ORIGINAL ARTICLE

Increased rate of acute caesarean sections in women with epilepsy: results from the Oppland Perinatal Database in Norway

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Background and purpose: Studies in women with epilepsy (WWE) regarding pregnancy and labour complications have disclosed contradictory results. Our purpose was to investigate whether WWE have a higher risk of acute caesarean section (CS) or pregnancy complications than women without epilepsy or women with other chronic diseases and, if we found a higher risk, to explore potential explanations.

Methods: The study used prospectively registered obstetric data from the Oppland Perinatal Database in the period 2001–2011, containing information on 18 244 births, including 110 singleton pregnancies in mothers with validated epilepsy. Data regarding epilepsy were collected retrospectively from medical records.

Results: Epilepsy was a significant risk factor for acute CS, breech presentation and low birth weight in offspring [odds ratio (OR), 1.93, 95% confidence interval (CI), 1.2–3.1; OR, 2.29, 95% CI, 1.2–4.6 and OR, 2.10, 95% CI, 1.0–4.2, respectively]. In multivariate logistic regression analysis, antiepileptic drug exposure was an independent risk factor for acute CS (OR, 2.00; 95% CI, 1.06–3.77) and polytherapy was a significant risk factor for breech presentation (OR, 5.37; 95% CI, 1.13–25.57). Seizure frequency during pregnancy had no influence on the complication rate.

Conclusions: We found that WWE using antiepileptic drugs during pregnancy had increased rates of acute CS, breech presentation and low birth weight, and that seizure frequency during pregnancy did not influence the complication rate.

Introduction

Previous studies have shown increased occurrence of complications related to pregnancy and labour in women with epilepsy (WWE), but results have been contradictory [1–5]. The American Academy of Neurology and American Epilepsy Society's practice parameter update [3] concluded that WWE using antiepileptic drugs (AEDs) probably did not have a substantially increased risk of caesarean section (CS). A recent meta-analysis concluded that epilepsy

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together with AEDs was associated with increased risk of CS, labour induction, pre-term birth, haemorrhage and foetal growth restriction [2]. A Swedish study concluded that epilepsy was associated with increased risks of several adverse outcomes, but AEDs did not increase the risk [5].

Caesarean section, in particular acute CS, is associated with an increased health-related risk to both mother and child [6–8]. A study from Norway reported an increased rate of acute CS among WWE [9]. Explanatory factors were not investigated, but increased foetal stress during delivery was suggested. Between 30% and 40% of WWE experience seizures during pregnancy [10,11]. Data from the EURAP registry (International Registry of AEDs and Pregnancy)

reported poorer seizure control in 16% of pregnancies in the second and third trimesters relative to the first trimester [11]. Further assessments concerning pregnancy outcomes and their associations with seizure control, use of individual AEDs and pregnancy complications have been recommended in a meta-analysis [2].

The aim of this study was to use a prospective obstetric database to investigate whether the risk of acute CS and pregnancy complications differed between WWE, healthy women and women with other chronic diseases. If we found an increased risk, a second aim was to estimate the possible effect of AED exposure and seizure frequency during pregnancy.

Materials and methods

The Oppland Perinatal Database contains prospectively collected data from almost 95% of all completed pregnancies in Oppland County (189 000 inhabitants), Norway, between 1989 and 2012. In Oppland County, there are two delivery hospitals with obstetricians, midwives and anaesthesiologists on duty at all times. Inclusion into the Oppland Perinatal Database was initiated at first contact with one of the two obstetric departments within the county. Medical history, smoking habits, maternal age and parity were registered at start of pregnancy in the compulsory outpatient pregnancy record. Epilepsy data (AED treatment and epileptic seizures) were collected retrospectively based on the woman's medical record.

The current study included 18 244 births from 2001 to 2011 (prospective collection stopped in 2012 and last collected data were only 'raw data' when the current study was commenced and therefore not included in analysis). The study was approved by the Regional Ethical Committee.

Outcome variables

The twofold outcome variables, pregnancy and obstetric complications, were selected based on results from earlier studies [1–5] and information recorded in the Oppland Perinatal Database.

Pregnancy complications
Pregnancy complications were gestational diabetes, pre-term birth, pre-eclampsia, poly- or oligohydramnios and vaginal bleeding.

Obstetric complications
Obstetric complications were delivery by acute or planned CS, breech presentation, induction of labour, pre-term birth and birth weight <2500 g. According to Scandinavian literature and clinical practice, a 'planned'

CS is decided a minimum of 8 h before it is conducted, whereas acute CS is conducted within 8 h after decision. Acute CSs are subdivided into different urgency categories [12,13]. Cases with acute CS and epilepsy were studied with regard to indication for acute intervention. Breech presentation was included in the analysis as it is associated with pre-term birth, obstetric risk factors and CS [14,15]. Pre-term birth was defined, according to international definitions, as a live baby born in the term of gestation from the complete 22nd week to the complete 37th week of gestation (154–258 days).

Exposure variables
The exposure variable was active, non-resolved epilepsy. Subgroup exposure variables were AED treatment for epilepsy and seizures.

Predictors
Selection of possible predictors for complications was based on clinical experience and previous studies [1–8,16–18]. They included smoking habits, pre-term birth and overweight/obesity [World Health Organization definition: body mass index (BMI) >25 kg/m^2], underweight (World Health Organization definition: BMI < 18) previous CS, parity (primipara; first born) and maternal age.

Study groups
We defined two main study groups, i.e. the epilepsy group and healthy group (women without registered chronic diseases). The validation procedure of epilepsy is described elsewhere [19,20]. The frequency of epilepsy was 0.60%. Epilepsy was defined according to the International League Against Epilepsy [21] (epilepsy is considered to be resolved for individuals with age-dependent epilepsy syndrome who are past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years). Thus, 110 singleton pregnancies in women with active, non-resolved epilepsy were included in the epilepsy group, including 17 women not treated with AEDs (five with seizures within the last 10 years and 12 with AED use during the last 5 years). A total of 70 pregnancies in women with resolved epilepsy were included in the healthy group (n = 16 783). Subgroups were defined with regard to AED types and registered chronic disease (Fig. 1). Eight pregnancies in six women using AEDs for indications other than epilepsy (anxiety, bipolar disorder and trigeminal neuralgia) were excluded from analysis.

Sample characteristics
A total of 97% of WWE had a minimum of two appointments with a neurologist or epilepsy nurse
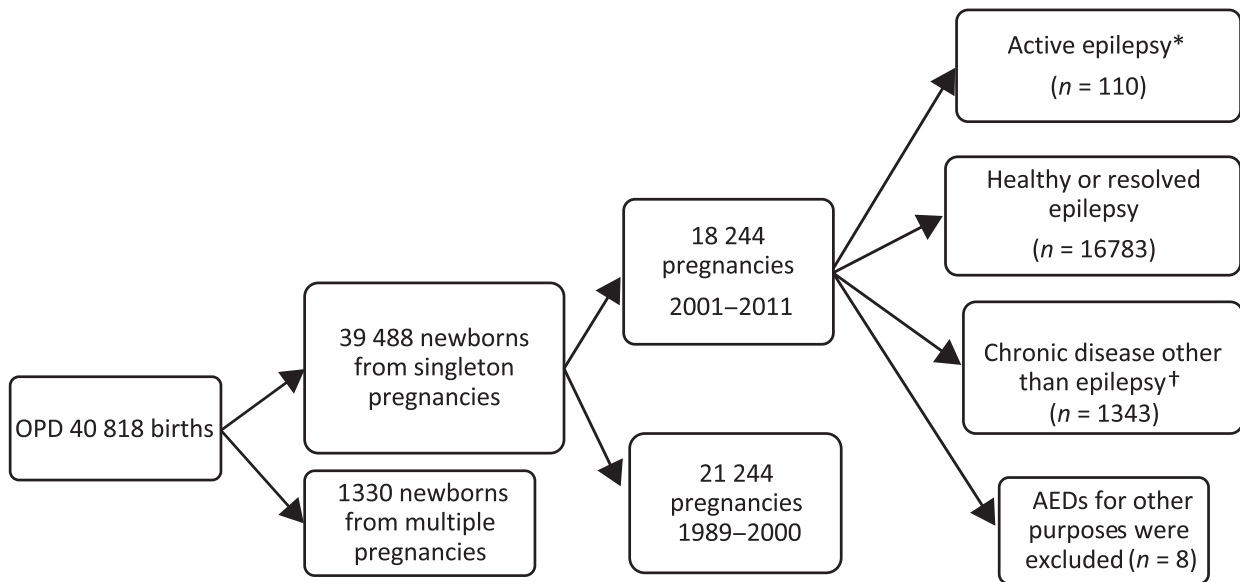
Figure 1 Flow-chart of groups and subgroups used in this study from the Oppland Perinatal Database (OPD). *Active epilepsy: lamotrigine (*n* = 23), valproate (*n* = 20), carbamazepine (*n* = 25), other monotherapy (*n* = 13), polytherapy (*n* = 12), not using antiepileptic drug (AED) (*n* = 17) not using antiepileptic drugs (*n* = 17). †Kidney (*n* = 76), heart (*n* = 98), rheumatism (*n* = 90), cancer (*n* = 37), thyroid (*n* = 345), hepatitis/human immunodeficiency virus (*n* = 107), migraine (*n* = 173), other (*n* = 419).

during pregnancy. Seizures, medication and AED doses were considered. Three WWE had only one or no neurology consultation. At the start of pregnancy, WWE were more often smokers (Table 1) and BMI was lower compared with the chronic disease group. There were no significant differences regarding sample within the epilepsy group. The most commonly used AEDs in monotherapy were lamotrigine [*n* = 23, mean dose 278 (range 50–600) mg], carbamazepine [*n* = 25, mean dose 643 (range 200–1600) mg] and valproate [*n* = 20, mean dose 784 (range 300–1500) mg]. AED polytherapy was used in 12 pregnancies. Dosage changes are routinely registered in medical records in our department. No note regarding dosage change means stable, unchanged medication. Dosage increases were most often registered in the lamotrigine group, in eight out of nine cases due to low serum level and in one case due to seizures. Valproate was increased in four cases due to seizures and in two cases due to pregnancy. Carbamazepine was increased in two cases due to seizure and reduced in two cases due to pregnancy.

Epileptic seizures during pregnancy were most common among those using polytherapy (58%). Seizures were registered in 23 of the 93 WWE using AEDs (25%). Tonic-clonic seizures with or without focal onset accounted for 49%, focal seizures with and without reduced awareness accounted for 29% and myoclonic, absence or unclassifiable seizures accounted for 22%.

Statistical analysis

Possible group differences in characteristics and frequencies of complications and outcomes were tested using the Pearson's chi-squared test and an independent two-sample *t*-test for categorical and continuous data, respectively. BMI was, as the only factor, nonnormally distributed. Because of the large sample size we chose to apply the two-sample *t*-test, due to the central limit theorem and as the Mann–Whitney test is strongly influenced by large sample size and large number of ties. The groups were compared for baseline characteristics and frequency of pregnancy-related and obstetric complications. Based on results from the frequency analysis, the outcome variables acute CS and breech presentation were tested separately in bivariate logistic regression analyses. Potential confounding factors were included in the multivariate logistic regression analysis by including factors that were significant at the 15% level in the bivariate model into the multivariate model according to Hosmer's step-down procedure [22]. The level of 0.15 was chosen to ensure that weak, but still important, predictors were included. Only presumed independent factors were included. Results are given as odds ratio (OR) with the corresponding 95% confidence interval (CI) and *P* values. All tests were two-sided and levels of significance were set to 5% (0.05) unless otherwise stated. Statistical analyses were performed using SPSS 23 (released 2015; IBM SPSS

Table 1 Sample characteristics from the Oppland Perinatal Database

	Epilepsy[a] (n = 110)	Healthy (n = 16 783)	P-value	Chronic disease (n = 1345)	P-value[b]
Age (years)	**28.8 (5.6)**	29.3 (5.2)	0.29	**30.3 (5.2)**	**< 0.01**
BMI at start of pregnancy	**24.2 (4.6)**	24.7 (4.8)	0.24	**25.4 (5.4)**	**0.03**
Mean placenta weight (g)	683.2 (172.0)	699.0 (158.1)	0.30	691.6 (168.1)	0.62
Mother > 35 years (%)	15.5	16.6	0.74	22.2	0.10
Parity (primipara) (%)	44.5	41.7	0.55	41.4	0.52
Smoking at start of pregnancy (%)	**34.6**	**22.9**	**< 0.01**	**22.2**	**< 0.01**
Smoking at time of labour (%)	17.3	12.3	0.12	13.3	0.25
Pre-gestational diabetes (%)	0.0	0.6	0.43	2.2	0.12

Significance is indicated in bold. Data are given as mean (SD) unless otherwise stated. BMI, body mass index. [a]Active epilepsy according to International League Against Epilepsy definition. [b]Compared with epilepsy.

Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA).

Results

The frequency of acute CS, breech presentation and low birth weight was significantly higher among WWE than the healthy reference group (Table 2).

Acute caesarean section

Epilepsy was a significant predictor for acute CS (OR, 1.93; 95% CI, 1.19–3.14) in bivariate logistic regression analyses. Usage of AEDs, and lamotrigine in particular, was a significant predictor in subgroup analysis (OR, 2.23; 95% CI, 1.34–3.70 and OR, 3.07; 95% CI, 1.21–7.79, respectively, Table 3). Seizures during pregnancy did not predict acute CS. AEDs predicted acute CS in multivariate logistic regression analysis controlling for the pre-defined predictors (OR, 2.00; 95% CI, 1.06–3.77; Table 3). Lamotrigine had the highest odds for acute CS and cancer second highest odds in bivariate subgroup analysis within the

group of chronic disease (OR, 3.00; 95% CI, 1.18–7.61 and OR, 2.73; 95% CI, 1.29–6.21, respectively; data not shown).

Indications for acute caesarean section among women with epilepsy

Rationales for acute CSs among WWE were diverse. Breech presentation was the main reason in four, prolonged cervix opening time in four and one had a tonic-clonic seizure during labour. Combinations of factors were reported in the rest (breech presentation, failure to progress, asphyxia and rupture of placenta). There were twice as many planned CSs before delivery in the healthy group than in the epilepsy group (6% vs. 3%, data not shown).

Pregnancy and obstetric complications

Low birth weight in offspring was more frequent in the epilepsy group than among controls (7.3% vs. 3.7%, P = 0.05, Table 2). There was a non-significant tendency of more pre-term birth in the epilepsy and

	Epilepsy (n = 110)	Healthy (n = 16 783)	P-value	Chronic disease (n = 1345)	P-value[a]
Acute CS	**18.2**	**10.3**	**< 0.01**	12.9	0.12
Total CS	20.9	15.4	0.11	22.7	0.67
Oligohydramnios	10.0	7.8	0.39	8.5	0.60
Breech presentation	**8.2**	**3.7**	**0.02**	**4.1**	**0.04**
Pre-term	8.3	5.9	0.30	8.6	0.92
Induction	20.9	16.5	0.21	18.4	0.51
GDM	**2.7**	**0.9**	**0.05**	1.3	0.24
Pre-eclampsia	5.5	5.2	0.92	7.9	0.36
Previous CS	8.2	8.3	0.97	11.7	0.26
Birth weight < 2500 g	**7.3**	**3.7**	**0.05**	4.9	0.28

Table 2 Frequency of pregnancy and obstetric complications in the epilepsy group compared with the healthy group and chronic disease group

Significance is indicated in bold. Data are given as percentages. CS, caesarean section; GDM, gestational diabetes mellitus; previous CS, CS once or more before index pregnancy. [a]Compared with epilepsy group.

Table 3 Predictors for acute caesarean section (CS) in the Oppland Perinatal Database (active epilepsy and healthy)

Acute CS	Bivariate ($n > 16\ 022$)		Multivariate ($n > 15\ 784$)		Multivariate ($n > 15\ 784$)		Multivariate ($n > 15\ 784$)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Epilepsy	**1.93 (1.19–3.14)**	**< 0.01**	1.64 (0.88–3.06)	0.12				
AED	**2.23 (1.34–3.70)**	**< 0.01**			**2.00 (1.06–3.77)**	**0.03**		
LTG	**3.07 (1.21–7.79)**	**0.02**					**2.48 (1.19–10.20)**	**0.02**
Maternal age >35 years	**1.48 (1.31–1.67)**	**< 0.001**	**1.29 (1.12–1.48)**	**< 0.001**	**1.29 (1.12–1.48)**	**< 0.001**	**1.29 (1.12–1.47)**	**< 0.001**
Birth weight < 2500 g	**7.33 (6.20–8.67)**	**< 0.001**	**7.11 (5.87–8.61)**	**< 0.001**	**7.11 (5.87–8.61)**	**< 0.001**	**7.14 (5.89–8.65)**	**< 0.001**
Smoking at start	1.12 (1.00–1.26)	0.06						
GDM	**2.04 (1.37–3.05)**	**< 0.001**	1.38 (0.89–2.16)	0.16	1.39 (0.89–2.16)	0.15	1.39 (0.89–2.18)	0.14
UW	**0.67 (0.48–0.94)**	**0.02**	0.72 (0.50–1.05)	0.09	0.72 (0.60–1.22)	0.09	0.72 (0.50–1.05)	0.09
OWOB	**1.74 (1.57–1.94)**	**< 0.001**	**1.71 (1.53–1.92)**	**< 0.001**	**1.71 (1.53–1.92)**	**< 0.001**	**1.72 (1.53–1.92)**	**< 0.001**
Previous CS	**2.98 (2.60–3.42)**	**< 0.001**	**3.03 (2.60–3.52)**	**< 0.001**	**3.02 (2.60–3.52)**	**< 0.001**	**3.03 (2.60–3.52)**	**< 0.001**
Breech presentation	**6.72 (5.72–7.88)**	**< 0.001**	**6.20 (5.14–7.49)**	**< 0.001**	**6.19 (5.13–7.48)**	**< 0.001**	**6.21 (5.15–7.50)**	**< 0.001**
Seizures	1.78 (0.92–3.42)	0.69	0.98– (0.36–2.63)	0.96	0.81 (0.32–2.42)	0.81	1.04 (0.42–2.55)	0.94

Odds ratio (OR) and 95% confidence interval (CI) for acute CS. Logistic regression analysis, bivariate and multivariate models were used. Significance is indicated in bold. Epilepsy (light shading): bivariate and multivariate controlling for risk factors. Use of antiepileptic drugs (AEDs) for epilepsy (medium shading): bivariate and multivariate controlling for risk factors. Lamotrigine for epilepsy (dark shading): bivariate and multivariate controlling for risk factors. GDM, gestational diabetes; LTG, lamotrigine; OWOB, overweight and obesity at start of pregnancy [body mass index (BMI) > 25 kg/m^2]; previous CS, CS once or more before index pregnancy; smoking at start, registered as smoker at start of pregnancy; UW, underweight (BMI < 18.5 kg/m^2).

chronic disease groups compared with the healthy women. Breech presentations occurred significantly more often in the epilepsy group (8.2% vs. 3.7%, $P = 0.02$, Table 2). Epilepsy, AED use and AED polytherapy were significant risk factors for breech presentation in bivariate logistic regression analysis (OR, 2.29, 95% CI, 1.16–4.56; OR, 2.42, 95% CI, 1.17–5.03; OR, 5.13, 95% CI, 1.12–23.44; Table 4). In multivariate logistic regression analysis controlling for established risk factors for breech presentation (preterm delivery, oligohydramnios and low birth weight) [12], AED polytherapy had OR, 5.37, 95% CI, 1.13–25.57, use of AED had OR, 2.13, 95% CI, 0.97–4.68 and epilepsy had OR, 1.78, 95% CI, 0.81–3.90 (Table 4).

There were no significant differences regarding the frequency of hydramnios, induction of labour or pre-eclampsia. Vaginal bleeding during pregnancy was more common in the chronic disease group (4.6% vs. 8.4% $P = 0.03$, data not shown). The frequency of gestational diabetes was significantly higher in the epilepsy group (Table 2).

Discussion

We found that WWE using AEDs during pregnancy had increased rate of acute CS, breech presentation and low birth weight, but that seizures during pregnancy did not influence the complication rate. Increased risk of emergency CS among WWE has been reported previously [4,5], but without information about seizure frequency or comparison with women with other diseases.

Antiepileptic drugs are previously reported as risk factors for intrauterine growth retardation [19, 23]. It could be argued that low birth weight might be a confounding factor for acute CS in this study as it is a factor that is also associated with breech presentation [14] and breech presentation is associated with acute CS. However, controlling for breech presentation and low birth weight still left AEDs as an independent risk factor for acute CS.

The trend of increased risk of acute CS in women with lamotrigine is not due to seizures or maternal age. In eight out of nine women, the lamotrigine doses were increased due to fall in serum level. The seizure frequency during pregnancy was much the same as has been reported by others [10,11]. As expected, seizures were most frequent among those using polytherapy, probably reflecting more severe epilepsy.

The mothers' own preferences and the obstetricians' concern regarding 'high-risk labour' are important reasons for CS [7,13]. In-depth examination revealed multiple obstetric reasons for acute CS in WWE. As most of the AEDs used in this study are sodium or calcium channel blockers, one factor of possible importance might be that uterine excitability is modulated by sodium channels and calcium-channel blockers are used as tocolytic drugs [24,25]. Reasons for increased acute CS risk in WWE are probably multifactorial and use of AEDs appears to be the most important epilepsy-related risk factor. Low birth weight and breech presentation are also associated with acute CS and AEDs may contribute directly and indirectly.

Table 4 Predictors for breech presentation in the Oppland Perinatal Database (active epilepsy and healthy)

Breech presentation	Bivariate (n > 16 022) OR (95% CI)	P-value	Multivariate (n > 15 784) OR (95% CI)	P-value	Multivariate (n > 15 784) OR (95% CI)	P-value	Multivariate (n > 15 784) OR (95% CI)	P-value
Epilepsy	**2.29 (1.16–4.56)**	**0.02**	1.78 (0.81–3.90)	0.19				
AED	**2.42 (1.17–5.03)**	**0.02**			2.13 (0.97–4.68)	0.06		
Polytherapy	**5.13 (1.12–23.44)**	**0.04**					**5.37 (1.13–25.57)**	**0.04**
Maternal age >35 years	1.42 (1.17–1.73)	< 0.001	**1.63 (1.33–2.00)**	**< 0.001**	**1.63 (1.33–2.00)**	**< 0.001**	**1.63 (1.33–2.00)**	**< 0.001**
Primiparity	1.52 (1.30–1.78)	< 0.001	**1.62 (1.37–1.92)**	**< 0.001**	**1.62 (1.37–1.92)**	**< 0.001**	**1.62 (1.37–1.92)**	**< 0.001**
Smoking at start	1.07 (0.88–1.29)	0.05						
Birth weight < 2500 g	5.07 (4.01–6.43)	< 0.001	**3.16 (2.23–4.47)**	**< 0.001**	**3.16 (2.23–4.47)**	**< 0.001**	**3.16 (2.23–4.47)**	**< 0.001**
Pre-term birth	3.50 (2.81–4.37)	< 0.001	**1.73 (1.25–2.38)**	**0.001**	**1.73 (1.25–2.38)**	**0.001**	**1.73 (1.25–2.38)**	**0.001**
Oligohydramnios	0.68 (0.48–0.96)	0.03	**0.70 (0.49–0.99)**	**0.05**	**0.70 (0.49–0.99)**	**0.05**	**0.70 (0.49–0.99)**	**0.05**
Seizures	1.71 (0.64–4.54)	0.28						

Odds ratio (OR) and 95% confidence interval (CI) for breech presentation. Logistic regression analysis, bivariate and multivariate models were used. Significance is indicated in bold. Epilepsy (light shading): bivariate and multivariate controlling for risk factors. Use of antiepileptic drugs (AEDs) for epilepsy (medium shading): bivariate and multivariate controlling for risk factors. Polytherapy for epilepsy (dark shading): bivariate and multivariate controlling for risk factors. Smoking at start, registered as smoker at start of pregnancy.

In contrast to some studies [2,16] and in line with others [18], we did not find increased rates of pre-eclampsia or vaginal bleeding in WWE compared with controls.

Contrary to most other similar studies, our cohort is thoroughly validated regarding epilepsy and includes 95% of the WWE in the catchment area. The study benefits from the detailed information about the subjects' epilepsy diagnoses, seizure types and frequency, treatment and detailed obstetric information. The inclusion of two reference groups consisting of healthy women and women with other chronic conditions is another advantage.

The main limitation of this study is the relatively low number of WWE. Results from the subgroup analyses should therefore be interpreted with caution. Those with chronic diseases did not have their diagnoses validated, which prevented further analyses. Finally, WWE may be monitored more closely during pregnancy. However, as most obstetric factors analysed are routinely assessed, such surveillance bias seems unlikely.

We suggest that further studies investigate the possible impact of AEDs on pregnancy complications, by comparing with those using AEDs for non-epilepsy indications. A systematic study regarding the causes for acute CS would also be warranted.

In this study, women with active epilepsy had higher rates of acute caesarean deliveries, breech presentation and low birth weight in offspring. Our findings emphasize the need for special interdisciplinary healthcare for WWE during pregnancy.

Disclosure of conflicts of interest

A.H.F. has received a speech honorarium from UCB Pharma. M.I.L. has been part of an expert panel for EISAI and given lectures for UCB and ESAI. The other authors declare no financial or other conflicts of interest.

References

1. MacDonald SC, Bateman BT, McElrath TF, Hernández-Díaz S. Mortality and morbidity during delivery hospitalization among pregnant women with epilepsy in the United States. *JAMA Neurol* 2015; **72:** 981–988.
2. Viale L, Allotey J, Cheong-See F, *et al.* Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet* 2015; **386:** 1845–1852.
3. Harden CL, Hopp J, Ting TY, *et al.* 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:** 126–132.
4. Borthen I, Eide MG, Veiby G, Daltveit AK, Gilhus NE. Complications during pregnancy in women with epilepsy: population-based cohort study. *BJOG* 2009; **116:** 1736–1742.
5. Razaz N, Tomson T, Wikström AK, Cnattingius S. Association between pregnancy and perinatal outcomes among women with epilepsy. *JAMA Neurol* 2017; **74:** 983–991.
6. Häger RM, Daltveit AK, Hofoss D, *et al.* Complications of cesarean deliveries: rates and risk factors. *Am J Obstet Gynecol* 2004; **190:** 428–434.
7. Tollånes MC. Increased rate of Caesarean sections – causes and consequences. *Tidsskr Nor Legeforen* 2009; **129:** 1329–1331.
8. Haerskjold A, Hegaard HK, Kjaergaard HJ. Emergency caesarean section in low risk nulliparous women. *J Obstet Gynaecol* 2012; **32:** 543–547.

9. Veiby G, Daltveit AK, Engelsen BA, Gilhus NE. Pregnancy, delivery, and outcome for the child in maternal epilepsy. *Epilepsia* 2009; **50:** 2130–2139.

10. Vajda FJ, O'Brien T, Lander C, Graham J, Eadie M. The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy. *Epilepsia* 2014; **55:** 1229–1234.

11. Battino D, Tomson T, EURAP Study Group. Seizure control and treatment changes in pregnancy: observation from the EURAP epilepsy pregnancy registry. *Epilepsia* 2013; **54:** 1621–1627.

12. Norwegian Society of Gynecology and Obstetrics. Veileder i fødselshjelp, 2014. http://legeforeningen.no/Fagmed/Norsk-gynekologisk-forening/Veiledere/Veileder-i-fodselshjelp-2014/ (accessed 20/05/2018).

13. Kolås T, Hofoss D, Daltveit AK, *et al.* Indications for cesarean deliveries in Norway. *Am J Obstet Gynecol* 2003; **188:** 864–870.

14. Hofmeyr GJ, Hannah M, Lawrie TA. Planned caesarean section for term breech delivery. *Cochrane Database Syst Rev* 2015; **7:** CD000166.

15. Macharey G, Gissler M, Rahkonen L, *et al.* Breech presentation at term and associated obstetric risk factors – a nationwide population based cohort study. *Arch Gynecol Obstet* 2017; **295:** 833–838.

16. Borthen I. Obstetrical complications in women with epilepsy. *Seizure* 2015; **28:** 32–34.

17. Borthen I, Gilhus NE. Pregnancy complications in patients with epilepsy. *Curr Opin Obstet Gynecol* 2012; **24:** 78–83.

18. Viinikainen K, Heinonen S, Eriksson K, Kälviäinen R. A community-prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. *Epilepsia* 2006; **47:** 186–192.

19. Farmen AH, Grundt JH, Tomson T, *et al.* Intrauterine growth retardation in fetuses of women with epilepsy. *Seizure* 2015; **28:** 76–80.

20. Farmen AH, Grundt JH, Tomson T, *et al.* Age-specific birth rates in women with epilepsy: a population-based study. *Brain Behav* 2016; **6:** e00492.

21. Fisher RS, Acevedo C, Arzimanoglou A. A practical clinical definition of epilepsy. *Epilepsia* 2014; **55:** 475–482.

22. Hosmer DW, Lemeshow S. *Applied Logistic Regression*, 2nd edn. John Wiley: New York, USA, 2000.

23. Kilic D, Pedersen H, Kjaersgaard M, *et al.* Birth outcomes after prenatal exposure to antiepileptic drugs – A population-based study. *Epilepsia* 2014; **55:** 1714–1721.

24. Herington JL, Swale DR, Brown N, *et al.* Throughput screening of myometrial calcium-mobilization to identify modulators of uterine contractility. *PLoS ONE* 2015; **10:** 1–24.

25. Reinl E, Cabeza R, Gregory IA, Cahill AG, England SK. Sodium leak channel, non-selective contributes to the leak current in human myometrial smooth muscle cells from pregnant women. *Mol Hum Reprod* 2015; **21:** 819–824.