Original Article

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Comparison of the Different Definition Criteria for the Diagnosis of Amniotic Fluid Embolism

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: There are several sets of criteria for the diagnosis of Amniotic Fluid Embolism (AFE), but little is known about their degree of agreement.

Aim: To evaluate the concordance of the Japan criteria for AFE in comparison with two definitions: the US AFE registration entry criteria (the US criteria) and UK Obstetric Surveillance System criteria for defining cases of amniotic fluid embolism (the UK criteria).

Materials and Methods: A retrospective observational study was conducted in which the AFE cases registered in the Obstetrical Gynaecological Society of Kinki District in Japan for the period of April 2005 to December 2012 have been analysed by the expert steering obstetric committee, organized by the members of the Obstetric Research group. Cohen's kappa coefficient was used to calculate the agreement among three clinical diagnoses. For inter-group comparison, the Pearson Chi-square test was used (for categorical) and Mann-Whitney test was used (for continuous variables).

Results: Among the 26 cases registered for this period, a total of 18 women were selected as having AFE according to the Japan criteria. Five women died (case fatality rate 27.8%). Agreement between the Japan criteria and the US and UK criteria was k = 0.453 and k = 0.538, respectively, reflecting moderate agreement. However, only 38.9% were given a diagnosis of AFE according to all three criteria. The factor that most often caused disagreement in diagnosis between the Japan criteria and the US criteria was "onset within 30 minutes postpartum". The UK criteria excluded "women with postpartum haemorrhage as the first presenting feature in whom there was no evidence of cardiorespiratory compromise". The case fatality rates in US and UK are higher than in Japan (50.0% and 38.5% vs 27.8%), but this did not result in a significant difference (p=0.497).

Conclusion: The groups of subjects identified as having AFE by the Japan criteria had a medium agreement with the US (k=0.453) or UK criteria (k=0.538). These three definition criteria identified different subgroups of patients. Such disagreement has serious implications for research and treatment.

Keywords: Amniotic fluid embolism, Criteria, Definition, Disagreement

INTRODUCTION

Maternal mortality is mostly due to direct and indirect maternal disorders [1-4]. In Japan, Massive Obstetric Haemorrhage (MOH) (23%), resulting from the failure of normal obstetrical, surgical and/or systemic haemostasis, followed by brain disease (16%) and Amniotic Fluid Embolism (AFE) (12%) were the three main direct causes of maternal death in Japan [4]. Cardiovascular diseases and stroke were the two leading indirect causes of maternal death. The maternal mortality rate was 8.8 in 1992 and 4.0 per 100 000 births in 2012, respectively [4]. The analysis from the Japanese autopsy registry showed that the three major causes of maternal death could be AFE, Disseminated Intravascular Coagulation (DIC) and brain disease [5].

Amniotic fluid embolism is a life-threatening obstetric emergencies that arises in 2 to 8 of every 100,000 deliveries, with a mortality of 11% to 44% [4,6]. The clinical presentation commonly includes: acute hypotension or cardiac arrest, acute hypoxia (dyspnea, cyanosis or respiratory arrest) and coagulopathy (intravascular coagulation or severe haemorrhage), which usually occur during labour or caesarean section [7,8]. A case of AFE was defined either as a clinical diagnosis or as a post mortem diagnosis (presence of foetal or amniotic fluid components in the pulmonary circulation) [9].

Since the coining of the term 'AFE' 76-91 years ago by Meyer JR, Steiner PE and Lushbaugh CC [10,11], several investigators have tried to establish a clinically applicable criteria or definition [12]. The diagnosis is based on several categories of clinical symptoms and signs and a careful clinical history. Several criteria in defining AFE have been proposed: for example, "the US AFE registration entry criteria (the US criteria)" [13], "the UK Obstetric Surveillance System criteria for defining cases of amniotic fluid embolism (the UK criteria)" [14] and "the Japan consensus criteria for the diagnosis of AFE (the Japan criteria)" [15]. The characteristics of the case definitions depend on different combinations of the clinical presentation, different time interval between delivery and clinical onset of symptoms and the variations in the exclusion criteria [12]. Different criteria of AFE can have different disease conditions or diagnostic conclusions. There is no international consensus between researchers on the definition of AFE. Therefore, it is difficult to compare maternal deaths worldwide [4].

Little is known about the degree of agreement or disagreement between the diagnostic criteria. In the present paper, we aimed to evaluate baseline characteristics of patients who were diagnosed with AFE according to the Japan criteria and assessed the degree of concordance within patients using two commonly used criteria: the US criteria and the UK criteria.

MATERIALS AND METHODS

This retrospective observational study project was approved on December 2015 by the Obstetrical Gynaecological Society of Kinki District (OGSKD) in Japan. The study period was from April 2005 to December 2012, in which total of 26 patients with clinically suspected AFE were registered in the Obstetric Committee of OGSKD. Permission was obtained from the OGSKD for this audit to be conducted and presented. The data were analysed by the expert steering Obstetric Committee, organized by the members of the Nara Medical University research team under the direction of the principal investigator. All members of research team had full access

The US criteria [13]	The UK criteria [14]	The Japan criteria [15]
The US AFE registration entry criteria	**UK Obstetric Surveillance System criteria for defining cases of amniotic fluid embolism**	**The Japan consensus criteria for the diagnosis of AFE**
1. Acute hypotension or cardiac arrest 2. Acute hypoxia, defined as dyspnea, cyanosis or respiratory arrest 3. Coagulopathy, defined as laboratory evidence of intravascular consumption or fibrinolysis or severe clinical haemorrhage in the absence of other explanations* 4. Onset of the above during labor, caesarean section or dilatation and evacuation or within 30 minutes post partum 5. Absence of any other significant confounding condition or potential explanation for the signs and symptoms observed *Patient meeting all other criteria including abrupt cardiorespiratory arrest who died before coagulopathy could be assessed were included in the primary analysis.	Either In the absence of any other clear cause 1. Acute maternal collapse with one or more of the following features: Acute foetal compromise, Cardiac arrhythm Acute foetal compromise, arrhythmias or arrest, coagulopathy, convulsion, hypotension, maternal haemorrhage, premonitory symptoms, eg., restlessness, numbness, agitation, tingling, shortness of breath or arrest, 2. Excluding women with maternal haemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardiorespiratory compromise Or 3. Women in whom the diagnosis was made at post-mortem examination by finding foetal squames or hair in the lungs.	1. If symptoms appeared during pregnancy or within 12 hour of delivery; 2. If any intensive medical intervention was conducted to treat one or more of the following symptoms/diseases: Cardiac arrest, severe bleeding of unknown origin within two hour of delivery (≥1500 mL), disseminated intravascular coagulation, respiratory failure 3. If the findings or symptoms obtained could not be explained by other diseases. 4. As for AFE, consumptive coagulopathy/DIC due to evident aetiologies such as abnormal placentation, trauma during labor and delivery and severe preeclampsia/eclampsia, should be excluded.

[Table/Fig-1]: An overview of different diagnostic criteria of AFE.

to all the data, including statistical reports and tables. They also analysed and interpreted the data. The data were provided using a Power Point presentation. At a clinical-consensus meeting, the subjects were classified as having AFE or no AFE according to the Japan criteria [15]. This study was performed in seventeen hospitals involving high-volume obstetric centers in the OGSKD Clinical Research Network (Acknowledgements section). The permission was obtained from these seventeen hospitals to conduct the study. Case files with complete data were available for assessment, data extraction and analysis. The clinical records were analysed for their clinical features and outcome. Patient demographic variables considered were age and parity. General factors, obstetric history and outcomes such as mode of delivery, medical induction of labour, premature rupture of membranes, other complications and death were recorded for each group.

The degree of concordance according to different definitions: A total of three different diagnostic criteria of AFE were used in our analysis [Table/Fig-1]. The clinical presentation commonly includes: acute hypotension or cardiac arrest, acute hypoxia (dyspnea, cyanosis or respiratory arrest) and coagulopathy (intravascular coagulation or severe haemorrhage), which usually occur during labour or cesarean section [7,13-16]. Diagnostic criteria based on measurements of serum markers were not used in this comparison.

Amniotic fluid embolism analysed in this study was defined based on the Japan consensus criteria for the diagnosis of AFE (the Japan criteria). The patients' clinical characteristics, general factors, obstetric history, complications and outcomes were retrospectively reviewed. Next the impact of various factors in determining diagnostic agreement or disagreement and the degree of concordance according to two commonly used criteria were compared: The US AFE registration entry criteria (the US criteria) and UK Obstetric Surveillance System criteria for defining cases of amniotic fluid embolism (the UK criteria).

STATISTICAL ANALYSIS

Cohen's kappa coefficient was used to calculate the agreement among three clinical diagnoses [17]. For inter-group comparison, the Pearson chi-square test was used (for categorical) and Mann-Whitney test was used (for continuous variables).

RESULTS

Twenty-six cases were registered for this period, with complete hospital case files available for assessment and data analysis. Almost 69.2% (18/26) of total patients were diagnosed with AFE according to the Japan criteria in the obstetric committee and then eligible for analysis. [Table/Fig-2] displays baseline characteristics and clinical outcomes. All of the patients were Japanese, with a mean age of 35.3 years (range: 25-45 years) and a parity of less than 2. Three women (16.7%) underwent either an induction or augmentation of labour and 7 (38.9%) underwent a cesarean section. Four women (22.2%) conceived using assisted reproduction technology. Twelve (66.7%) women required cardiopulmonary resuscitation, 44.4% (n=8) had a hysterectomy and 100% (n=18) received a transfusion of blood or blood products. Five women died (case fatality rate 27.8%). The histological findings of AFE at autopsy were the presence of embolic particles of foetal squamous cells or amniotic fluid materials in the maternal pulmonary circulation, pulmonary oedema and alveolar haemorrhage.

[Table/Fig-3] shows the distribution of patients identified as AFE according to the different diagnostic criteria. Eighteen patients who were diagnosed with AFE based on the Japan criteria led to a diagnosis of AFE in 10 women according to the US criteria and in 13 women according to the UK criteria. The rate of concordance varied from 55.6% (10/18) when we used the US criteria to 72.2% (13/18) when the UK criteria were used. The clinical signs and symptoms such as cardiovascular collapse (55.6% vs 70.0% and 76.9%) and respiratory failure (44.4% vs 50.0% and 61.5%) were lower by the Japan definition compared with the US and UK criteria, but this did not result in a significant difference (p=0.442 and p=0.641). DIC and maternal haemorrhage as the initial presentation was significantly

Variables		n	%
Age	<35 years old	7	38.9
	≥35 years old	11	61.1
Parity	<2	15	83.3
	≥2	3	16.7
Mode of delivery	Normal vaginal	6	33.3
	Cesarean delivery	7	38.9
	Forceps delivery	1	5.6
	Vacuum delivery	4	22.2
Medical induction of labor		3	16.7
Premature rupture of membranes		2	11.1
death		5	27.8

[Table/Fig-2]: Baseline characteristics of the samples (n=18).

Variables	Criteria					
	Japan		US		UK	
	n=18		n=10		n=13	
	n	%	n	%	n	%
Cardiovascular collapse	10	55.6%	7	70.0%	10	76.9%
Respiratory failure	8	44.4%	5	50.0%	8	61.5%
DIC as the initial presentation	8	44.4%	3	30.0%	3	23.1%
Women with maternal haemorrhage as the first presenting feature in whom there was no evidence of early coagulopathy or cardiorespiratory compromise	5	27.8%	3	30.0%	0	0%
Onset within 30 minutes postpartum	10	55.6%	10	100%	7	53.8%
Death	5	27.8%	5	50.0%	5	38.5%

[Table/Fig-3]: The degree of concordance according to different definitions.

higher by the Japan definition (p=0.030). The kappa agreement coefficient value indicates a "moderate" agreement between the Japan criteria and the US criteria (k=0.453). The strength of agreement between the Japan criteria and the UK criteria was also "moderate" (k=0.538). Lower agreement between the US definition and the UK definition was observed, as seen through the Kappa agreement coefficient (k=0.308). The diagnosis based on the Japan criteria differed from those according to the US and UK criteria.

We analysed patient characteristics in the subgroup who were diagnosed with AFE only in the Japan criteria. The factor that caused disagreement in diagnosis between the Japan criteria and the US criteria were "onset within 30 minutes postpartum". There has been considerable interest and controversy around its definition in terms of time from delivery to symptom onset; symptoms occur within 30 minutes (The US criteria) or 12 hours (The Japan criteria) post partum. The severity of symptoms could be detected objectively using the US criteria. The UK criteria excluded five women with massive postpartum haemorrhage as the first presenting feature. Uterine atony was considered to be the main cause of bleeding. These three definition criteria identified different subgroups of patients; only 7 patients (38.9%) were given a diagnosis of AFE according to all three definition systems. The mortality was lower by the Japan criteria compared to the US and UK criteria (27.8% vs 50.0% and 38.5%), but this did not result in a significant difference (p=0.497).

DISCUSSION

In the present study, we evaluated the concordance of the Japan criteria, the US criteria and the UK criteria for the diagnosis of AFE. We found that there is substantial overlap among three diagnostic criteria, but the case fatality rates in Japan tend to exhibit lower than in US and UK. The clinical presentation of AFE commonly includes acute hypotension or cardiac arrest, acute hypoxia and coagulopathy which usually occur during labour or cesarean section [7]. One of the major reasons of the limited data on AFE is due to the differences in the definition among various working groups [12]. We assessed the concordance of the Japan criteria for AFE in comparison with two definitions: the US criteria and the UK criteria. Agreement between the Japan criteria and the US and UK criteria was k = 0.453 and k = 0.538, respectively, reflecting moderate agreement. However, only 38.9% of patients satisfied three sets of AFE definition criteria. A tendency for higher fatality rates was observed in the US and UK criteria compared with the Japan criteria.

Firstly, there is substantial overlap among three diagnostic criteria which are based on the clinical presentation. However, the use of these criteria can produce somewhat different estimates of the diagnosis of AFE. Several investigators have recently reported an isolated coagulopathy with maternal haemorrhage without cardiopulmonary collapse [4,6,15,18,19]. The Japan criteria exclude "DIC due to evident aetiologies such as abnormal placentation, trauma during labour and delivery and severe preeclampsia/eclampsia" [15] and most Japanese obstetricians include "women with maternal haemorrhage as the first presenting feature in whom there was no evidence of cardiorespiratory compromise" as having AFE [4,15,18].

Recently, a new term, uterine AFE, has been developed to describe a relevant disease subgroup of AFE. The local flow of amniotic fluid into uterine tissues may cause an anaphylactoid reaction in the uterus, resulting in DIC or atonic bleeding [15]. Members of the Maternal Mortality Evaluation Committee in the Japan Association of Obstetricians and Gynaecologists reported that the severe cases of DIC or atonic bleeding which are refractory to various treatments are considered as mild AFE [15]. AFE can be divided into the following two subgroups based on initial symptoms and autopsy (pathological) findings: (i) the first subgroup; AFE that starts with cardiopulmonary collapse and characterized by pulmonary/respiratory symptoms (defined AFE with autopsy finding {pathologically proven AFE} [13,14] or cardiopulmonary type AFE without autopsy finding {clinically diagnosed AFE} [13,14]); and (ii) the second subgroup; AFE that starts with atonic bleeding/DIC (uterine AFE with pathological finding [4,5,15] or DIC type AFE without pathological finding [15,18]). In the patients with cardiopulmonary collapse type AFE, amniotic components and foetal elements were detected in the pulmonary vessels, resulting in cardiopulmonary shock. On the other hand, in the patients with uterine AFE, uterine atony (a large, oedematous uterus) was macroscopically observed and amniotic components were not microscopically detected in the lungs, but observed in the uterine vessels. The consensus definition was identified by the Maternal Mortality Evaluation Committee in the Japan Association of Obstetricians and Gynaecologists: Uterine AFE could be diagnosed on the basis of the detection of amniotic components and foetal elements in the uterine vasculatures.

However, the presence of maternal intravascular amniotic fluid components and foetal materials in the uterus is not a specific indicator for AFE [20]. Maternal intravascular foetal material at the time of peripartum hysterectomy for treatment of uterine rupture, abruption, uterine atony, placenta previa, accreta, coagulopathy and retained placenta was present in up to one third of patients and did not invariably result in DIC or AFE [21]. Therefore, foetal-to-maternal tissue transfer through the maternal uterine vasculature may be common at some time during the labour and delivery process, as well as even in peripartum patients without clinical AFE [22,23]. Entry of amniotic fluid and foetal material in the maternal uterine vasculature do not lend credibility to the specificity for AFE. The terminology "uterine AFE" might complicate the situation unnecessarily. In other words, AFE is not one of the possible consequences of uterine atonic bleeding. Differences between these two entities, uterine AFE and uterine atony for massive obstetric haemorrhage, may have implications for outcomes research. The definition based on the pathological finding of uterine vasculature fails to match with those based on the clinical presentation.

Secondly, patients who were diagnosed based on the Japan criteria showed a lower case-fatality rate (27.8%) than those diagnosed based on the US (50.0%) or UK (38.5%) criteria, suggesting that a strict definition of AFE is used in the US and UK criteria. The Japan criteria include "patients with symptoms appeared within 12 hour of delivery". Subgroups classified according to the Japan criteria appear to have distinct clinical profiles and outcomes. The first subgroup has a severe uncontrolled, irreversible and early onset phenotype. The second subgroup contains patients who start with atonic bleeding/DIC, with a mild and late onset phenotype. Amniotic

fluid embolism may be overdiagnosed in the setting of critical illness, particularly when the second subgroup developed coagulopathies. Although prompt recognition and treatment of this entity is crucial to survival, understanding the aetiology can be more complicated by diverse diagnostic approaches [12].

LIMITATION

Retrospective design and relatively small sample size. Our results raise the important question of how many individuals who meet symptom criteria according to the US or UK definition will not meet the Japan criteria is unknown. We must compare the categorization agreement or disagreement among three definitions. Such disagreement has serious implications for research and treatment.

CONCLUSION

Only 38.9% of patients satisfied three sets of AFE definition criteria. Our findings also clearly demonstrate the different selection of patients diagnosed with AFE using various criteria. There are concerns about the validity of comparisons between studies using different criteria to diagnose AFE. Such disagreement has serious implications for epidemiology, diagnosis, prognosis, research and treatment.

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