Fetal loss and malformations in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) study of pregnant women with epilepsy

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Pregnancy registries established in the 1990's have advanced our knowledge of antiepileptic drug (AED) teratogenicity. Some AEDs (such as Valproate) have higher risk than others. However, many AEDs require further study of their teratogenicity. As such, the objective of this study was to examine the occurrence of severe adverse fetal outcomes (SAOs), including fetal loss and major congenital malformations (MCMs), as well as other maternal and child outcomes in pregnant women with epilepsy (PWWE) versus healthy pregnant women (HPW).

Experimental design and statistics: The MONEAD study was a prospective, observational, multicenter investigation of pregnancy outcomes for both mother and child; it was a continuation of the original NEAD study, which primarily assessed SAOs associated AEDs in PWWE. The MONEAD study recruited women from December 2012 to January 2016. Inclusion criteria for PWWE were ages 14-45 years and less than 20 weeks of gestational age. Exclusion criteria included an IQ <70 and a history of PNES, progressive cerebral disease, other major medical illness, or changes in AEDs during pregnancy prior to enrollment. All PWWE, regardless of AED regimen (mono or polytherapy) were recruited, and MONEAD additionally recruited 2 control groups: 1) non-pregnant women w/epilepsy (NPWWE) and 2) healthy pregnant women (HPW). The sample sizes for MONEAD were powered to assess for the primary outcomes of seizures, obstetric complications, depression, and neurodevelopmental outcomes. The major primary outcome was the occurrence of overall SAOs in offspring of PWWE vs. HPW. Secondary outcomes included spontaneous fetal losses and MCMs; periconceptional folate dosage was also assessed, as was total AED dose. Statistically, odds ratios and Fischer exact tests for SAOs and MCMs were used to compare primary outcomes in PWWE vs. HPW.

Results: Demographics for HPW and PWWE are included in Table 1. In general, most PWWE had focal epilepsy (62%) and were on AED monotherapy (74%) with either Lamotrigine (41%) or Levetiracetam (37.5%). **In terms of the primary outcome, overall SAOs occurred at a higher rate in PWWE vs. HPW (7.9% vs 1.9%, OR: 4.45, *p*=0.025),** however, there were no significant group differences for fetal losses alone (2.8% vs 0%, *p*=0.126) or for MCMs alone (5.2% vs 1.9%, *p*=0.185). Further, these outcomes were not affected by periconceptional folate use, the occurrence of unplanned/unwanted pregnancies, prior maternal pregnancy history, or AED type/AED levels (Tables 2-3). Of note, the risk of fetal loss did appear to be related to AED blood levels: each unit increase in the % therapeutic range AED blood level was associated with an increase in the odds of fetal death by a factor of 6 (95% CI: 1.23-29.23, Tables 4-6). However, after adjusting for AED category (poly or monotherapy), the effect was no longer significant; rather, AED polytherapy seems to increase the risk of fetal loss more substantially. Finally, maternal or paternal family history of MCM was associated with a slight increase in SAOs (*p*=0.046). As noted, most PWWE in this study were on Lamotrigine, Levetiracetam, or both, and Table 3 lists the specific malformations associated with each AED. With Lamictal, aortic coarctation, cryptorchidism, hydronephrosis, morning glory syndrome, and pectus excavatum were observed; with Levetiracetam, atrial septal defects, buried penis syndrome, cryptorchidism, hypoplastic aortic valve, and ventricular septal defects were observed.

Conclusions and Discussion: Overall, this study showed that the risk of combined SAO in PWWE is elevated compared to HPW, though a large majority of pregnancies in PWWE do not have SAOs and are normal. Regarding the lack of significant differences in MCMs between PWWE and HPW- the sample

size likely limited statistical power. Additionally, while the rate of MCMs in PWWE not taking AEDs was similar to those taking AEDs, other, larger studies have reported lower risks for PWWE not taking AEDs. (Weston, 2016). Similarly, the lack of effect of AED levels on MCMs was likely related to small sample size, as AED dose-dependent effects on MCMs have been reported in larger studies (Tomson, 2011). Regarding the differences in blood level of AEDs with fetal loss, after adjusting for AED monotherapy or polytherapy, the association was no longer significant, suggesting that the increase in risk is related to polytherapy. The authors note that this may be reflective of a direct effect of multiple AEDs or indirectly related to possible genetic differences in PWWE on AED polytherapy. Finally, while folate did not impact SAOs in this study, it should be noted that other studies have shown that folate improves neurodevelopmental outcomes in women taking AEDs. Strengths of this study include the prospective design and detailed observational data collection, while limitations include the lack of randomization (for ethical reasons) and the small sample size.

Summary created by Jake Carolan, MD

Additional Reading, if interested:

Meador KJ, et al. In utero antiepileptic drug exposure: fetal death and malformations. Neurology 2006; 67:407–412.

Other Studies Cited:

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Thomas SV, Jose M, Divakaran S, Sankara Sarma P. Malformation risk of antiepileptic drug exposure during pregnancy in women with epilepsy: results from a pregnancy registry in South India. Epilepsia 2017;58:274–281.

Ban L, Fleming KM, Doyle P, et al. Congenital anomalies in children of mothers taking antiepileptic drugs with and without periconceptional high dose folic acid use: a population-based cohort study. PLoS One 2015;10:e0131130.

Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12:244–252.

Husebye ESN, Gilhus NE, Riedel B, Spigset O, Daltveit AK, Bjørk MH. Verbal abilities in children of mothers with epilepsy: association to maternal folate status. Neurology 2018;91:e811–e821.

Bjørk M, Riedel B, Spigset O, et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. JAMA Neurol 2018;75:160–168.