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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

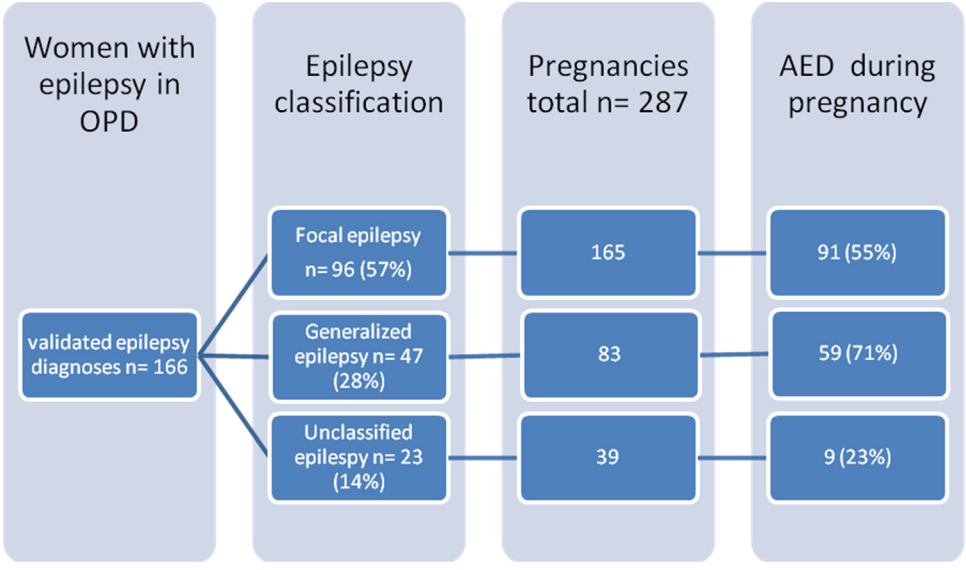

Fig. 1. Epilepsy group.