Use of Recombinant Factor VIIa in Patients with Amniotic Fluid Embolism

To the Editor:

We read with interest the article by Leighton *et al.* describing the use of recombinant factor VIIa (rFVIIa) in women with amniotic fluid embolism.[1] The authors report this as a systematic review. We are concerned, however, that the methods used have limitations that render the results seriously flawed. The authors identified only five cases from the literature using their search strategy, and identified the remaining cases through hemostasis and rFVIIa registries and data sources. They failed, however, to contact any amniotic fluid embolism registries or databases to identify cases treated with rFVIIa. The authors report that the Amniotic Fluid Embolism Register in the United Kingdom collected data on cases between 1997 and 2004,[2] but failed to note that the United Kingdom Obstetric Surveillance System has been prospectively collecting information on cases through active negative surveillance since 2005.[3] We have previously reported a national, population-based series of 60 women with amniotic fluid embolism, who delivered between February 2005 and January 2009, and note in our report[3] that 15 of these women were managed with rFVIIa. These cases would thus more than have doubled the number of cases included in the review, adding significantly to the power and robustness of the analysis. These additional cases have the advantage of being a national, population-based cohort, identified prospectively through active, negative surveillance and thus free from selection bias, unlike case reports from the literature.

In addition, we were not entirely clear why the authors of the review excluded from their comparison cohort women with amniotic fluid embolism who did not receive any surgery to control hemorrhage. This will immediately exclude from the comparison cohort the severest cases of amniotic fluid embolism: women who die very rapidly before there is time for any operative intervention to control hemorrhage. The observed increased risk of death or disability associated with rFVIIa may thus simply reflect this potentially biased selection of the comparison cohort. As we note in our analysis,[3] only one of the 15 women treated with rFVIIa had a surgical intervention to control hemorrhage, further reinforcing our belief that to include only a comparison cohort managed with surgery for hemorrhage is inappropriate.

We believe that the only robust way to advance our management of rare conditions such as amniotic fluid embolism is through prospective, population-based data collection and combined analysis of cases confirmed using an agreed case definition. For this reason, we have established the International Network of Obstetric Survey Systems to facilitate such studies. Data on women with amniotic fluid embolism are being collected prospectively in Australia, Austria, Germany, the Netherlands, New Zealand, and the United Kingdom, and will be used in the future to address this and other management issues in detail.

Marian Knight, D.Phil.,* Kate Fitzpatrick, M.Sc., Jennifer J. Kurinczuk, M.D., Derek Tuffnell, M.B., Ch.B. *University of Oxford, Oxford, United Kingdom. marian.knight@npeu.ox.ac.uk

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In Reply:

The United Kingdom Obstetric Surveillance System (UKOSS) report was published after we had finished collecting data and shortly before we submitted our manuscript to ANESTHESIOLOGY.[1,2] We apologize for the oversight; we certainly would have contacted Knight had we been aware of UKOSS at that time. However, it is unclear how many of the cases in the UKOSS database would have qualified for our review. We employed the traditional definition of amniotic fluid embolism (AFE) used by the United Kingdom AFE register and the United States AFE registry.[3,4] Patients had to have at least one major cardiac and one major pulmonary symptom (or cardiopulmonary arrest) plus consumptive coagulopathy to be diagnosed with AFE. In contrast, UKOSS used a much broader definition of AFE; for example, 38% of the UKOSS AFE patients did not have a coagulopathy.[1] This is not a trivial distinction, for patients who do not meet the traditional definition of AFE seem to have better outcomes after receiving recombinant factor VIIa (rVIIa) than patients who do meet the definition, as seen in these case reports.[5,6] We believe that the broader definition of AFE used by UKOSS permitted the enrollment of patients with similar but different diseases.

We also used a different measure of successful therapy than that used by UKOSS.[1] UKOSS reported the number of patients who died after receiving rVIIa, but not the number with new permanent disability. Our primary outcome was

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intact survival *versus* a negative outcome (new permanent disability or death).[2] We don't consider surviving in a coma or with a stroke to be a successful outcome.

All of our AFE patients who received rVIIa also had surgery to control hemorrhage. We therefore chose AFE patients who had surgery to control hemorrhage but did not receive rVIIa as our comparison cohort. Patients who die very rapidly of AFE generally expire before surgical intervention or rVIIa treatment can be given.

We agree that identifying cases through a prospective, population-based reporting mechanism such as UKOSS is an excellent way to identify the incidence of complications. However, we are seriously concerned that the broad definition of AFE, including patients without coagulopathy, and the lack of information on morbidity weaken the ability of UKOSS to assess rVIIa complications in AFE patients.

Patients with AFE have high circulating levels of tissue factor, which is why rVIIa treatment is particularly risky both in theory and in practice.[2] We urge UKOSS and the rest of the obstetric community to explore the use of potentially safer hemostatic alternatives, such as fibrinogen concentrate and tranexamic acid, rather than prematurely embracing rVIIa, the agent with the greatest potential for thrombotic complications.

Barbara L. Leighton, M.D.,* Michael H. Wall, M.D., F.C.C.M., Ellen M. Lockhart, M.D., Louise E. Phillips, B.Sc., M.P.H., Ph.D., Amanda J. Zatta, B.Sc., Ph.D.
*Washington University in St. Louis School of Medicine, St. Louis, Missouri. leightob@wustl.edu

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Flow Chart for Amniotic Fluid Embolism Management: A Tricky Tool

To the Editor:

We read with interest the educational case scenario of amniotic fluid embolism (AFE) by Dean *et al.*[1] The authors propose a flow chart for clinical management of AFE. However, we believe that the authors' diagram may depict an oversimplified approach for acquired coagulopathy during the course of AFE.

Although coagulopathic bleeding is not absolutely necessary for the diagnosis of AFE, it is still a prominent feature and one of the most challenging complications for which appropriate early intervention is crucial. The event of AFE introduces both procoagulant and anticoagulant factors into the maternal bloodstream, and ensuing imbalance of coagulation can evolve into disseminated intravascular coagulation. Alternatively, coagulopathy can result from the dilution of procoagulant factors after aggressive fluid resuscitation. The exact mechanism of bleeding during AFE remains unclear and is likely multifactorial, but hypofibrinogenemia is frequently reported.[2,3] Delayed fibrinogen replacement can impair hemostasis and increase morbidity and mortality from inadequate clot formation, ongoing hemorrhage, acidosis, and hypothermia.

Cryoprecipitate is mentioned in the case scenario, although the use of fibrinogen-rich products, such as cryoprecipitate or fibrinogen concentrate, is not mentioned in the flow chart or emphasized in the discussion section. The flow chart proposed by Dean *et al.* suggests considering hysterectomy, recombinant factor VIIa, or uterine artery embolization for persistent uterine hemorrhage, and discontinuation of resuscitation if these efforts do not achieve hemostasis. Early fibrinogen replacement should be emphasized, and the use of recombinant factor VIIa discouraged except for cases of hemorrhage refractory to massive component transfusion. We urge caution on the use of recombinant factor VIIa when AFE is suspected, as a recent analysis of such cases revealed that the use of recombinant factor VIIa was associated with significantly increased major organ thrombosis and death.[3]

The Food and Drug Administration approved fibrinogen concentrate (RiaSTAP) for treatment of congenital hypofibrinogenemia in 2009, and its successful use has been reported in the management of disseminated intravascular coagulation related to both AFE[2,3] and postpartum hemorrhage.[4] In contrast to cryoprecipitate, which takes 30–60 min to thaw before use, fibrinogen concentrate can be reconstituted and administered rapidly. Stocked at room temperature in lyophilized form, fibrinogen concentrate is a viable option even in remote locations. Moreover, it requires much less volume infused to restore adequate fibrinogen for clot integrity than cryoprecipitate or fresh frozen plasma.[5]

Although there may be no flow chart that perfectly captures every potential decision point, we believe that careful coagulopathy control plays a major role in survival after AFE, and deserves more emphasis. We suggest expansion of the flow chart with greater attention on coagulopathy management. Clearly defined transfusion guidelines can be integrated with institution-specific transfusion protocols, and along with staff education, may improve AFE-related hemorrhage management.[6] Amendments to the existing flow