JOURNAL OF FORENSIC SCIENCES

J Forensic Sci, January 2011, Vol. 56, No. S1
doi: 10.1111/j.1556-4029.2010.01588.x
Available online at: onlinelibrary.wiley.com

CASE REPORT

PATHOLOGY/BIOLOGY

Dragan Ječmenica,[1] Ph.D.; Ivanka Baralić,[1] Ph.D.; Djordje Alempijević,[1] Ph.D.; Snežana Pavlekić,[1] Ph.D.; Milosav Kiurski,[2] M.D.; and Milan Terzić,[3] Ph.D.

Amniotic Fluid Embolism—Apropos Two Consecutive Cases*

ABSTRACT: Amniotic fluid embolism (AFE) is a sporadic, unpredictable, and usual fatal obstetric complication. The paper deals with two cases of maternal deaths because of AFE verified by medicolegal autopsy. In both the cases, several known risk factors associated with AFE, such as increased maternal age (41 and 35 years), diabetes, augmented labor, and cesarean delivery, were identified. Clinical features were typical, including sudden onset of cardiovascular and respiratory symptoms. In the patient who survived longer, both clinical and autopsy signs of disseminated intravascular coagulopathy were present, while they were absent in the case where death occurred rapidly. This paper describes briefly the particular features to look for at autopsy and stresses the importance of histology examination and staining techniques.

KEYWORDS: forensic science, amniotic fluid embolism, pregnancy complications, pathology, forensic pathology, medicolegal aspects

The maternal mortality ratio is an important indicator of the adequacy of health care in society. The issue of identification and categorization of maternal deaths is important because some maternal deaths may be potentially preventable, while others may be related to subsequent medicolegal investigation and malpractice claims (1). Hemorrhage, pulmonary embolism, complications of pregnancy-induced hypertension, and infection are the most frequently reported causes of maternal deaths (2–5).

Amniotic fluid embolism (AFE) is one of the most dangerous and untreatable conditions in obstetrics. AFE is not predictable, and no preventive measures are available (6,7). Abrupt presentation of symptoms including dyspnea, hypotension, seizures, and disseminated intravascular coagulopathy (DIC) in previously healthy and asymptomatic women are typical for AFE (8,9). Although the prognosis and mortality of AFE have improved significantly with early recognition of this syndrome and prompt and early resuscitative measures, it still bears a high mortality risk (10).

Thorough postmortem investigation in cases of maternal death is of paramount importance for accurate cause of death determination, where for a clinical pathologist, the sole detection of AFE will be sufficient to explain the clinical course and to close the case. Quite the opposite, in forensic practice, the diagnosis of AFE may explain an unfavorable course of events that led to the death and discharge the medical staff from accusations by relatives, who often suspect medical malpractice in a case of sudden and unexpected death during parturition (11,12).

[1]Institute of Forensic Medicine, Faculty of Medicine, University of Belgrade, Serbia.
[2]Clinical Center "Zemun," Belgrade, Serbia.
[3]Institute of Gynecology and Obstetrics, Faculty of Medicine, University of Belgrade, Serbia.

*Presented as a poster at the 21th Congress of the International Academy of Legal Medicine, May 27–29, 2009, in Lisbon, Portugal.

Received 14 Aug. 2009; and in revised form 30 Nov. 2009; accepted 2 Dec. 2009.

We are presenting two cases of AFE where forensic pathologists have performed postmortem examination upon court orders because of alleged medical malpractice. We assess complete medical records for both cases as well.

Case Reports

Patient No. 1

A healthy 41-year-old multipara (gravida 3 para II) at 36 weeks of gestation was admitted for clinical follow-up because of gestational diabetes. A month later, uterine contractions started spontaneously. Labor was augmented by parenteral Syntocinon and vaginal PGE2 administration. Approximately 6 h later, while still in labor, the patient rapidly deteriorated, becoming unconscious, manifesting respiratory depression with marked cyanosis, and signs of cardiovascular collapse (systolic blood pressure 60 mm Hg; heart rate 150/min). Cardiopulmonary resuscitation (CPR) was begun immediately, and emergency surgery started in the best interests of the fetus. Emergency cesarean section was performed giving birth to a male newborn (weight 4850 g; length 57 cm; APGAR score 5/8). The placenta was apparently normal. Throughout the surgery and 20 min following it, intensive CPR continued. The patient was pronounced dead *c.* 30 min following the onset of symptoms and 5 min following cessation of myocardial electrical activity, which was refractory to further CPR. Because of abrupt onset of symptoms and emergency cesarean section, no clinical samples were collected for laboratory analysis.

The newborn was discharged from the hospital 10 days later with no remarkable pathology; further follow-up of the child was not available because of lack of information and medical records.

In the mother's autopsy on the second day postmortem, marked postmortem lividity, facial and neck cyanosis, and sparse conjunctival suffusions were evident. The weights of the lungs were 450 g, right; 350 g, left. They were edematous, with *c.* 100 mL exudate in

both pleural cavities. The heart was of normal size, weighing 350 g. Postmortem histological examination did not reveal signs of DIC. Microscopically, massive amniotic debris—epithelial squamous cells, granules of bile pigment, meconium, and even several lanugo hairs—was present in pulmonary microcirculation and was clearly visible both on routine H&E staining and as cytokeratin-positive structures on immunohistology (Fig. 1). The examination of the uterus did not reveal any lacerations. With the exception of marked congestion and suffusions of tracheal mucosa, gross and microscopic examination of other organs did not reveal any pathology. Cause of death was given as massive AFE.

Patient No. 2

A healthy 35-year-old multipara (gravida 2 para I) was admitted to obstetric clinic at 34th week of gestation for the evaluation of asymmetrical development of twins. Clinical evaluation revealed no pathological findings. Ten days following hospital admission, spontaneous labor had started. Cesarean section was performed because of pelvic presentation of both fetuses, giving birth of vital male twins (length 42 and 43 cm; weight 1720 and 2100 g, respectively; APGAR score 9/9 for both). No pathology of placenta was recorded. The patient duly woke up following surgery. Six hours later, she suddenly expressed dyspnea, nausea, and complained of dyplopia and back pain. At that moment, she was hypertensive (140/100 mm Hg). Half an hour later, the patient deteriorated rapidly expressing severe dyspnea and signs of cardiovascular collapse. No signs of uterine bleeding were present. Laboratory revealed decreased platelet count (32×10^9/L), fall of hematocrit (0.298 L/L), and prolonged prothrombin time (29.6 sec). Bruising became apparent in the vicinity of the surgical incision as well as adjacent to injection sites, but no signs of active uterine bleeding were present. The patient was immediately transferred to the intensive care unit where intensive therapy was administered including transfusion of full blood, plasma, and thrombocytes. Clinical presentation was considered as DIC, and an acute abdominal bleeding was suspected because of abdominal distension and hemorrhagic content obtained by gastric suction. Therefore, the decision was made to perform surgical exploration of the abdomen. The surgery revealed the presence of about about *c.* 100 mL of dark, hemorrhagic fluid in the abdominal cavity, and extensive suffusion over the parietal and visceral peritoneal surfaces. A diagnosis of DIC became apparent, leading to further decision to terminate surgery and continue resuscitation and respiratory support. Despite the treatment, the patient underwent further deterioration and died 4 h following the onset of clinical symptoms.

Newborn twins were discharged from the hospital 7 days later in good condition. The mother's autopsy was performed on the second postmortem day. Numerous petechia on head and torso, extensive skin bruising and subcutaneous hematoma at injection sites and adjacent to surgical incision, as well as suffusions of oral mucosa, were recorded on external examination. The weights of the lungs were 750 g, right; 600 g, left. There were considerable subpleural suffusions, lungs were edematous, and *c.* 300 mL of exudate was in both pleural cavities. The heart was of normal size, weighing 250 g, with marked subendocardial suffusions.

Microscopically, massive amniotic debris in pulmonary microcirculation (like in the previous case with exception of lanugo hairs) was present, as well as abundant fatty globules seen on both H&E and Sudan III stained sections (Fig. 2). Hyaline membranes were present in intra-alveolar spaces.

Small quantities of hemorrhagic fluid were free in the abdominal cavity, with dense serosae suffusions present. The stomach contained 200 mL of hemorrhagic fluid, while intensive hemorrhages were noticeable in the gastric wall, on both surfaces (Fig. 3). The examination of the uterus did not reveal any lacerations, but microscopic examination disclosed amniotic debris in dilated venous sinuses. The brain was edematous with sparse fibrin thrombi in small arteries. A gross and microscopic finding on other organs revealed congestion, but no other pathology. Cause of death was given as massive AFE.

Note on Histological Methods

Paraffin-embedded tissues were obtained for each case for routine H&E staining and immunohistologic markers for cytokeratin (CK 5/6). Another set of samples was, designated for Sudan III stain for fat collected at autopsy and fixed in 10% formaldehyde as

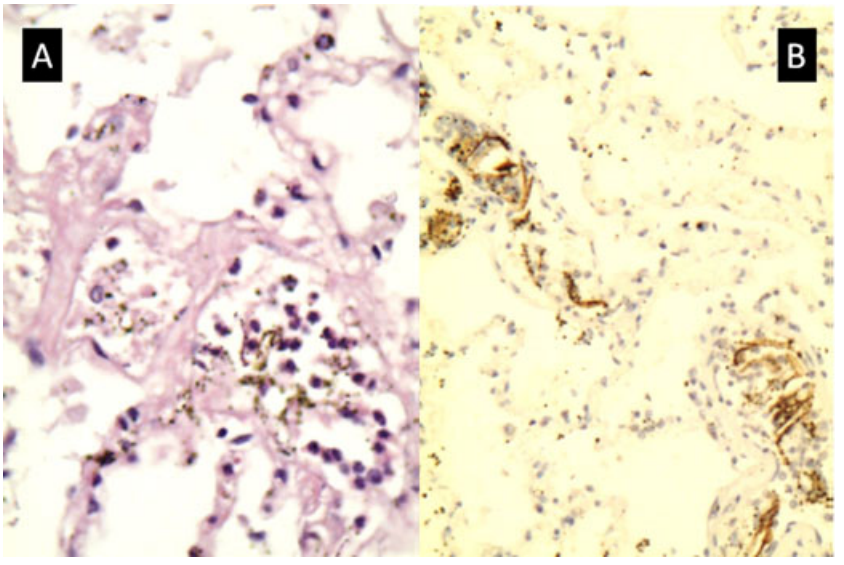

FIG. 1—*Patient No. 1: Histological section of the lung—A: Epithelial squamous cells and bile pigments derived from the meconium in pulmonary microcirculation (H&E stain; original magnification 200×); B: Multiple keratin squamous cells in pulmonary microcirculation (anticytokeratin CK 5/6, original magnification 250×).*

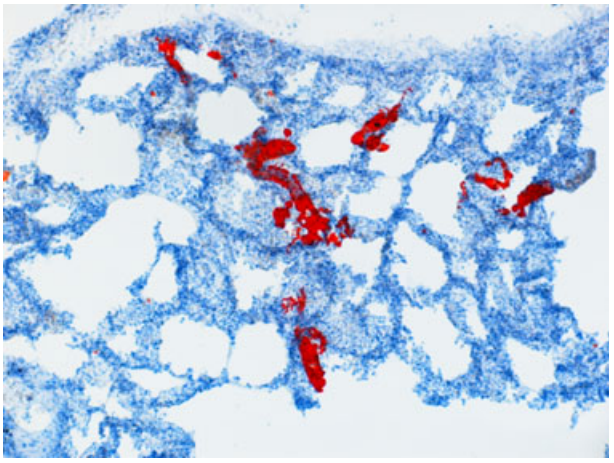

FIG. 2—*Patient No. 2: Abundant fatty globules in lungs (Sudan III stain; original magnification 50×).*

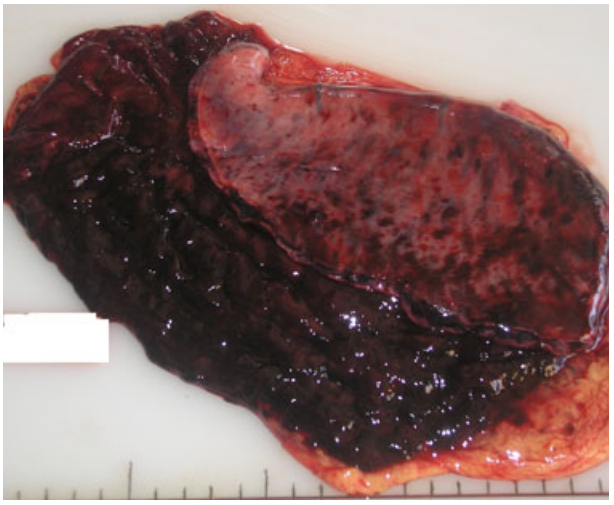

FIG. 3—*Patient No. 2: Intensive hemorrhages on both surfaces of gastric wall.*

nonfat dissolving fixer. Following fixation, tissue sections were made using freezing microtome. Sections were stained with a saturated alcoholic solution of the Sudan to outline all fat in brilliant red.

Discussion

The AFE syndrome was first described by Meyer in 1926 (13). AFE is one of the most dangerous, nearly incurable conditions in obstetrics occurring in 1:8000–1:80,000 pregnancies (14) with high rates of mortality. However, it is difficult to estimate overall incidence because nonfatal cases go unreported (10). Earlier studies reported mortality rates of *c.* 86%, while in recent reports, fatal outcome seems to be less frequent (15). Decrease of mortality could be attributed to the rising awareness of physicians and improved diagnostic techniques and therapeutic procedures, but unfortunately, among survivors only 15% are neurologically intact (15). The AFE syndrome primarily occurs in term childbirths or during the early postpartum period. Nevertheless, deaths because of AFE following abortion in the first or second trimester of pregnancy in relation to abdominal trauma and amniocentesis are communicated (8). If AFE occurred before birth, the incidence of fetal death is between 21% and 50% (10).

Pathophysiology of AFE is multifactor and poorly understood (16). Previous theories attributed AFE syndrome to acute obstruction of maternal pulmonary microvascular caused by amniotic fluid and debris of fetal origin. The embolization subsequently leads to transient vasospasm, pulmonary hypertension, right heart failure, and hypoxia. Results published by Clark et al. (15) suggested that exposure of maternal circulation to even a small quantity of amniotic fluid may act as a trigger of sequential events resembling anaphylactic or septic shock resulting in multisystem organ failure characteristic for AFE. This theory relies on autopsy findings in cases of AFE where fetal elements of amniotic origin were present in maternal pulmonary blood vessels in 27% of cases (8,15). Some authors suggest that complement system activation, rather than anaphylaxis plays a role in pathophysiology of the syndrome (17), while others emphasize the importance of meconium that to a great extent triggers the DIC mechanisms (18).

Although little is known about the cause of AFE, several risk factors have been identified so far (19). Strong uterine contractions might increase the risk of AFE, and induction and augmentation of labor have been raised in the past as possible contributing factors (20–23). Other risk factors are cesarean, vacuum, and forceps deliveries, increased maternal age, diabetes, fetal macrosomia, placenta previa or abruption, cervical laceration or uterine rupture (23). Our cases were associated with some risk factors for AFE—increased maternal age (41 and 35 years, Patient No. 1 and Patient No. 2, respectively), diabetes and augmented labor (Patient No. 1), and cesarean delivery (Patient No. 2.). Maternal age of 35 years or older nearly doubled the risk of AFE, as well as medical induction of childbirth (23). Cesarean delivery was associated with a substantial increase in risk for AFE (23).

In Patient No. 2, AFE developed in a twin pregnancy, somehow contradicting the observation made by de Rooij et al. (24), that the occurrence of AFE syndrome is very rare in twin pregnancy supported by a cohort study on slightly more than 3 million deliveries with 33,804 multiple-birth deliveries where only five AFE cases arose, all having nonfatal outcomes (23).

Clinical features of AFE in most cases include cardiovascular collapse ranging from hypotension to cardiac arrest, respiratory distress with pulmonary edema, encephalopathy (usually of hypoxic origin) and, if death does not occur rapidly, disseminated intravascular coagulation and renal failure (6,10). Sometimes rapid onset of dramatic symptoms is preceded by less severe symptoms such as anxiety, fear, cold shivers, nausea, vomiting, and the urge to urinate (6,25). In both cases that we are presenting, the onset of symptoms was abrupt, predominantly related to cardiovascular and respiratory functions, while in Patient No. 2, clear signs of DIC were present as well.

Because of the abrupt onset and progression of symptoms, differential diagnosis of AFE includes uterus rupture, eclampsia, air embolism, placental abruption, myocardial and cerebral vascular accidents, gram negative septic shock, bilateral pneumothorax, and anaphylactic reaction to medicaments (6).

The postmortems were performed in a routine manner because an autopsy on a maternal death does not require extensive modification of good standard technique (26). Autopsy findings in AFE are rarely dramatic. In the cases with rapid fatal outcome, the dilatation of the right heart could be present. Far more frequently, the macroscopic finding includes pulmonary and cerebral edema, congestion of internal organs, and conjunctival, pleural, endocardial, and epicardial suffusions (6). Microscopic findings of fetal elements (squamous cells, meconial mucine, lanugo hairs, and fatty globules) in the pulmonary vascular system are confirmatory for the diagnosis of AFE. They are

usually readily visible on H&E stained sections, although special staining techniques (e.g., Sudan, human keratin) may greatly improve the visibility of certain fetal elements (27,28). The identification of epithelial squamous cells in the pulmonary circulation solely is not confirmatory for the diagnosis of AFE. These cells may not originate from the fetus, but from the deceased woman herself as suggested by Clark et al. (29) who identified squamous cells in the pulmonary arterial circulation not only in pregnant women undergoing pulmonary arterial catheterization but in control specimens from nonpregnant patients presuming bloodstream contamination from sites of venous access. Despite a variety of precautions, it proved impossible to eliminate contamination by exogenous squamous cells contributing to false-positive results in the cytologic diagnosis of AFE (30). In our cases, as well as indicated in similar studies, presence of squamous cells in the pulmonary circulation was massive, indicating their fetal origin (29).

It is necessary to take as many samples as possible from all lung lobes for histological examination (31). A detailed examination of the placenta and the uterus might expose the portal entrance site of the emboli (26). Clinicians recorded no apparent damage to placenta in both cases, whereas placentas were not available to us for further examination. We were not able to demonstrate uterine injuries, although in Patient No. 2, amniotic debris was demonstrated microscopically in dilated uterine venous sinuses.

In Patient No. 1, AFE rapidly led to death, while in the case of Patient No. 2, the surviving period was sufficiently long (*c.* 4 h) for full development of clinical features of DIC that were presented on autopsy as well, both at gross examination and microscopically. We are aiming to raise the awareness of clinicians on possible occurrence of AFE and to emphasize the importance of their prompt reaction in suspected cases. Moreover, as the other authors (32), we are pointing out the significance of postmortem examination in cases of maternal deaths, including the cases of suspected AFE.

Conclusions

Amniotic fluid embolism is an acute obstetrical condition, which, in spite of emergency treatment and support, still has a high mortality rate. Investigation of maternal deaths, including the cases of clinically diagnosed or otherwise suspected AFE, must relay on appropriate postmortem examination. An accurate diagnosis of AFE in maternal death is of particular importance if such death allegedly may be attributable to medical negligence and/or malpractice claims. Clinicopathological correlations in cases of AFE are of benefit both for pathologists and in particular for clinicians to raise their awareness on the possibility of AFE, the necessity of its early diagnosis and prompt therapeutical response, as well as for the exploration of medicolegal aspects of the case.

Conflict of interest: The authors have no relevant conflicts of interest to declare.

Acknowledgment

The authors are acknowledging technical help of Mr. Vasilije Spasojevic in preparation of figures for the manuscript.

References

1. Panting-Kemp A, Geller SE, Nguyen T, Simonson L, Nuwayhid B, Castro L. Maternal deaths in an urban perinatal network, 1992–1998. Am J Obstet Gynecol 2000;183:1207–12.
2. Bødker B, Hvidman L, Weber T, Møller M, Aarre A, Nielsen KM, et al. Maternal deaths in Denmark 2002–2006. Acta Obstet Gynecol Scand 2009;88:556–62.
3. Akar ME, Eyi EG, Yilmaz ES, Yuksel B, Yilmaz Z. Maternal deaths and their causes in Ankara, Turkey, 1982–2001. J Health Popul Nutr 2004;22:420–8.
4. Alexander S, Wildman K, Zhang W, Langer M, Vutuc C, Lindmark G. Maternal health outcomes in Europe. Eur J Obstet Gynecol Reprod Biol 2003;111:S78–87.
5. Schuitemaker N, van Roosmalen J, Dekker G, van Dongen P, van Geijn H, Bennebroek Gravenhorst J. Confidential enquiry into maternal deaths in The Netherlands 1983–1992. Eur J Obstet Gynecol Reprod Biol 1998;79:57–62.
6. Salazar H, Stock JR. Extragenital pathology in obstetrics and gynecology. In: Gompel C, Silverberg GS, editors. Pathology in gynecology and obstetrics. 4th edn. Philadelphia, PA: J.B. Lippincott Company, 1994;622–49.
7. Gist RS, Stafford IP, Leibowitz AB, Beilin Y. Amniotic fluid embolism. Anesth Analg 2009;108:1599–602.
8. DiMaio VJ, DiMaio D. Amniotic fluid embolism. In: DiMaio VJ, DiMaio D, editors. Forensic pathology. 2nd edn. Boca Raton, FL: CRC Press, 2001;459–62.
9. Fletcher S, Parr M. Amniotic fluid embolism: a case report and review. Resuscitation 2000;43:141–6.
10. Moore J, Baldisseri MR. Amniotic fluid embolism. Crit Care Med 2005;33(Suppl. 10):S279–85.
11. Jobba G, Bajnóczky I, Földes V, Kósa F, Szilvásy L, Leinzinger L, et al. Unusual cases of maternal death caused by amniotic fluid embolism. Morphol Igazsagugyi Orv Sz 1977;17:211–6.
12. Sinicina I, Pankratz H, Bise K, Matevossian E. Forensic aspects of postmortem histological detection of amniotic fluid embolism. Int J Legal Med 2009;2010;124:55–62.
13. Meyer J. Embolia pulmonar amnio caseosa. Bras Med 1926;2:301.
14. Aguilera LG, Fernandez C, Plaza A, Gracia J, Gomar C. Fatal amniotic fluid embolism diagnosed histologically. Acta Anaesthesiol Scand 2002;46:334–7.
15. Clark SK, Hankins GDV, Dudly GA, Porter TF. Amniotic fluid embolism: analysis of the national registry. Am J Obstet Gynecol 1995; 172:1158–69.
16. O'Shea A, Eappen S. Amniotic fluid embolism. Int Anesthesiol Clin 2007; 45:17–28.
17. Benson L, Kobayashi H, Silver RK, Oi H, Greenberger PA, Terao T. Immunologic studies in presumed amniotic fluid embolism. Obstet Gynecol 2001;97:510–4.
18. Petroianu GA, Altmannsberger SH, Maleck WH, Assmus HP, Friedberg C, Bergler WF, et al. Meconium and amniotic fluid embolism: effects on coagulation in pregnant mini-pigs. Crit Care Med 1999; 27:348–55.
19. Tramoni G, Boisson C, Gamerre L, Clement HJ, Bon C, Rudigoz RC, et al. Amniotic fluid embolism: a review. Ann Fr Anesth Reanim 2006;25:599–604. Article in French.
20. Geoghegan FJ, O'Driscoll MK, Comerford JB. Amniotic fluid infusion. J Obstet Gynaecol Br Commonw 1964;71:673–80.
21. Gregory MG, Clayton EM. Amniotic fluid embolism. Obstet Gynecol 1973;42:236–44.
22. Weiwen Y, Ningyu A, Lanxiang Z, Yu L. Study of the diagnosis and management of amniotic fluid embolism: 38 cases of analysis. Obstet Gynecol 2000;95:38S.
23. Kramer MS, Rouleau J, Baskett TF, Joseph KS. Maternal health study group of the Canadian Perinatal Surveillance System. Amniotic-fluid embolism and medical induction of labour: a retrospective, population-based cohort study. Lancet 2006;368:1444–8.
24. de Rooij GM, Gelissen HP, Wester JP, Spijkstra JJ, Go AT, Girbes AR. Severe maternal respiratory distress due to the amniotic fluid embolism syndrome in a twin pregnancy. Neth J Med 2003;61(10): 337–40.
25. Attwood HD. Fatal pulmonary embolism by amniotic fluid. J Clin Pathol 1956;9:38–46.
26. Rushton DI, Dawson IM. The maternal autopsy. J Clin Pathol 1982;35:909–21.
27. Garland IW, Thompson WD. Diagnosis of amniotic fluid embolism using an antiserum to human keratin. J Clin Pathol 1983;36:625–7.
28. Balazic J, Rott T, Jancigaj T, Popović M, Zajfert-Slabe M, Svigelj V. Amniotic fluid embolism with involvement of the brain, lungs, adrenal glands, and heart. Int J Legal Med 2003;117:165–9.

29. Clark SL, Pavlova Z, Greenspoon J, Horenstein J, Phelan JP. Squamous cells in the maternal pulmonary circulation. Am J Obstet Gynecol 1986;154:104–6.
30. Giampaolo C, Schneider V, Kowalski BH, Bellaver LA. The cytologic diagnosis of amniotic fluid embolism: a critical reappraisal. Diagn Cytopathol 1987;3:126–8.
31. Karayel F, Arican N, Kavas G, Turan AA, Pakis I. Maternal death due to non-traumatic fat embolism. J Forensic Sci 2005;50:1201–3.
32. Dawson I. The confidential enquiry into maternal death: its role and importance for pathologists. J Clin Pathol 1988;41:820–5.

Additional information and reprint requests:
Djordje Alempijević, Ph.D.
Institute of Forensic Medicine
31a Deligradska Street
Belgrade 11000
Serbia
E-mail: djolea@fon.rs