Amniotic fluid embolism - Investigation of fatal cases in Slovakia in the years 2005-2010 compared with fatal cases in the United Kingdom

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Background. Amniotic fluid embolism (AFE) is a rare, often severe complication of pregnancy. The clinical diagnosis is difficult to establish and is one of exclusion. The aim of this study was to investigate 6 fatal cases of AFE in Slovakia and compare the incidence, risk factors, course, management and neonatal outcomes with fatal cases of AFE in the United Kingdom (UK).

Materials and Methods. Data on fatal cases of AFE in Slovakia were analysed and compared with fatal cases in the UK in the years 2005-2010.

Results. The incidence in Slovakia was significantly higher than in the UK from 2005-2010 (RR 5.03, 95% CI 1.98-12.75, $P=0.003$). However, 5/6 deaths occurred in 2009 coinciding with the H1N1 flu virus pandemic in Slovakia. There were no significant differences in the characteristics of women who died, with the exception of gestational age at delivery; significantly higher in Slovakia (median 41 versus 39 weeks, $P=0.01$). In Slovakia most of the cases occurred after delivery, 83.3%, compared with 52.9% in the UK. There were no significant differences in clinical signs, use of recombinant factor VIIa or performance of obstetric hysterectomy. In Slovakia 83.3% and in the UK 94.7% of infants survived, but 20% and 27.8% had some long-term sequelae.

Conclusion. AFE is now the leading cause of maternal deaths in Slovakia. However, we found no significant differences in the possible risk factors, course, management or outcomes between Slovakia and the UK. This analysis is limited by study power; we propose that establishment of a national register of cases of AFE in Slovakia would help further investigate and monitor mortality from this condition.

Key words: amniotic fluid embolism, incidence of amniotic fluid embolism, risk factors of amniotic fluid embolism, maternal mortality, neonatal outcome by amniotic fluid embolism

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INTRODUCTION

Amniotic fluid embolism (AFE) is a rare and life-threatening complication unique to pregnancy. The condition was first reported in 1926, when Meyer described fetal debris in the pulmonary vessels of a mother who had died suddenly in labour¹. The work of Steiner and Lushbaugh in 1941 served to establish the condition as an important pregnancy complication². In the last decades, AFE has accounted for 5 - 15% of all maternal deaths in developed countries³. AFE is characterized by an unexplained sudden and rapidly progressive clinical course with respiratory distress, cyanosis, cardiac dysrhythmias, cardiovascular collapse, and disseminated intravascular coagulation^{3,4}. The clinical diagnosis is one of exclusion and most fatal cases are only definitively diagnosed at autopsy^{3,5}. This, coupled with the rarity of the condition make it difficult to study⁶. On a worldwide basis, register and population-based studies of AFE have been undertaken to incorporate large numbers of pregnant women and have sufficient statistical power to estimate the incidence, examine possible risk factors, and better understand the clinical course and management of the condition⁶⁻⁸.

In the United Kingdom (UK), prospective surveillance of AFE has been undertaken through the United Kingdom Obstetric Surveillance System (UKOSS) since 2005 (ref.⁹). During the active monitoring of maternal deaths in Slovakia, we identified 6 fatal cases of AFE in the years 2005 - 2010. The aims of this work were to describe these cases and compare the incidence, possible risk factors, neonatal outcomes and the clinical course of fatal cases of AFE in the years 2005 - 2010 in Slovakia and in the UK.

MATERIALS AND METHODS

Data on fatal cases of AFE in Slovakia were analysed and compared with data on fatal cases in the UK occurring in the years 2005 - 2010. The incidence, possible risk factors and clinical course of cases of AFE were examined. Given the type of the study no ethical approval or informed consent were required.

Slovakia

The data on cases of fatal AFE and the numbers of live births (323 594 live births) and deliveries (319 294 deliveries) in the years 2005 - 2010 were obtained from reports of maternal deaths kept by the chief of Gynaecology and Obstetrics of the Ministry of Health in Slovakia. Reporting maternal death cases in this way is compulsory for all hospitals. In all cases, clinical suspicion of AFE was confirmed by autopsy. The data on pregnancy, risk factors, labour, course and management of amniotic fluid embolism were extracted from medical records.

United Kingdom

The data on fatal AFE cases in the UK were extracted from the UKOSS database, which includes reports of both fatal and non-fatal cases. The UKOSS methodology has been described in detail elsewhere¹⁰. The numbers of deliveries (4 460 909 deliveries) and live-births (4 510 052 live-births) from February 2005 to December 2010 in the UK were obtained from available national statistics¹¹⁻²⁰.

Statistical analysis

Incidences with 95% confidence intervals (CI) are presented using as a denominator the number of maternities. Data were compared using Risk Ratios (RR) with 95% CI, Chi-squared test or Fishers exact tests and Mann-Whitney U-test as appropriate. All statistical analyses were carried out using STATA 11 SE software.

RESULTS

Case reports of Slovakian fatal cases of AFE

From 2005 - 2010, there were 6 fatal cases of AFE; 5 occurred in 2009.

Case report 1

A 33-year old primiparous woman, after induction of labour due to post term pregnancy, gave birth by vacuum extraction (girl 3000 g with Apgar score 7/9, with minimal spina bifida without clinical consequences). After suture of birth injuries (rupture of cervix, rupture of right vaginal wall and left sided episiotomy) more intensive bleeding from the suture sites occurred; the uterus was well contracted without significant bleeding. Coagulopathy was suspected and confirmed on further testing. Transfusion with fresh frozen plasma and erythrocytes was initiated. The woman became hypotensive and was anaesthetised in preparation for laparotomy. Shortly after intubation, ventricular fibrillation occurred and the woman had successful cardiopulmonary resuscitation, following which she was admitted to intensive care. A Bakri balloon catheter was inflated in the uterus. In spite of further intensive management with blood products, the coagulopathy remained uncontrolled and the woman died 5 h and 15 min after the first signs of AFE.

Case report 2

This 34-year old secundiparous woman was admitted 3 days after her estimated date of delivery with regular

contractions. She had a spontaneous vaginal delivery of a girl weighing 3740 g (Apgar score 3/6/8). Five min after delivering, she became transiently unconscious, after which she had visual disorders and appeared confused. Blood samples were taken. The woman had a retained placenta, and therefore underwent general anaesthesia and manual removal with suture of birth injuries (rupture of cervix and left side episiotomy). By the end of the operation, the woman became cardiovascularly unstable and bled from the uterus. Prostaglandin was given into the uterine wall and a Bakri balloon catheter was inserted in the uterus. Although a hysterectomy was clinically indicated, the woman was unable to be sufficiently stabilised to allow surgery. Despite cardiopulmonary resuscitation and blood products substitution, the woman died 4 h and 30 min after the first signs of AFE.

Case report 3

A 36-year old tertiparous woman was admitted one week after the estimated date of delivery with contractions. Intrauterine fetal demise was diagnosed. Antibiotics and low-molecular weight heparin were given and induction of labour was started. After augmentation of labour with oxytocin, the woman delivered a stillborn girl (3100 g) and placenta without any complications. Approximately 15 min after the delivery the woman became restless, nauseous, short of breath, pale and sweaty. Her clinical condition deteriorated very rapidly. She became hypotensive with a thready pulse, unconscious and dyspnoeic. Cardiopulmonary resuscitation was initiated and intubation was performed but no cardiac activity was regained. There were no signs of major bleeding, although a blood sample taken one hour after the initial event showed a coagulopathy. The woman died 2 h and 10 min after the first signs of AFE.

Case report 4

A 27-year old quadriparous woman was admitted 5 days after her estimated date of delivery with irregular contractions. The next day induction of labour was initiated and the woman gave birth at 41+1 weeks' gestation. During her labour she became hypertensive and was managed with antihypertensive drugs. Approximately 40 min after a normal vaginal delivery (healthy girl, 2900 g, Apgar score 9/10) the woman started to become restless, hypotensive and tachycardic. She complained of nausea and shortness of breath. She rapidly became shocked, and despite cardiopulmonary resuscitation died 1 h and 55 min after the first sign of AFE.

Case report 5

A 26-year old primiparous woman with regular contractions was admitted two days before her estimated date of delivery and spontaneously gave birth to a healthy girl weighing 4270 g (Apgar score 10/10). The placenta was delivered without any problems and the suture of a left-sided episiotomy was performed. Approximately 55 min after the delivery ongoing vaginal bleeding was noted. Bleeding from the upper pole of the episiotomy was recognised and sutured under general anaesthesia. After the suture

the woman was cardiovascularly stable; the overall blood loss together with blood loss at the delivery was 700 mL. Red cell transfusions were given. The woman became restless and pale and complained of nausea. Cardiac arrest occurred shortly afterwards. Cardiopulmonary resuscitation started immediately and cardiac activity was initially recovered, but after a further 20 min ventricular fibrillation occurred and in spite of intensive cardiopulmonary resuscitation the woman died 2 h and 5 min after the first signs of AFE.

Case report 6

This 41-year old secundiparous woman was admitted in the 41st gestational week for induction of labour. In the first stage of labour, after insertion of an epidural catheter the woman suddenly lapsed into unconsciousness. During intubation, cardiac arrest occurred, cardiopulmonary resuscitation was initiated and cardiotocography showed a fetal bradycardia. An emergency caesarean section was performed. During the caesarean section uterine atony occurred with massive haemorrhage and an emergency hysterectomy was performed. Disseminated intravascular coagulation was diagnosed and therapy was initiated with blood products. After 15 h a relaparotomy was indicated because of bleeding into the abdominal cavity. This woman died 36 h and 38 min after the possible first signs of AFE. The newborn - girl, 3890g, Apgar score 0/3/6 was resuscitated and has some neurological sequelae.

Results of the comparison

In the UKOSS data 17 fatal cases of AFE in the time period from February 2005 to December 2010 were recognised and used for comparison.

Incidence

The incidence of fatal cases of AFE in Slovakia was 1.88/100 000 deliveries (95% CI 0.69 - 4.09), significantly higher than in the UK (0.38/100 000 deliveries, 95% CI 0.22 - 0.61; RR 4.93, 95% CI 1.94 - 12.51, $P=0.003$). This equates to a maternal mortality ratio (MMR) due to AFE of 1.85/100 000 live births versus 0.38/100 000 live births, RR 4.92 (95% CI 1.94 - 12.48, $P=0.003$).

Maternal characteristics

The complete maternal data together with results of comparison with fatal cases from UKOSS data are shown in Table 1. There were no statistically significant differences in the characteristics of women who died in Slovakia compared with the UK, with the exception of gestational age at delivery. In Slovakia the median gestational age at delivery was 41 (39 - 41), significantly higher than the median of 39 (31 - 41) in UK ($P=0.01$).

Labour

Women who died from AFE in Slovakia were more likely to delivery vaginally than women who died in the UK (5/6, 83% versus 5/17, 29%, RR 2.83, 95% CI 1.43 - 5.63, $P=0.052$). There were no significant differences in the proportion of women who were induced 4/6, 67% versus 8/17, 47% ($P=0.64$). Two women (33.3%) who died in Slovakia were managed with oxytocin, compared with two (12%) in the UK (4 cases unknown use of oxytocin, RR 2.17, 95% CI 0.39 - 11.92, $P=0.56$). There were no differences in the distribution of cases in relation to timing of delivery: 1/6 cases (17%) occurred before delivery in Slovakia, compared with 7/17 (41%) cases in the UK ($P=0.369$). In Slovakia cervical laceration was reported to have occurred in two women (33.3%).

Table 1. Maternal characteristics in Slovakia and UK and the comparison.

Maternal characteristics	Slovakia (6 cases)	United Kingdom (17 cases)	
	median (range)	median (range)	Comparison (P)
Maternal age (years)	33.5 (26-41)	35 (28-47)	0.23
Parity	1 (0-3)	1 (0-2)	0.66
Gravidity	1.5 (0-3)	2 (0-3)	0.88
Body weight (kg)	83 (64-115)	70.5 (50-135)	0.39
BMI	26.5 (20.2-35.9)	27.8 (19.1-42.6)	0.69
Gestational age (weeks)	41 (39-41)	39 (31-41)	0.01
	n (%)	n (%)	Comparison (P)
Employed	5/6 (83.3)	12/17 (70.6)	1.00
Non-Smokers	6/6 (100.0)	14 (82.4)	0.54
History of allergy	0/6 (0)	4/17 (23.5)	0.54
Current pregnancy problems	4/6 (66.7)	11/17 (64.7)	1.00
Gestational diabetes	1/6 (16.7)	1/17 (5.9)	0.48

Course and management of AFE

The first clinical signs and overall clinical signs of AFE are shown in Tables 2 and 3. There were no significant differences between Slovakia and the UK.

In Slovakia the course of AFE appeared to be more rapid than in the UK, however these differences were not statistically significant. The times from the event to the death, from the delivery to the death and the time from start of labour to the event and to death are shown in Table 4.

There were no significant differences in use of recombinant factor VIIa (3/6, 50% versus 2/17, 1.8%, RR 4.25, 95% CI 0.92 - 19.59, $P=0.09$) and in the performance of emergency obstetric hysterectomy (1/6, 16.7% versus 5/17, 29.4%, RR 0.56, 95% CI 0.08 - 3.92, $P=1.00$) for the management of AFE between Slovakia and UK.

Neonatal outcomes

There were no significant differences in neonatal outcomes. There was no significant difference in birth weight ($P=0.57$). In each group there was one stillbirth (RR 2.83, 95% CI 0.21 - 38.56, $P=0.46$). The perinatal mortality appeared lower in Slovakia 16.7% (95% CI 0.42 - 64.1) versus UK 21.1% (95% CI 6.1 - 45.6), but was not

statistically significantly different. There were no differences in the proportion of live-born infants with ongoing morbidity: 1/5 (20%) versus 5/18 (27.8%), RR 0.72, 95% CI 0.11 - 4.84.

DISCUSSION

Worldwide the maternal mortality rate associated with AFE has been reported to range between 0.5 - 1.7 deaths per 100 000 live-births or deliveries³. The mortality rate we observed in Slovakia was higher than these previously reported rates, whereas that in the UK was lower. In Slovakia five of the AFE cases occurred in 2009. Whilst we have no evidence that this was not simply a chance phenomenon, the overall maternal mortality ratio in 2009 was the highest observed in recent years in Slovakia at 29.9/100 000 live births (95% CI 17.43 - 47.91).

The immune system and inflammation are also involved in the development of AFE (ref.^{21,22}). There are significant changes in cytokines and chemokines in patients with H1N1 influenza even with mild symptoms²³. The influenza H1N1 pandemic occurred in 2009, and was associated elsewhere with significantly higher ma-

Table 2. First clinical signs of AFE in fatal cases in Slovakia and in the UK.

1 st sign	Slovakia (6 cases)	United Kingdom (17 cases)	Comparison
	n (%)	n (%)	(<i>P</i>)
Premonitory symptoms and shortness of breath	3 (50.0)	4 (23.5)	0.32
Maternal haemorrhage and coagulopathy	1 (16.7)	2 (11.8)	1.00
Unconsciousness and seizure/convulsions	2 (33.3)	3 (17.7)	0.58
Cardiac arrest	0	4 (23.5)	0.54
Acute fetal compromise	0	4 (23.5)	0.54

Table 3. Occurrence of clinical signs of AFE in fatal cases in Slovakia and UK.

Clinical signs of amniotic fluid embolism	Slovakia		United Kingdom		Comparison
	n	(%)	n	(%)	(<i>P</i>)
Acute fetal compromise	1	(16.7)	6	(35.3)	0.62
Cardiac arrest	6	(100.0)	15	(88.2)	1.00
Cardiac rhythm problems	4	(66.7)	4	(23.5)	0.13
Hypotension	5	(83.3)	7	(41.2)	0.16
Coagulopathy	4	(66.7)	11	(64.7)	1.00
Maternal haemorrhage	3	(50.0)	13	(76.5)	0.32
Premonitory Symptoms (restlessness, agitation...)	3	(50.0)	6	(35.3)	0.64
Seizure	1	(16.7)	4	(23.5)	1.00
Shortness of breath	3	(50.0)	7	(41.2)	1.00

Table 4. Time course of fatal cases of AFE in Slovakia and UK.

Times (h:min)	Slovakia	United Kingdom	Comparison (<i>P</i>)
Event → death	08:46	22:07	0.65
	1:55-36:38	0-292:48	
Delivery → death	09:13	22:46	0.65
	2:25-35:05	0:17-292:49	
Start of labour → death	13:04	12:12	0.88
	4:20-38:10	1:02-33:10	
Start of labour → event	04:18	07:39	0.30
	1:32-10:25	0:36-22:28	

ternal morbidity and mortality²⁴. This was also seen in Slovakia; six pregnant women died during November and December 2009 from complications associated with H1N1 influenza²⁵. Three cases of fatal AFE occurred in this time and in the same area of Slovakia as the influenza-associated maternal deaths. This coincidence of AFE and the H1N1 influenza gives rise to a suspicion that the weakened immune system due to the H1N1 pandemic may have played a role in the higher incidence of maternal deaths and sudden increase in AFE in Slovakia in 2009. However, this temporal association with influenza has not been reported in other AFE studies.

Nevertheless, the absolute number of fatal cases of AFE in Slovakia is small, and the wide confidence intervals around the estimated mortality rate means that it is comparable with mortality rates observed elsewhere, including in Canada in the years 1991 - 2002 (0.8/100 000 deliveries, 95% CI 0.5 - 1.2) (ref.⁶), the USA in years 1999 - 2003 (1.7/100 000 deliveries, 95 % CI 1.23 - 2.2) (ref.²⁶) and Australia where the incidence of fatal cases varied between 1.0 - 1.2/100 000 maternities in years 1994 - 2008 (ref.⁶). However, there appears to be a real difference in the mortality rate between Slovakia and the UK. This may either be explained by a difference in the fatality rate of AFE cases, or in overall AFE incidence. It is unlikely to be explained by a difference in case definitions, since all cases were pathologically confirmed.

Associations between social status, maternal age and obesity and case fatality from severe maternal morbidity (including AFE cases) have been described²⁷. However, we found no clear differences in these characteristics amongst the fatal cases from the UK and Slovakia. A previous analysis of UK data found an association between ethnic group and mortality from AFE (ref.¹⁰), however, white ethnic groups predominate in Slovakia, and this is unlikely to be an explanatory factor. The gestational age at delivery of the women who died in Slovakia was significantly higher than in the United Kingdom. Oi et al. (2010) reported that higher gestational age appeared to be associated with case fatality from AFE (ref.²⁸), thus this may be a possible explanation for the observed difference in mortality rates.

Although there are data on non-fatal cases of AFE occurring in the UK (ref.¹⁰), we do not currently have these data for Slovakia and cannot therefore directly compare incidence rates. Examination of differences in the prevalence of known risk factors for AFE may give us an indication of whether incidence rates are likely to be very different. Induction of labour is a known risk factor for AFE (ref.^{6,10,29}). There is, however, higher rates of overall induction in the UK (20.2 - 22.1% in years 2005 - 2012) and Slovakia (11.6 - 13.8% overall induction in years 2007 - 2010) (ref.^{30,31}). An association between operative delivery and AFE has been observed by several studies²⁶. This is unlikely to be a cause of higher incidence of AFE; in Slovakia as the overall rate of instrumental vaginal deliveries is significantly lower than in UK (vacuum delivery 1.3% in Slovakia versus 6.5% in England and forceps delivery 0.6% versus 5.7 %) (ref.³¹⁻³⁵). AFE has also been associated with cervical laceration and uterine rupture^{29,36}. There were two cases of cervical rupture in the Slovak group, but there are no data on this in the UKOSS database.

In Slovakia the time from the onset of the AFE to death appears shorter than in the UK. This raises the possibility that the Slovakian cases were more severe, or the treatment used in the UK prolonged life slightly. On the basis of some studies and individual reports, recombinant factor VIIa has been proposed for treatment of the coagulopathy associated with AFE (ref.^{10,37-39}), although its efficacy is by no means established. Recombinant factor VIIa was used proportionately more frequently in Slovakia than in the UK; nevertheless the incidence of fatal AFE is higher in Slovakia. This may be explained by the fact that it is being administered late in the course of the disease, since in Slovakia it has to be prescribed by the consulting haematologist or anaesthetist, although this is very speculative.

The clear limitation of this study is the small number of fatal cases of AFE, so we cannot exclude the possibility that some differences exist, but these have not been detected as statistically significant due to low study power.

AFE has become the leading cause of maternal deaths in Slovakia in years 2005 - 2010. However we have not

identified any factors to clearly explain the significantly higher mortality rate in Slovakia compared with the UK. It is important to note that the small number of cases of this rare condition limit the power of this study. However, there are no data on non-fatal cases of AFE in Slovakia to allow us to assess whether the observed higher mortality rate is the result of a higher case fatality rate or a higher incidence. The continuation in population-based studies of AFE, such as through UKOSS is a useful route to identify risk factors for AFE and to investigate different management strategies which could decrease the mortality from this condition. We propose that establishment of a national register of cases of AFE in Slovakia would help to further investigate and monitor mortality from this condition.

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