Using the Norwegian Mother and Child Cohort Study to determine risk factors for delayed development and neuropsychiatric symptoms in the offspring of parents with epilepsy

Marte Helene Bjørk[1,2], Gyri Veiby[1,2], Olav Spigset[3] and Nils Erik Gilhus[1,2]

1) Department of Clinical Medicine, University of Bergen, Bergen, Norway
2) Department of Neurology, Haukeland University Hospital, Bergen, Norway
3) Department of Clinical Pharmacology, St. Olav University Hospital and Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

Correspondence: Marte Bjørk, Department of Neurology, Haukeland University Hospital, Jonas Lies vei 65, N-5021 Bergen, Norway
E-mail: mebk@helse-bergen.no; marte.bjork@gmail.com; Marte.Bjork@k1.uib.no Telephone: +4796976755

ABSTRACT

Introduction: Antiepileptic drug (AED) teratogenicity is suspected to be the main cause of impaired development in children of women with epilepsy. However, many factors may confound the reported risks. The purpose of this review is to characterize the epilepsy cohort in the Norwegian Mother and Child Cohort Study (MoBa) and show how it can be used to detangle various risk factors for adverse outcome in children of mothers with epilepsy.

Methods: MoBa is a large, long-term prospective, family-based cohort study. The database is linked to the Medical Birth Registry of Norway. The epilepsy cohort consists of mothers and their children representing more than 700 pregnancies. Blood samples were obtained from the mother during pregnancy and from the umbilical cord after delivery, and AED concentrations were measured. Validated screening tools determined the frequency of maternal confounding risk factors and adverse offspring outcomes. Risk estimates were reported as adjusted odds ratios with confidence intervals using the remaining MoBa cohort as a reference (n=107,597). Outcome in offspring of women with epilepsy without AED treatment in pregnancy and of fathers with epilepsy were used to separate the effect of epilepsy from the effect of *in utero* exposure to AEDs.

Results: Socioeconomic and psychiatric risk factors for adverse offspring outcomes were more frequent in mothers with epilepsy. The frequency of adverse offspring outcome was increased at 6, 18 and 36 months for verbal, motor and social development. Children of women with epilepsy without AED treatment and of fathers with epilepsy were generally similar to children of women without epilepsy.

Conclusion: Children of mothers with epilepsy are at risk of adverse outcomes. AED exposure emerges as the most important risk factor.

INTRODUCTION

Women with epilepsy account for 0.8% of all deliveries in Norway, and 0.3-0.5% of newborns have been exposed to antiepileptic drugs (AEDs) *in utero* (1). Although AED exposure increases the malformation risk (2,3), women with epilepsy are usually encouraged to continue their medication during pregnancy since severe epileptic seizures may cause fetal hypoxia and death, and also be harmful to the mother. Reportedly, 5% of maternal deaths during pregnancy are caused by epilepsy (4).

Recently, a possible association between fetal AED exposure and cognitive deficits and behavioral disorders has emerged (5). In utero AED exposure has been linked to lower IQ, delayed motor, verbal and social development, and neuropsychiatric disease such as autistic disorders and attention deficit hyperactive disorder (ADHD) (6-8). However, three major methodological challenges render the interpretation of these findings difficult. First, subjects with epilepsy may differ from the reference population socioeconomically and genetically. Second, the impact of epileptic seizures in pregnancy on the developing child is uncertain (9). Third, the relationship between the degree of AED exposure and the risk of adverse outcome is not well known. In most studies where maternal pre-pregnancy AED doses have been included, a dose-effect relationship has been demonstrated (6,10). However, due to pharmacokinetic variability, AED blood levels in the mother and fetus are not closely correlated to the reported dose (11-13). Hence, the degree of fetal AED exposure is unpredictable, even when dose information is available.

The Norwegian Mother and Child Cohort Study (MoBa) is well suited to target these three challenges. Prospective registration of a multitude of possible risk factors for adverse outcomes in the child has been included. Through validated screening tools (14-16), the woman is evaluated for psychiatric disorders. Hence, it

Figure 1. Adjusted odds ratio with 95% confidence interval (log scale) for adverse development in children of parents with epilepsy compared to the reference group. SCQ: Social Communication Questionnaire (previously Autism Screening Questionnaire). * P value < 0.05. ** P value < 0.01. Reprinted with kind permission from Epilepsia. Copyright John Wiley and Sons 2013.

anxiety was also increased late in pregnancy, in the postpartum period as well as 18 and 36 months after delivery for mothers with epilepsy using AEDs compared to women without epilepsy. No specific AED type was found to protect against peripartum depression. High seizure frequency and previous anxiety and/or depression were the strongest risk factors (23). Women with epilepsy had a higher life-time prevalence of eating disorders, and more often had binge eating disorder during pregnancy than women without epilepsy (21,22).

Adverse offspring outcomes

At 6 months of age, children of mothers reporting AED use during pregnancy (n=223) had a higher risk of impaired fine motor skills compared to the reference group (n=77,770) (OR 2.1, 95% CI 1.3–3.2 when adjusted for maternal age, education, folate supplement, smoking, breastfeeding and child malformation) (45). The risk was similar for monotherapy with lamotrigine, valproate, or carbamazepine. Children of mothers reporting use of multiple AEDs had the highest risk. In this group, 25% had impaired fine motor skills and 23% had impaired social skills, in contrast to 4.8% and 10%, respectively, in the reference group ($p<0.05$ after adjustment). Continuous breastfeeding during the first 6 months after delivery was associated with a tendency towards improved outcome for all the developmental domains, regardless of maternal AED treatment (45).

At 18 months of age, children of mothers reporting AED use (n=184) had increased risk of autistic features (adjusted OR 2.7, 95% CI 1.1–6.7), impaired fine motor skills (adjusted OR 1.8, 95% CI 1.0–3.4), gross motor skills (adjusted OR 2.0, 95% CI 1.1–3.7) and social skills (adjusted OR 2.2, 95% CI 1.3-3.6, Table 4) compared to the reference group (n=60, 583) (46). At 36 months of age, these children (n=139) had a higher frequency of abnormal gross motor skills (adjusted OR 2.2, 95% CI 1.1–4.2), poor sentence skills (adjusted OR 2.1, 95% CI 1.2–3.6), and autistic traits (adjusted OR 3.4, 95% CI 1.6–7.0, Figure 1) than the reference group (n=43,571). The frequency of ADHD symptoms was similar between groups, but more aggressive behavior was seen in children of mothers reporting AED use (adjusted OR 1.8, 95% CI 1.0–3.4) (46). Compared to the reference group, risk estimates (confidence intervals) for all individual AED types were overlapping at 18 and 36 months, hence the individual AEDs were not different from each other. Children of fathers with epilepsy had a higher risk of

Table 4 Risk for adverse development score at 18 months in children of parents with epilepsy [1] compared to a reference group of children of parents without epilepsy

		MATERNAL EPILEPSY : Antiepileptic drug exposure in utero [2]							PATERNAL EPILEPSY [2]	
ADVERSE SCORE	**Reference**	**All exposures**	**Monotherapy**	**Lamotrigine**	**Valproate**	**Carbamazepine**	**Polytherapy**	**Unexposed**	**No treatment [4]**	**Treatment [4]**
Age 18 months	n = 60,583	n = 184	n = 158	n = 65	n = 25	n = 41	n = 26	n = 221	n = 216	n = 147
Gross motor skills [5]	**2.9 %**	* **7.1 %** (13)	**5.7 %** (9)	**7.8 %** (5)	* **16.0 %** (4)	**0.0 %** (0)	* **15.4 %** (4)	**3.2 %** (7)	**3.7 %** (8)	**4.1 %** (6)
OR (95 % CI) [3]		2.0 (1.1-3.7)	1.6 (0.8-3.4)	1.7 (0.6-5.1)	7.0 (2.4-21.0)	NA	4.1 (1.3-13.3)	1.2 (0.6-2.6)	1.3 (0.7-2.7)	1.6 (0.7-3.6)
Fine motor skills [5]	**3.1 %**	* **6.1 %** (11)	**4.5 %** (7)	**3.1 %** (2)	**4.0 %** (1)	* **10.0 %** (4)	* **15.4 %** (4)	**5.1 %** (11)	* **5.6 %** (12)	**3.5 %** (5)
OR (95 % CI) [3]		1.8 (1.0-3.4)	1.4 (0.7-3.0)	0.9 (0.2-3.7)	1.3 (0.2-9.7)	3.3 (1.1-9.2)	4.3 (1.4-13.0)	1.7 (0.9-3.1)	1.9 (1.0-3.4)	1.0 (0.4-2.6)
Personal-Social skills [5]	**4.2 %**	* **9.4 %** (17)	**6.5 %** (10)	**3.1 %** (2)	**0.0 %** (0)	***12.2 %** (5)	* **26.9 %** (7)	**3.7 %** (8)	**5.6 %** (12)	* **10.3 %** (15)
OR (95 % CI) [3]		2.2 (1.3-3.6)	1.5 (0.8-2.9)	0.6 (0,2-2.7)	NA	3.2 (1.3-8.3)	7.1 (2.9-17.8)	0.9 (0.4-1.8)	1.4 (0,8-2.5)	2.3 (1.3-4.1)
Autism checklist [6]	**7.8 %**	* **14.0 %** (24)	**10.9 %** (16)	**15.6 %** (10)	**8.3 %** (2)	**8.8 %** (3)	* **33.3 %** (8)	**10.0 %** (20)	**11.1 %** (24)	**11.0 %** (16)
OR (95 % CI) [3]		1.7 (1.1-2.6)	1.3 (0.7-2.2)	1.8 (0.9-3.8)	1.0 (0.2-4.5)	1.1 (0.3-3.6)	4.5 (1.8-11.1)	1.3 (0.8-2.0)	1.4 (0.9-2.2)	1.6 (1.0-2.7)
Autistic traits [6]	**0.9 %**	* **3.5 %** (6)	**2.0 %** (3)	**3.1 %** (2)	**0.0 %** (0)	**2.9 %** (1)	* **12.5 %** (3)	**0.5 %** (1)	**1.4 %** (3)	* **2.8 %** (4)
OR (95 % CI) [3]		2.7 (1.1-6.7)	1.4 (0.3-5.6)	1.5 (0.2-11.0)	NA	3.3 (0.5-24.8)	8.3 (2.3-30.0)	0.5 (0.1-3.7)	1.6 (0.5-5.0)	3.7 (1.4-10.1)

[1] Each cell contains the percentage (No.) of adverse outcomes within groups and corresponding odds ratio (OR) with 95 % CI
[2] Numbers may not equal 100 % within groups due to variation of missing values. NA = Not applicable. * *P* value < 0.05
[3] ORs are adjusted for maternal age, parity, education, smoking, anxiety/depression, periconceptional folate use, and child low birth weight and malformation
[4] Antiepileptic drug use by father within 6 months prior to conception
[5] The Ages and Stages questionnaire
[6] Assessable for 92 % of the 18 months' cohort. Autism checklist: Modified Checklist for Autism in Toddlers (MCHAT). Autistic traits: Early Screening of Autistic Traits (ESAT)

abnormal social skills (adjusted OR 2.3, 95% CI 1.3–4.1) and autistic traits (adjusted OR 3.7, 95% CI 1.4–10.1) at 18 months of age compared to children of fathers without epilepsy, but this finding was not reproduced at 36 months of age (Figure 1).

Children of women with epilepsy who did not report use AEDs had normal development at all assessment points (Figure 1).

DISCUSSION

The MoBa epilepsy cohort

The validity of self-reported epilepsy diagnosis and AED use was very good. Consequently, information on maternal disease and medication use during pregnancy registered in the MoBa database and the MBRN appears to be highly reliable. These results are of importance for researchers investigating other disorders in the MoBa cohort, as the reliability might also apply for similar, chronic conditions, such as multiple sclerosis. As expected, AED plasma concentrations showed a low correlation to AED dose, which can be attributed to intraindividual variability in drug metabolism and considerable changes in pharmacokinetics during pregnancy (11,12). Differences in drug-adherence and recall bias may also play a role. The results indicate that plasma concentrations are a more reliable measure for AED exposure than dose. In previous studies, dose at the start of pregnancy has usually been used as a measure for degree of AED exposure (6,7,10).

The MoBa epilepsy cohort was representative for women with epilepsy in general. The self-reported epilepsy characteristics were similar to the cohort of Norwegian women included in the European and International Registry of Antiepileptic Drugs in Pregnancy (EURAP) database. The proportion of women with self-reported localization-related epilepsy in our cohort was 53% in the hospital records. The corresponding proportion in EURAP was 46% (50). However, the proportion of women with juvenile myoclonic epilepsy (22% in the self-reported group, 15% in hospital records) was larger than the 5-10% normally seen in non-pregnant epilepsy populations. (51). This overrepresentation probably reflects that the MoBa cohort mainly consists of young (between 19 and 41 years) and female participants, as there is a female preponderance in juvenile myoclonic epilepsy (51). Fewer women had seizures during pregnancy according to our studies (17% in the self-reported group, 15% in hospital records) than among the Norwegian women in EURAP (37%) (50). However, the women in EURAP were recruited from neurological departments and a tertiary epilepsy center; hence the patients probably had more severe epilepsy compared to those in the population based MoBa cohort. However, the proportion of women having seizures during birth was similar between our data and the EURAP data (3.1% vs. 2.7%).

The impact of AED exposure during pregnancy

Our studies showed that exposure to AEDs *in utero* was associated with adverse effects on several key developmental domains at all measured time points. The exposed group did not reach motor milestones at the expected age, had poorer language skills, and more autistic behavior. The risk of impaired motor skills was detectable already at 6 months of age. The risk was generally highest for children exposed to multiple drugs. There was no difference between the various drugs when used in monotherapy. This is in contrast to previous studies which have found adverse developmental outcomes mainly in relation to valproate exposure *in utero* (3). Adverse socioeconomic factors and psychiatric disease were more frequent in women with epilepsy. However, the effect of AED exposure on offspring development persisted even after adjusting for these factors.

Children of mothers with epilepsy who did not use AEDs scored within the normal range for all developmental domains, and children of fathers with epilepsy were mainly similar to the reference population. Thus, our results point to the *in utero* AED exposure as the main risk factor for adverse development in children of women with epilepsy. Maternal epilepsy severity was higher in the group using AEDs than in those not using AEDs (23). However, disease severity should be similar in fathers and mothers with epilepsy using AEDs, accounting for potential genetic or psychosocial effects on development in offspring of parents with active epilepsy. Frequent seizures during the pregnancy may affect later cognitive function (9). However, only 21 women had generalized tonic clonic seizures during pregnancy or birth, and of these only 1 woman had more than 3 seizures. Prior research has indicated that less than 5 tonic clonic seizures during pregnancy do not seem to affect developmental outcome (9). Women using AEDs should be encouraged to breastfeed, as no harmful effects from maternal AED use during the breastfeeding period were detected. Breastfeeding has also been shown to improve cognitive outcome (52,53).

The main strengths of the MoBa epilepsy cohort is the prospective study design, the ability to adjust for numerous possible confounders, and the recruitment of a large and representative reference group that is normally not available in such studies (5,54). Including fathers with epilepsy as well as women with epilepsy not treated with AEDs as internal control groups is a unique feature of our study design. Due to the population-based enrollment, selection bias in the MoBa epilepsy cohort is probably much lower than in clinic-based studies, thereby providing results that may be more representative for general epilepsy populations. Even so, some degree of selection is probably present. It has e.g. been shown that the subjects in the MoBa study are more resourceful than the general population; however this selection does not seem to affect exposure-outcome associations (55). Other weaknesses

in MoBa include a self-reported epilepsy diagnosis, developmental assessment based on maternal ratings, and a moderate response rate at 36 months. Even though the screening tools employed are validated, the short versions used in the questionnaires are not always so. The construct validity of the developmental MoBa screening tools has been criticized, e.g. with regard to what extent differences in scores actually represent meaningful clinical differences (56). This criticism does not necessarily apply to cut-offs that are set distant from the mean score, as performed in our studies. The construct validity is probably improved when the instruments are used to detect severe deviations, such as in relation to considerable developmental delay.

This paper reports previously unpublished data on AED plasma levels measured in maternal and umbilical cord plasma, and information on AED doses used during pregnancy. These data will be correlated to offspring developmental scores to search for dose/effect and concentration/effect relationships. The possibility to correlate the levels of AED exposure to future child outcomes from early age and throughout childhood in a population-based setting is unique. Moreover, the collection of clinical epilepsy data from a subcohort in MoBa has assured the quality of the dataset. Information on seizures during pregnancy and epilepsy subtype is now at our disposal and we will assess the effect of these variables on various offspring outcomes. Finally, we have found higher BMI in women with epilepsy before and during pregnancy (22,46) and are currently studying the frequency of and risk factors associated with overweight, obesity and weight gain during pregnancy in the cohort. These factors are of considerable interest, as they are known to increase pregnancy complications in women without epilepsy (57,58). We will assess their impact on pregnancy outcome in women with epilepsy in relation to AED use.

CONCLUSIONS

The validity of epilepsy-related information in the MoBa database was very good. The MoBa epilepsy cohort may be more representative for general epilepsy populations than studies based upon clinical materials. Use of the epilepsy cohort in MoBa has shown that AED exposure *in utero* is associated with impaired development and increased risk of autistic traits in the child. We will proceed with this cohort and analyze the impact of AED plasma concentrations and the contribution of seizures during pregnancy, socioeconomic variables, psychiatric disease, vitamin deficiency and maternal overweight on the developing children born to mothers with epilepsy. The combination of such data is not available in other population-based studies of women with epilepsy in pregnancy. Hence, the unique design of the MoBa study will enable us to expand the knowledge within this field, entangling the various risk factors for adverse outcomes in children of women with epilepsy.

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CONFLICTS OF INTEREST

Marte Helene Bjørk and Gyri Veiby have received lecture honoraria from Glaxo Smith Kline and congress travel support from UCB pharma. NE Gilhus has received lecture fee from Octapharma, Baxter, and Merck Serono. O Spigset has no conflict of interests.

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