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Intrauterine growth retardation in foetuses of women with epilepsy

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ABSTRACT

Purpose: Various factors may affect intrauterine foetal growth, amongst which conditions such as epilepsy and the use of anti-epileptic drugs (AED) may play a role. This study investigated intrauterine growth of foetuses in women with epilepsy, as compared with controls, and explored whether intrauterine growth was affected by prenatal exposure to AED.
Method: Data were obtained from prospectively registered data regarding pregnancy and prenatal and perinatal factors in women in Oppland County in Norway. The final analysis included information from 166 mothers with epilepsy and 287 children. The control group consisted of 40,553 pregnancies in women without epilepsy registered in the same database.
Results: There was a significantly higher risk of the ponderal index being below the 10th percentile and infants being small for gestational age (SGA) in the epilepsy group; exposure to AED increased the risk. The frequency of SGA and low ponderal index was highest in Lamotrigine exposed infants. In the AED group, head circumference was significantly smaller among Carbamazepine exposed.
Conclusion: Impaired intrauterine growth of foetuses in women with epilepsy was identified. The frequency of SGA and low ponderal index was highest in Lamotrigine exposed infants. The epilepsy group had a higher risk profile for having smaller babies, in being younger at age, lower in body weight and more frequent smokers. However despite these differences, the effects of epilepsy and AED exposure were significant. The ponderal index may be a useful supplement to more established measures assessing intrauterine growth in epilepsy.

1. Introduction

Maternal health, diet, medication, smoking habits, placenta function, and genetic factors have all been assumed to affect intrauterine foetal growth. Limited data suggest that intrauterine growth in foetuses is decreased in women with epilepsy [1,2,3]. Low birth weight, reduced head circumference, and increased risk of being small for gestational age (SGA) have been associated with epilepsy, and in particular exposure to anti-epileptic drugs (AED) in pregnancy [2,4,5]. In some recent studies, increased rates of small head circumference have been demonstrated in children exposed to carbamazepine (CBZ), topiramate and AED polytherapy in utero [2,6,7]. Veiby et al. [7] reported a significantly increased risk of SGA < 10 percentile in infants born to mothers with epilepsy. This applied not only to mothers using AED, but also women with epilepsy not using AED. A recent study based on Danish Medical Birth Registry data (Kilic et al., 2014) found AED exposure associated with lower birth weight and increased risk of SGA among children of mothers with epilepsy, whereas AEDs were associated with increased risk of preterm birth only among mothers without epilepsy. On the other hand, small head circumference was associated with AED exposure only among children of mothers with epilepsy [2]. The mechanisms behind the apparent reduction in intrauterine growth have not been identified. The Norwegian part of the EURAP study, a multinational registry of women using AEDs in

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pregnancy, reported only minimal differences in birth weight within the group of 296 AED exposed infants [8]. These observations highlight the importance of taking into account maternal factors e.g. the indication for treatment, and this is unfortunately where registers with un-validated epilepsy diagnoses may fall short. Another factor in intra uterine growth is the maternal weight before and during pregnancy, a factor that has not been controlled for in recent studies [2,7].

An estimation of gestational age depends upon provision of a reliable date of last menstruation. Women with epilepsy may have more cycle disturbances [9] than women without epilepsy, thus determination of true gestational age, and thereby also SGA, may be difficult. Small parents and genetic variations in growth must also be taken into account. Furthermore, SGA and birth weight are also influenced by the mother's weight or body mass index (BMI). The ponderal index (kg/m^3), however, is less dependent on gestational age and parental size, and thus has the potential of providing more accurate information [10]. In Norway, all pregnant women are offered a routine ultrasound investigation at gestational week 17 or 18. The estimated date of delivery (EDD) can be estimated based on these ultrasound measurements. Small measurements at this time point will indicate a later EDD, whereas large measurements indicate an earlier EDD. Thus, early intrauterine growth restriction on a group level would result in negative difference between the EDD based on the Naegele's rule (date for most recent menstruations last day + 7 days – 3months + 1 year) and the EDD based on ultrasound measurements.

The purpose of this study was to assess intrauterine growth of foetuses in women with epilepsy as compared with intrauterine growth in controls and where unlike previous register studies the epilepsy diagnoses has been validated and classified. Furthermore, we wanted to explore whether intrauterine growth restriction (IUGR) was associated with prenatal exposure to AED.

2. Material and methods

2.1. Data source

This study was based on prospectively registered data regarding pregnancy and prenatal and perinatal factors in women in Oppland County in Norway.

The Oppland Perinatal Database (OPD) contains prospectively registered information on all pregnant women who gave birth at one of the two obstetric departments in Oppland County during the period from 1989 to 2012, and includes information on 43,490 pregnancies and births. The OPD information is derived from approximately 95% of all pregnant women in the county during the relevant period. The women with active epilepsy were mainly investigated and followed up by neurologists at the same hospital, and medical records were shared. The cohort includes all births of residents in the county, except for very preterm births and approximately 50 births annually that occurred outside the county. In addition, approximately 200 births per year are included from a large municipality of a neighbouring county.

Demographic and medical information, as well as information on smoking and alcohol habits, were systematically collected in conjunction with the routine ultrasound examination (week 17–19), at birth, and also if the woman was monitored for medical reasons at the obstetric departments in the interim period. Data regarding the women's health, including chronic illness, were registered in a standard pregnancy health record, and added to the OPD at delivery. Pregnancy records reporting epilepsy were registered in OPD as chronic illness and specified epilepsy.

2.2. Inclusion of mothers with epilepsy

All women in OPD with a validated diagnosis of epilepsy at one point in their lives were included in this study. The women received a letter with information on the study and the option to exclude themselves from participation, according to the Health Research Act §35. Epilepsy was registered in a total of 346 pregnancies. After validation of all diagnoses, there were 303 pregnancies by 173 women with validated active or earlier epilepsy. Women without a validated diagnosis or ongoing drug abuse were excluded from further analysis. Seven women did not wish to be included in the study, and thus 166 mothers of 287 children were eligible for the final analysis. The epilepsy diagnosis was validated by a neurologist (AHF) according to the International League Against Epilepsy (ILAE) criteria and by evaluation of medical records and EEG-descriptions. Epilepsy classification was carried out by three independent neurologists (KON, ML, AHF). Among the 287 pregnancies included in the study, 165 were by mothers with focal epilepsy, 83 by mothers with generalized epilepsy, and 39 by mothers with unclassifiable epilepsy (Fig. 1, Table 1). Pregnancies in women without epilepsy

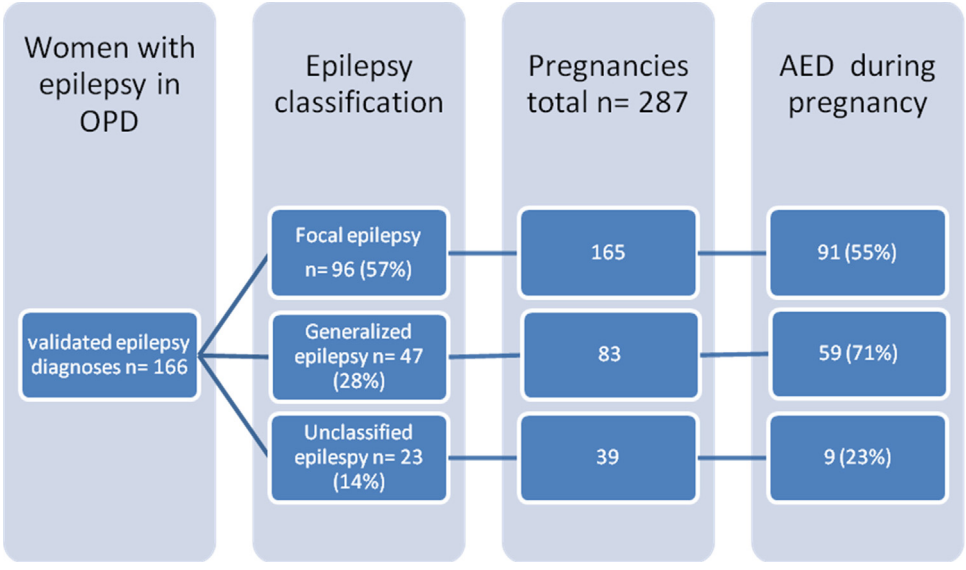

Fig. 1. Epilepsy group.

Table 1
Epilepsy group characteristics.

	Focal, *n* (%)	Generalized, *n* (%)	Unclassified, *n* (%)	Total
Women	96 (57)	47 (28)	23 (14)	166
Number of pregnancies, *n* (% of total in epilepsy group)	165 (57.5)	83 (29)	39 (13.5)	287
AED during pregnancy (%)	91/165 (55)	59/83 (71.1)	9/39 (23)	159
CBZ	43/91 (47)	16/59 (27)	2/9 (22)	61
VPA	9/91 (10)	19/59 (32)	3/9 (33)	31
LTG	13/91 (14)	10/59 (17)	0/9 (0)	23
Polytherapy	12/91 (13)	10/59 (17)	2/9 (22)	22
Other (LEV: 5, TPM: 3)	14/91 (15)	4 (7)	2/9 (22)	18

CBZ, carbamazepine; VPA, valproate; LTG, lamotrigine; LEV, levetiracetam; TPM, topiramate.

who were registered in OPD served as controls. In 55% of cases, AEDs were used throughout the pregnancy (Fig. 1). For 12 pregnancies, AEDs were discontinued by week 12, and these were classified as "untreated".

3. Statistics

The statistical analyses were performed using SPSS 18. Possible group differences were tested using the Pearsons's Chi square test and independent sample *t* test for categorical and continuous data, respectively. All tests were two-sided and were performed at a 5% significance level. Odds ratios (OR) for reduced intrauterine growth were estimated with the corresponding 95% confidence intervals (CI) and *p* values using logistic regression analysis, with low ponderal index and SGA as dependent variables respectively, and epilepsy, AED, smoking, BMI (body mass index), psychiatric co morbidity and drug abuse as the independent variables. Missing data in the analysis are due to failure of registry at time of registry into the OPD.

4. Results

Basic characteristics of the total epilepsy group and the sub groups using AED and not using AED were compared to controls (Table 2). Mean age and age at first registered birth was significantly younger in the epilepsy group. The mothers' BMI before pregnancy was significantly lower in the women with epilepsy than in the controls. Mean weight gain during pregnancy was approximately the same in both groups, and there was no difference in mean height between women with epilepsy and without epilepsy (data not shown). There were small, but significant, differences between the two groups regarding smoking habits at time of conception and substance abuse.

4.1. Ponderal index

There was a significantly higher risk of the ponderal index being below the 10th percentile (16.0% vs 11.9%, $p = 0.027$) (ponderal index percentiles derived from the total OPD material) and SGA below 10th percentile (10.6% vs 7.5%, $p = 0.040$) in the epilepsy group [11], and exposure to AED increased the risk of low ponderal index (Table 3). 19% of lamotrigine exposed versus 11.9% of the controls had ponderal index below the 10 percentile ($p = 0.31$). Mean ponderal index was significantly lower both in the total epilepsy group and the subgroups of AED exposed and unexposed. Controlling for siblings by analysing only for the first registered child demonstrated the same trend (data not shown).

AED exposure was the strongest predictor for low ponderal index in univariate and multivariate analysis, with odds ratio (OR) of 1.76 ($p < 0.01$, CI 2.6–1.2) and OR 1.86 ($p = 0.02$, CI 3.12–1.08) respectively, controlling for smoking, BMI prior to pregnancy, drugs and psychiatric co morbidity (Table 4). Controlling for low BMI in the mothers did not significantly alter the estimated risk.

4.2. SGA

Infants of mothers with epilepsy had a significant elevated risk of SGA (Table 3), and in particular the CBZ exposed infants (14.8% vs 7.5%, $p = 0.03$). The LTG exposed group had a nearly significant elevated risk (18.2% vs 7.5%, $p = 0.056$) (Table 3), i.e. four out of 22 Lamotrigine-exposed newborns had SGA below the 10 percentile. The risk of SGA and ponderal index in the non-exposed epilepsy group was just slightly increased (Table 3).

There was a significantly lower mean BMI in mothers with epilepsy (Table 2). Low BMI and drug abuse were more strongly associated with SGA being below 10 percentile with OR 2.44 ($p < 0.001$, CI 1.95–3.06) and 3.63 ($p < 0.001$ CI 2.17–6.06) in univariate and OR 2.23 ($p < 0.001$, CI 1.72–2.81) and 2.32 ($p < 0.01$ CI 1.23–4.20) in multivariate analysis respectively (Table 4).

4.3. Birth weight and head circumference

Mean birth weight was significantly lower in the total epilepsy group (mean difference: 79 g, $p = 0.029$). Although the mean birth weight in infants from mothers with untreated epilepsy was lower than in infants in the control group, the head circumference was not significantly smaller in this group. In the AED-exposed group and in particular the CBZ-exposed infants, head circumference was

Table 2
Basic characteristics of the total epilepsy group and subgroups (AED and No AED) compared to the controls (women without epilepsy).

	Controls *n* = 40,553	WWE *n* = 287	*p*	AED *n* = 158	*p*	No AED *n* = 129	*p*
Mean age (y)	28.8	27.8	0.001	27.8	0.02	27.6	0.02
Age at first registered birth (y)	27.8	26.4	<0.001	27.8	0.02	26.0	<0.01
Smoking at time of conception (%)	24.3	34.0	0.001	36.3	<0.01	31.4	0.10
Smoking at 18 weeks (%)	19.7	20.6	0.11	22.9	0.33	18.0	0.65
Smoking at time of partus (%)	14.9	15.0	0.97	16.4	0.66	13.4	0.68
Psychiatric illness (%)	1.9	2.7	0.31	0.6	0.24	5.2	0.01
Substance abuse (%)	0.2	0.7	0.08	0.6	0.24	0.7	0.17
BMI < 18.5 (%)	3.2	6.1	0.03	4.9	0.35	7.4	0.02

AED, antiepileptic drug; WWE, women with epilepsy; BMI, body mass index.

Table 3
Group differences in chi-square and independent *t*-test between total epilepsy cohort, epilepsy group on AED and on different AED compared with controls.

	Controls $n=40,553$	Epilepsy $n=287$	p	AED $n=158$	p	No AED $n=130$	p	CBZ $n=61$	p	VPA $n=31$	p	LTG $n=23$	p
SGA < 10 percentile (%)	7.5	10.6	0.04	12.7	0.012	8.2	0.74	14.8	0.03	6.5	0.83	18.2	0.056
PI < 10 percentile (%)	11.9	16.0	0.03	18.6	0.01	13.8	0.49	14.3	0.58	14.3	0.70	19.0	0.31
PI, mean (kg/m^3)	27.5	26.9	<0.001	26.9	0.01	26.8	<0.01	27.2	0.46	26.9	0.24	27.1	0.49
Birth weight (g)	3528.8	3449.8	0.03	3433.5	0.05	3462.3	0.22	3423.4	0.18	3416.7	0.31	3369.3	0.22
Head circumference	35.3	35.0	0.01	35.0	0.03	35.1	0.17	34.7	0.01	34.9	0.29	35.4	0.65
Placenta weight	703.6	676.5	0.02	679.9	0.13	672.8	0.06	691.7	0.66	712.9	0.78	666.0	0.32
BMI at start of pregnancy	24.92	23.99	0.008	24.13	0.11	23.8	0.032	23.44	0.09	24.07	0.44	22.9	0.05
Weight at start of pregnancy	69.91	67.38	0.015	68.21	0.243	66.5	0.022	66.59	0.203	67.2	0.407	65.7	0.16
Weight at end of pregnancy	83.43	80.45	0.005	81.7	0.255	79.1	0.004	80.50	0.274	80.05	0.315	78.6	0.12

SGA, small for gestational age, percentiles from Skjærven et al.; PI, ponderal index (kg/m^3); BMI, body mass index; AED, anti epileptic drugs; CBZ, carbamazepine; VPA, valproate; LTG, lamotrigine; No AED, women with no anti epileptic drug treatment; including no medication since childhood or ever, during pregnancy or who stopped taking the medicine within week 12 of pregnancy.

Table 4
Odds ratios (OR) and 95% confidence intervals (CI) for intrauterine growth restriction using univariate and multivariate logistic regression analysis in AED exposed and the total epilepsy group respectively.

	Univariate			Multivariate		
	OR	CI	p	OR	CI	p
Low ponderal index						
Epilepsy + AED	1.76	2.63–1.16	<0.01	1.86	3.12–1.08	0.02
Smoking at time of conception	1.08	1.19–0.98	0.11			
BMI < 18	1.42	1.79–1.12	<0.01	1.42	1.79–1.12	<0.01
Psychiatric co morbidity	1.25	1.02–0.63	0.07			
Drug abuse	1.46	2.65–0.80	0.21			
SGA < 10 percentile						
Epilepsy + AED	1.90	1.20–3.01	<0.01	1.86	1.04–3.31	0.04
Smoking at time of conception	2.06	1.85–2.28	<0.001	2.06	1.82–2.32	<0.001
BMI < 18	2.44	1.95–3.06	<0.001	2.23	1.79–2.82	<0.001
Psychiatric co morbidity	1.27	0.99–1.62	0.06			
Drug abuse	3.63	2.17–6.06	0.005	2.32	1.28–4.21	0.005
Low ponderal index <						
Epilepsy	1.45	2.00–1.00	0.02	1.52	2.28–1.00	0.05
Smoking at time of conception	1.08	1.19–0.85	0.11	1.07	1.20–0.95	024
BMI < 18	1.42	1.80–1.12	<0.01	1.43	1.81–1.13	<0.01
Psychiatric co morbidity	1.25	1.02–0.62	0.07	1.41	1.05–1.89	0.22
Drug abuse	1.46	2.64–0.80	0.21	1.01	2.28– 0.46-	0.86
SGA < 10 percentile						
Epilepsy	1.48	1.02–2.15	0.04	1.41	0.89–2.24	0.15
Smoking at time of conception	2.06	1.85–2.28	<0.0001	2.06	1.83–2.33	<0.0001
BMI < 18	2.44	1.95–3.06	<0.0001	2.23	1.77–2.81	<0.0001
Psychiatric co morbidity	1.27	0.99–1.62	0.06			
Drug abuse	3.63	2.17–6.06	<0.0001	2.32	1.23–4.20	<0.01

significantly smaller than in infants in the control group. Placenta weight was slightly lower in the epilepsy group than in the controls (Table 3).

In this study, the newer AED (topiramate, levetiracetam) were only used as monotherapy in a small number of pregnancies (Table 1). However, topiramate-exposed newborns demonstrated the lowest values for mean head circumference (33 cm, mean difference 2.3 cm) and birth weight (2926.7 g, mean difference 602.1 g) in the total epilepsy group. Two out of three topiramate-exposed newborns had SGA below the10 percentile ($p < 0.0005$). Levetiracetam-exposed newborns had higher values for ponderal index, ultrasound measurements, birth weight, and head circumference, but the differences were not significant.

The ultrasound measurements were generally smaller in the epilepsy group than among the controls, and significantly lower in the untreated epilepsy group (data not shown). When controlling for the difference between ultrasound EED and Naegele EED, no significant differences were identified.

5. Discussion

The main finding from this study is that the risk for SGA and ponderal index being below the 10 percentile was significantly higher in the epilepsy group than in the controls. In particular, newborns exposed to CBZ during pregnancy had a significantly higher risk of SGA being below 10 percentile and a smaller head circumference. However, it needs to be emphasized that statistical analysis of association with other AEDs is hampered by the considerable fewer exposures. In fact, the proportion of exposed infants with SGA < 10 and ponderal index < 10 with LTG was higher than with CBZ (18.2% vs. 14.8%, and 19.0% vs 14.3%, respectively). Additionally, LTG was associated with the lowest BMI and body weight in the mother, in addition to the lowest mean birth weight and placenta weight. The explanation for the growth restrictions is unclear, but is likely to be multi-factorial. More infants in the control group had a risk of low ponderal index than SGA, indicating that ponderal index may be a sensitive measure of intrauterine growth restriction.

Placenta weight was slightly lower in the epilepsy group than in the controls. Reduced placenta weight may indicate placenta dysfunction, which may lead to reduced growth of the foetus. A previous Norwegian study reported a tendency towards smaller birth weight in children of mothers with epilepsy not using AED [4], while the frequencies of placental disorders were not increased. However, low BMI before pregnancy may predispose for small placenta weight and, thus, smaller infants.

In the current study, BMI and bodyweight at the start, during, and end of pregnancy, were significantly lower in the epilepsy group than in the controls. This was an unexpected finding. Possible explanations may be that women with epilepsy may be more conscious of their weight because of warnings regarding AED being associated with weight-gain. Alternatively, among the female epilepsy population, those that are child bearing may be more active, and thus have a lower BMI, than other people with epilepsy. Eating disorders and depression have been found at increased rates in untreated epilepsy before pregnancy [12]. Also, weight before pregnancy was registered in the pregnancy record and was partly self-reported, thus reporting bias cannot be ruled out.

Although smoking was more common in women with epilepsy at the beginning of the pregnancy, at 18 weeks the deviation from the controls in this respect was modest. Studies have indicated that smoking early in pregnancy does not have such an impact on foetal growth as smoking later in pregnancy, when the oxygen demand over the placenta is more profound [13]. However, smoking and the mothers' BMI may be confounding variables influencing the placenta weight and function, particularly in the last part of the pregnancy. Substance abuse was more common among the women with epilepsy, though not significant (Table 2). Only one person was noted having an ongoing drug abuse during pregnancy and she was excluded from analyses. The frequency of psychiatric illness was lower than expected in the epilepsy group, possible due to the registry format of data, in which only established psychiatric diagnoses were included and there was no registry-specific screening for psychiatric symptoms.

The mean ultrasound measurements were significantly smaller in children of women with epilepsy, and in both sub groups (AED or no AED) (data not shown). However, there was no significant difference between the Naegele EED and ultrasound EED, and therefore the ultrasound measurements in week 17–18 do not necessarily indicate an early restriction in growth. It is rather possible that the smaller ultrasound measurements reflect the tendency towards early referral to ultrasound in higher risk pregnancies and the significant lower BMI in the mothers.

Many studies of intrauterine growth in women with epilepsy are based on register data. Such studies have important limitations as the epilepsy diagnoses and epilepsy classification are rarely validated, and the data on AED treatment is usually restricted. In the current study, the epilepsy diagnoses were validated and the epilepsies classified.

The clinical importance of intrauterine growth restriction associated with epilepsy is undecided. In general, foetal growth is strongly associated with pregnancy outcome. When studied as a single group, infants with intrauterine growth restriction, irrespective of cause, have increased mortality and morbidity [10]. The differences in ponderal index, birth weight and SGA in this study were mostly small, but significant and in line with other studies [2,6,7]. However, to evaluate whether growth restrictions in infants of mothers with epilepsy are associated with later morbidity or neurocognitive deficiencies, more studies with extensive follow up are required.

6. Conclusion

The impaired intrauterine growth of foetuses in women with epilepsy found in this study was statistical significant, but the clinical importance of these findings are to be studied further. The epilepsy group had a higher risk profile for having smaller babies, in being younger at age, lower in body weight and more frequent smokers. However despite these differences, the effects of epilepsy and AED exposure were significant. CBZ was the most frequently used AED, and the only AED that was significantly associated with smaller babies, but the frequency of low SGA and ponderal index was in fact higher in LTG exposed infants. The ponderal index may be a useful supplement to more established measures assessing intrauterine growth in epilepsy.

Conflict of interest

Anette Huuse Farmen does not have any conflicts of interest and has not achieved any grants other than mentioned under "acknowledgements". Jacob Grundt, Jakob Nakling, Karl Otto Nakken and Petter Mowinckel have no conflicts of interest. Torbjørn Tomson received research grants and/or speakers honoraria from Eisai, Glaxo Smith Kline, Novartis, Pfizer, Sanofi-Aventis and UCB Pharma. Morten Ingvar Lossius received research grants and/or speakers honoraria from Eisai and UCB pharma.

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