

IN UTERO EFFECTS OF AEDS

Long-term Health and Neurodevelopment in Children Exposed to Antiepileptic Drugs Before Birth

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OBJECTIVE: To investigate the frequency of neonatal and later childhood morbidity in children exposed to antiepileptic drugs in utero.

DESIGN: Retrospective population-based study.

SETTING: Population of the Grampian region of Scotland.

PARTICIPANTS: Mothers taking antiepileptic drugs in pregnancy between 1976 and 2000 were ascertained from hospital obstetric records, and 149 (58% of those eligible) took part. They had 293 children whose health and neurodevelopment were assessed. Main outcome measures: Frequencies of neonatal withdrawal, congenital malformations, childhood-onset medical problems, developmental delay, and behaviour disorders.

RESULTS: Neonatal withdrawal was seen in 20% of those exposed to antiepileptic drugs (AEDs). Congenital malformations occurred in 14% of exposed pregnancies, compared with 5% of nonexposed sibs, and developmental delay in 24% of exposed children, compared with 11% of nonexposed sibs. After excluding cases with a family history of developmental delay, 19% of exposed children and 3% of nonexposed sibs had developmental delay, 31% of exposed children had either major malformations or developmental delay, 52% of exposed children had facial dysmorphism compared with 25% of those not exposed, 31% of exposed children had childhood medical problems (13% of nonexposed sibs), and 20% had behaviour disorders (5% of nonexposed).

CONCLUSION: Prenatal AED exposure in the setting of maternal epilepsy is associated with developmental delay and later childhood morbidity in addition to congenital malformation.

COMMENTARY

Dean et al. investigated long-term outcomes in the births from 1976 through 2000 at a referral hospital in Scotland. They found 411 mothers who were taking antiepileptic drugs (AEDs) during pregnancy. Of these, 37% had moved or could not be contacted, and 27% refused participation. The remaining 149 (36%) mothers agreed to participate, yielding 261 pregnancies exposed to AEDs and 38 siblings not exposed to AEDs. Most of the mothers had epilepsy (97%), and most were receiving monotherapy (80%). In the assessed pregnancies, congenital malformations were present in 14% of AED-exposed versus 5% of nonexposed siblings. After accounting for family history, 19% of AED exposed versus 3% of nonexposed siblings exhibited developmental delay. Overall, 31% of AED-exposed children had major malformation or developmental delay. The risk was highest in the group receiving polytherapy.

The findings of Dean et al. confirm the increased risk of congenital malformations in children with in utero AED exposure, especially if receiving polytherapy. Their study also suggests that AEDs play a role in the increased risk of developmental delay seen in children of women with epilepsy. Weaknesses in the study include retrospective review for pregnancies prior to 1997, the low follow-up rate, the small control group, and disparity in age at follow-up. Critical questions remain unanswered. What are the differential risks across AEDs? Does folic acid reduce the risks associated with AED exposure? Can genetic risks be identified and used in patient management? What is the frequency and severity of cognitive and behavioral problems? Are there predictive factors for AED-associated developmental delay, and are certain AEDs more likely to cause it?

Women with epilepsy should understand that there is a two- to threefold increased risk of major malformations; however, the message should be balanced so that they understand that the large majority of children born to them are normal. Further, it is important that they understand the risks of seizures during pregnancy, which are substantially greater than those of AEDs for many women with epilepsy. They should know that there is a possibility of intellectual or behavioral difficulties in their children. Folate supplementation should be given before conception (1–4 mg/day) and continued during pregnancy. Pregnancies with AED exposure should be considered as having increased risk. High-grade ultrasonography and α -fetoprotein



screen should be conducted. AED pharmacokinetics are altered during pregnancy, so monitoring of free levels may be needed. Because several AEDs can interfere with vitamin K and increase the risk of perinatal hemorrhage, vitamin K should be given to the infant at birth (1 mg, i.m.) and probably to the mother during the last month of pregnancy (10 mg, p.o., per day).

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