma, and IL-8 could serve as its main risk factors (**Table 5**).

Discussion

AFE refers to a type of severe complication of childbirth, which is caused by the entrance of amniotic fluid into maternal circulation. It can trigger a series of pathological changes such as acute pulmonary embolism, anaphylactic shock, and disseminated intravascular coagulation (DIC). According to the traditional view, the diagnosis of AFE can be confirmed as long as the formed elements of amniotic fluid (squamous epithelial cells, lanugo, mucus, etc.) are found in the pulmonary arteries through pathological examinations [9]. In clinical practice, oil red O staining, Ayoub-Shklar staining, or the extraction of venae cavae blood from maternal women are applied to detect and search fetal fat, keratin, or formed elements of amniotic fluid, in order to make a confirmatory diagnosis. However, the application remains unsatisfactory due to its lack of sensitivity and the complex-

Table 2. Comparison of the obstetric situations between the AFE group and the healthy controls

Obstetric situation	AFE group (n=52)	Control group (n=52)	t/χ^2	*P*
Hypertensive disorders complicating pregnancy				
Yes	24 (46.15)	8 (15.38)	9.647	0.000
No	28 (53.85)	44 (84.62)		
Placental abruption				
Yes	9 (17.31)	2 (3.85)	7.593	0.001
No	43 (82.69)	50 (96.15)		
Placenta praevia				
Yes	11 (26.83)	3 (5.77)	7.465	0.001
No	41 (78.85)	49 (94.23)		
Whether they use oxytocin and misoprostol or not				
Yes	32 (61.54)	15 (28.85)	8.257	0.000
No	20 (38.46)	37 (71.15)		
Artificial rupture of the membrane				
Yes	39 (75.00)	9 (17.31)	11.203	0.000
No	13 (25.00)	43 (82.69)		
Amniotic opacity				
Opaque	33 (63.46)	10 (19.23)	16.073	0.000
Clear	19 (36.54)	42 (80.77)		
Precipitate delivery				
Yes	25 (48.08)	5 (9.62)	10.896	0.000
No	27 (51.92)	47 (90.38)		
Associated obstetric trauma				
Yes	29 (55.77)	6 (11.54)	20.518	0.000
No	23 (44.23)	46 (88.46)		

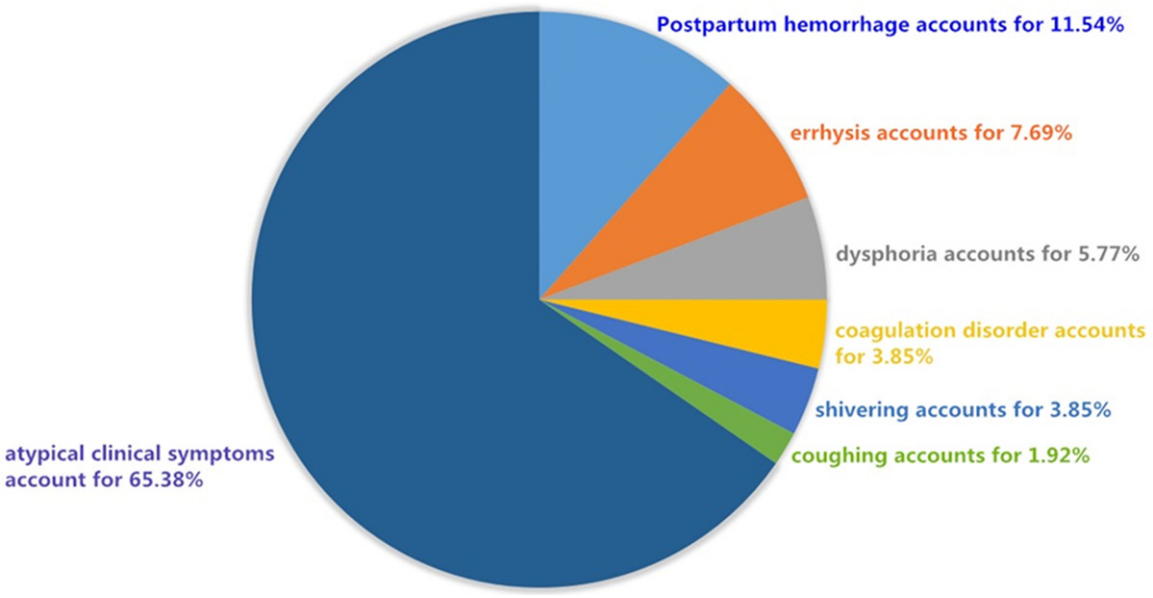

Figure 1. Constituent ratio of prodromal symptoms occurring in the AFE group. Note: Postpartum hemorrhage accounts for 11.54%, errhysis accounts for 7.69%, dysphoria accounts for 5.77%, coagulation disorder accounts for 3.85%, shivering accounts for 3.85%, coughing accounts for 1.92%, and atypical clinical symptoms account for 65.38%.

Table 3. Comparison of the inflammatory indexes between the AFE group and the healthy controls

Inflammatory index	AFE group (n=52)	Control group (n=52)	t/χ^2	*P*
IL-6 (μg/mL)	31.02±4.32	0.02±0.03	40.125	0.000
IL-8 (μg/mL)	24.05±5.81	0.18±0.15	28.637	0.000

Table 4. Univariate analysis of AFE resulting in death

Independent variable	Death group (n=32)	Survival group (n=32)	t/χ^2	*P*
Regular prenatal examination [n (%)]	3 (9.38)	7 (35.00)	11.243	0.002
Age (years old)	27.42±4.31	29.26±4.12	0.815	0.367
Parity [n (%)]	25 (78.13)	7 (35.00)	10.510	0.003
Mode of conception [n (%)]				
Spontaneous	29 (90.63)	19 (95.00)	1.642	0.071
ART	3 (9.38)	1 (5.00)		
Mode of delivery [n (%)]				
Caesarean section	11 (34.38)	5 (25.00)	1.783	0.082
Vaginal delivery	21 (65.63)	15 (75.00)		
Gestational age (week)	37.65±0.51	37.92±0.42	0.948	0.297
Hypertensive disorders complicating pregnancy [n (%)]	19 (59.38)	5 (25.00)	9.782	0.004
Placental abruption [n (%)]	7 (21.88)	2 (10.00)	3.347	0.015
Placenta praevia [n (%)]	9 (28.13)	2 (10.00)	4.125	0.011
Use of oxytocin and misoprostol [n (%)]	29 (90.63)	3 (15.00)	12.472	0.000
Artificial rupture of membrane [n (%)]	30 (93.75)	9 (45.00)	8.513	0.005
Amniotic opacity [n (%)]	29 (90.63)	4 (20.00)	10.543	0.003
Precipitate delivery [n (%)]	21 (65.63)	4 (20.00)	8.518	0.005
Associated obstetric trauma [n (%)]	27 (84.38)	2 (10.00)	12.243	0.000
IL-6	35.21±4.43	26.18±5.27	11.518	0.002
IL-8	27.58±5.14	20.49±4.61	12.407	0.000

ity of the operation. In recent years, new knowledge about the pathogenesis of AFE has been gained with the establishment of various animal models. After years of in-vivo studies on animal models and clinical case analyses, Clark et al. argue that no hazards may be caused by the entry of normal amniotic fluid into the maternal circulation [2]. One study also found that a few fetal epithelial cells do not induce AFE symptoms when they enter a pregnant woman's blood circulation [10]. Dib et al. did not find any fetal epithelial cells in the blood circulation of maternal woman with AFE by means of autopsy, suggesting that the existence of the formed elements of the amniotic fluid may not be a primary factor triggering AFE [11]. The complicated pathophysiology of AFE still cannot be explained simply by mechanical obstruction. Studies in recent years have revealed that the clinical manifestations of AFE are extremely similar to those of anaphylactic shock, and a series of allergies after the entrance of amniotic fluid into blood are crucial to the onset of AFE. Therefore, some scholars propose replacing "AFE" with "pregnancy-induced allergy syndrome" [3, 10].

Researchers have established that certain quantities of interleukins exist in amniotic fluid, the concentrations of which are increased along with the extension of gestational age [12]. IL-6 and IL-8, which are glycoproteins, are mainly derived from trophoblast cells, decidual cells, amnion cells, monocytes, epithelial cells and fibrocytes [13-15], most of which are produced by inflammatory cells and have close correlations with infectious diseases. The content of IL-6 and IL-8 in the amniotic fluid is elevated with the aggravation of infection [16]. In this study, the concentrations of both IL-6 and IL-8 in the AFE group were significantly higher than they were in the control group, which is in

Table 5. Multivariate analysis of AFE resulting in death

Variable	Regression coefficient	Standard error	Wald	*P*	Odds ratio (OR)	95% confidence interval
Regular prenatal examination	-1.143	0.523	4.973	0.019	0.310	0.102-0.915
Use of oxytocin and misoprostol	3.152	0.651	12.834	0.000	20.281	5.734-71.013
Associated obstetric trauma	1.645	0.582	7.458	0.005	5.162	1.624-15.376
IL-8	2.014	0.537	6.125	0.007	3.759	1.204-12.534

line with previous finding that the concentrations of IL-6 and IL-8 in positive and inflammatory amniotic fluid undergoing microbiological culture were higher than those in the normal control group [17, 18].

As a kind of peptide with a low molecular weight of 8.4 kD, IL-8 is a member of the chemokine-like factor superfamily. It can be produced under the stimulation of primary inflammatory factors [IL-1β and tumor necrosis factor-alpha (TNF-α)], and some kinds of bacteria and viruses [19]. IL-8 is also an inhibitor of neutrophil apoptosis [20], and its increasing level in the lungs of an AFE rat model can suppress the apoptosis of neutrophils. IL-8 may play a primary role in hypersensitivity reactions, which damage the airway. Chemotactic neutrophils can migrate, accumulate, and infiltrate into the site of inflammation and release such active substances as lysosome, as well as lead to the rupture of capillaries, thereby aggravating inflammatory responses. It results in tissue injury [21] and ultimately induces the occurrence of AFE.

IL-6 is a glycoprotein with a molecular weight of 21 kD and encoded by the IL-6 gene. IL-6 can bind to the cell membrane receptor complex that is comprised of soluble IL-6 connexin [the IL-6 receptor (IL-6R)] and glycoprotein gp130. It can be generated by various activated cells including T cells, B cells, natural killer (NK) cells and liver cells and can exert multiple immunomodulatory functions. The major biological effects of IL-6 involve participation in acute-phase responses and the exertion of anti-tumor effects by directly or indirectly enhancing the signal transmission between NK cells and toxic cells [such as the activation of transcription factor nuclear factor for IL-60 (NF-IL-60)] [22]. Meanwhile, IL-6 exerts the immunomodulatory effect by means of promoting B cell proliferation and differentiation and secreting antibodies. Moreover, it plays a vital role in hematopoiesis, metabolism interference, and autoimmune diseases. As a pro-inflammatory cytokine, IL-6 is a key factor that initiates antimicrobial and inflammatory responses, which can lead to a "waterfall reaction" through a cascade reaction and possibly give rise to multiple organ dysfunctions [23]. For pregnant women, the rise of IL-6 level in the blood can serve as a diagnostic indicator of premature rupture of the membranes, and premature rupture of the membranes is a crucial factor triggering AFE.

Although AFE is characterized by a high fatality rate, sudden onset, dangerous conditions, and other apparent features, it has no obvious prodromal symptoms in most cases. Once errhysis is observed in the wound, dysphoria and other typical symptoms occur in the parturients after childbirth, caesarean section, or a period of time after childbirth, which cannot be explained by other reasons, and it is extremely important to consider AFE. The identification and timely treatment may improve the patient's prognosis and decrease the mortality rate.

According to the findings of this study, there was a lower rate of regular prenatal examination and an increased multiparae rate in the AFE group. There were significant differences in hypertensive disorders complicating pregnancy, placental abruption, placenta praevia, the use of oxytocin and misoprostol, artificial rupture of the membrane, amniotic opacity, precipitate delivery, and associated obstetric trauma, suggesting that health education should emphasize the importance of regular prenatal examination, and that the indication and dosage of oxytocin and misoprostol should be noted in clinical practice to avoid obstetric trauma and closely monitor or reduce the risks of AFE in a timely way.

Conclusion

The results indicate that regular prenatal examinations should be regarded as a protective fac-

tor for death caused by AFE, and the use of oxytocin and misoprostol, associated obstetric trauma, and high concentrations of IL-6 and IL-8 are the main risk factors. Our data provides the basis for AFE diagnosis and treatment by obstetricians and facilitates the improvement of the prognosis of maternal women.

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Disclosure of conflict of interest

None.

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