Published in final edited form as:

JAMA Neurol. 2015 September ; 72(9): 973–974. doi:10.1001/jamaneurol.2015.1356.

Risks of Epilepsy During Pregnancy:

How Much Do We Really Know?

Jacqueline A. French, MD and **Kimford Meador, MD**

Department of Neurology, Comprehensive Epilepsy Center, Langone School of Medicine, New York University, New York (French); Department of Neurology and Neurological Sciences, Stanford Comprehensive Epilepsy Center, Stanford University School of Medicine, Palo Alto, California (Meador).

Epilepsy is a common disease that affects 1 in 26 individuals in their lifetime.[1] According to a National Institute of Neurological Disorders and Stroke assessment, with 2 million affected individuals, epilepsy ranks only fourth to migraine, stroke, and Alzheimer disease in the prevalence of neurological disorders. Epilepsy affects more people than autism, amyotrophic lateral sclerosis, cerebral palsy, multiple sclerosis, and Parkinson disease combined.[2]Approximately 0.3%to0.5% of all pregnancies are among women with epilepsy (WWE).[3] The risks during pregnancy in WWE have been uncertain.[4]

The MacDonald et al article[5] in this issue of *JAMA Neurology* highlights that childbearing may confer additional risk in WWE. The authors found increased rates of maternal complications, such as preeclampsia, antepartum hemorrhage, postpartum hemorrhage, preterm labor, cesarean delivery, and death.

The risk of death associated with epilepsy has been emphasized. Thurman and colleagues[6] noted that considering the mortality from sudden unexplained death in epilepsy (SUDEP) alone, life years lost to epilepsy ranked only second to stroke among all neurologic conditions. MacDonald and colleagues[5] found a 10-foldriskofmortalityinWWEduringtheprocessofdeliverycompared with the general population. One death during delivery puts 2 lives at risk. Other epidemiology studies have suggested that WWE represent a high-risk group during pregnancy. Several studies have reported the "Confidential Enquiry Into Maternal Deaths in the United Kingdom," and the most recent report from 2014 highlighted epilepsy as an important cause.[7] The MacDonald et al study[5] is unique because it focuses on the period surrounding delivery and highlights the risks associated with that time frame.

The MacDonald et al study[5] should sound a major alarm among physicians and researchers. The maternal death rate of 80 of 100 000 translates to almost 1 of 1000 WWE facing death during delivery hospitalization. If the authors' findings of increased risk for preeclampsia, antepartum hemorrhage, post-partum hemorrhage, preterm labor, and cesarean delivery are

Corresponding Author: Jacqueline A. French, MD, Comprehensive Epilepsy Center, Langone School of Medicine, New York University, 223 E 34th St, New York, NY 10016 (jacqueline.french@nyumc.org).

related to the increased maternal death rate, it might be assumed that many more women are experiencing near death or serious harm.

Unfortunately, the nature of the analysis, which sampled a large number of hospital medical records and identified WWE through *International Classification of Diseases, Ninth Revision* coding (codes 345.0x-345.5x, 345.7x-, 345 .9x, and 649.4x) leaves a lot of questions unanswered. Women with these diagnostic codes were compared with a large sample of women without these codes. The data presented are convincing but lack the detail to answer the most compelling questions that the results raise. Namely, who is at risk and why did the women die? The data suggest that there are some differences between WWE and women without epilepsy. For example, WWE were more likely to have long-term conditions, such as hypertension, diabetes mellitus, alcohol and substance abuse, and psychiatric conditions. Some of these differences were striking (9.1% of WWE vs 1.7% of women without epilepsy had psychiatric disorders). Could the elevated death rates and comorbid epilepsy both have occurred as a consequence of these other conditions? An article by Fazeletal[8] suggests that most increased mortality signals in epilepsy associated with external causes derive from the subgroup with psychiatric comorbidities and substance abuse. MacDonald et al[5] provided data on the differences between the 2 populations but did not provide information on whether the mortality was greater among WWE who also had comorbid conditions. There are other unanswered questions. Was mortality related to the use of antiepileptic drugs? Previous population-based studies have suggested that only women taking these medications are at greater risk of morbidity.[8] There are changes in pharmacokinetics during pregnancy for some antiepileptic drugs that can result in marked changes in antiepileptic drug blood levels if doses are not adjusted. Could this have contributed to seizures and death in the MacDonald et al article?[5] What about women whose epilepsy was well controlled vs women who were having breakthrough seizures? Was the type or cause of epilepsy important? These are critical questions, and, without the answers, we are left in the unsatisfying position of having to advise all WWE that they may be at higher risk. The inability to stratify risk, and therefore considering all WWE as high risk, might lead to unnecessary health care costs, as the authors suggest that their findings should lead to triage of all WWE to high-risk obstetric centers.

Why did WWE die at a higher rate in the MacDonald et al study?[5] The authors suggest a number of possibilities, ranging from obstetrical complications, complications resulting from seizures (aspiration or status epilepticus), and a high rate of SUDEP. A recent study[7] suggests that SUDEP deaths may play a large role in mortality of women during pregnancy. In the United Kingdom, all maternal deaths and the circumstances surrounding them must be reported to the Centre for Maternal and Child Enquiries. In the most recent analysis of these accounts covering 2009 to 2012, 14 deaths were reported among WWE (either during pregnancy or within 42 days following).[7] This represented 4% of all pregnancy deaths. Sudden unexplained death in epilepsy was responsible for 12 of the 14 deaths. The 2 other deaths were owing to drowning. These results are not directly comparable with the current study because deaths were included if they occurred at any time during the pregnancy or 42 days after compared with the MacDonald et al study,[5] which only addressed deaths during the delivery hospitalization. However, the absence of any deaths owing to delivery or obstetric complications is striking. In the same dataset from 2006 to 2008, at least 13of the

14deaths were also directly related to seizure (SUDEP, drowning, or chest trauma owing to seizure).[9] The absence of data on the causes of death in the MacDonald et al study[5] is unfortunate because these results, if known, could lead to different courses of action. If the deaths are indeed owing to obstetrical complications, the referral of women to high-risk obstetrical centers would be crucial. On the other hand, if the deaths were owing to SUDEP or seizure complications, ensuring optimized medication management would be critical. The conclusions from the British study[7] focused on preconception counseling. Edey and colleagues[9] had a particular concern for women receiving lamotrigine during pregnancy. There were 9 such women among the 14 deaths, which could reflect the preferential use of lamotrigine among WWE. However, there has also been an increasing concern that serious breakthrough seizures may be more likely among women receiving lamotrigine owing to a marked increase of clearance of the drug during pregnancy.[10]

The MacDonald et al study[5] provides important new information and demonstrates several risks associated with pregnancy in WWE. However, it raises far more questions than it answers. Most WWE have uncomplicated pregnancies. We need to understand the mechanisms underlying these risks, including death, so that we can identify the specific population at risk and devise interventions to reduce these risks. Future studies need to confirm and build on the present findings to improve the care of WWE during pregnancy.

Acknowledgments

Conflict of Interest Disclosures: Dr French has received research support from the National Institutes of Health, the Epilepsy Therapy Project, the Epilepsy Research Foundation, the Epilepsy Study Consortium, LCGH, Eisai Inc, Lundbeck, Pfizer, SK Life Science Inc, UCB, Upsher-Smith Laboratories, and Vertex Pharmaceuticals. The Epilepsy Study Consortium pays Dr French's employer for her research consultant time related to Acorda Therapeutics Inc, Anavex Life Sciences, Biotie Therapies, Brabant Pharma, BioPharm Solutions Inc, Eisai Inc, GlaxoSmithKline, GW Pharmaceuticals, Impax Laboratories, Johnson & Johnson, Marathon Pharmaceuticals LLC, Marinus Pharmaceuticals Inc, Neusentis, Novartis, Pfizer, SAGE Therapeutics, Sunovion Pharmaceuticals Inc, SK Life Science Inc, Supernus Pharmaceuticals, Takeda Pharmaceutical Company, UCB, Upsher-Smith Laboratories, Ultragenyx Pharmaceutical Inc, Vertex Pharmaceuticals, Zogenix Inc, and Zynerba Pharmaceuticals. Dr Meador has received research support from the National Institutes of Health, the Patient-Centered Outcomes Research Institute, and UCB and travel support from UCB. The Epilepsy Study Consortium pays Dr Meador's employer for his research consultant time related to Eisai Inc, GW Pharmaceuticals, NeuroPace Inc, Novartis, Supernus Pharmaceuticals, Upsher-Smith Laboratories, UCB, and Vivus Pharmaceuticals.

REFERENCES

1. Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies; England MJ, Liverman CT, Schultz AM, Strawbridge LM. Epilepsy Across the Spectrum: Promoting Health and Understanding. Washington, DC: National Academies Press; 2012.
2. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders? Neurology. 2007; 68(5):326–337. [PubMed: 17261678]
3. Levy RH, Yerby MS. Effects of pregnancy on antiepileptic drug utilization. Epilepsia. 1985;26 (suppl 1):S52–S57. [PubMed: 3922750]
4. Harden CL, Hopp J, Ting TY, et al.; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy—focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73(2):126–132. [PubMed: 19398682]

5. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States [published online July 6, 2015] JAMA Neurol. doi:10.1001/jamaneurol.2015.1017.

6. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. Epilepsia. 2014;55(10):1479–1485. [PubMed: 24903551]

7. Knight M, Kenyon S, Brocklehurst P, Neilson J, Shakespeare J, Kurinczuk JJ; MBRRACE-UK. Saving Lives, Improving Mothers' Care—Lessons Learned to Inform Future Maternity Care From the UK and Ireland Confidential Enquiries Into Maternal Deaths and Morbidity 2009–12. Oxford, England: National Perinatal Epidemiology Unit, University of Oxford; 2014.

8. Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet. 2013;382(9905): 1646–1654. [PubMed: 23883699]

9. Edey S, Moran N, Nashef L. SUDEP and epilepsy-related mortality in pregnancy. Epilepsia. 2014;55(7):e72–e74. [PubMed: 24754364]

10. Battino D, Tomson T, Bonizzoni E, et al.; EURAP Study Group. Seizure control and treatment changes in pregnancy: observations from the EURAP epilepsy pregnancy registry. Epilepsia. 2013; 54(9):1621–1627. [PubMed: 23848605]