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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