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Epilepsy, Female Reproductive Health and Neurodevelopment of the Offspring

Doctoral dissertation

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ABSTRACT

One of the most common neurological diseases in women of childbearing age is epilepsy, affecting approximately 0.8 percent of the women. An increased risk for both fetal and maternal complications, has been reported in women with epilepsy due to epilepsy itself, epilepsy related co-morbidities and antiepileptic drugs. Some of the frequent concerns are reproductive problems, pregnancy complications, congenital malformations and developmental problems in the offspring.

The purpose of this study was to evaluate the fertility and reproductive health in women with active epilepsy living in the Kuopio University Hospital area. The study was also extended to evaluate the pregnancy outcome of these women and to the assessment of the cognitive and neurological performance of the children exposed to valproate and carbamazepine monotherapy during pregnancy.

We found no difference between women with epilepsy and control women in their reproductive health and also the overall rate of women having children was the same, if we exclude the infertility caused by a higher proportion of severe co-morbid factors, which differentiate the women with active epilepsy from the general population. We followed the pregnant women throughout the pregnancy with a pre-decided protocol. The course of pregnancy was uncomplicated in the majority of the women with epilepsy. Congenital malformations were observed in 4.8 % of the live-births in women with epilepsy and the rate of small-for-date infants as well as the rate of admissions to a neonatal intensive care unit, were higher in the infants of the women with epilepsy. Women using valproate for epilepsy had a lower intelligence quotient than women using carbamazepine or women without antiepileptic drugs and also their level of education was lower, reflecting perhaps the nature of the epilepsies responding specifically to valproate. Children exposed to valproate had also lower mean intelligence scores, though the difference did not reach statistical significance. They also scored lower values in the neuropsychological tests and had received more educational support than children exposed to carbamazepine or children without drug exposure. In 62 % of the children exposed to valproate, one or more minor dysmorphic features were observed compared to 15% in other children. Children with carbamazepine exposure did not differ from controls.

In conclusion, women with active epilepsy represent a particularly challenging population for neurologists and other health care professionals. However, in our population with the pre-decided protocol used for the follow-up of pregnancies and well controlled epilepsy, the majority of the women with epilepsy have uncomplicated pregnancies. The risk for congenital malformations is nearly two-fold in the offspring of women with epilepsy exposed to antiepileptic drugs compared with the results of the national malformation registry. The cognitive outcome of children exposed to carbamazepine does not differ from controls, which is in line with previous reports. Our findings suggest that valproate may have a negative impact on neurocognitive development of the exposed offspring, though many confounding factors, including the type of epilepsy and level of schooling of the mother, may explain some of this result.

National Library of Medicine Classification: QV 85, WL 385, WQ 210, WQ 240

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To my family

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Jyväskylä, March 2007

Katriina Viinikainen

ABBREVIATIONS

AED	antiepileptic drug
CBZ	carbamazepine
CI	confidence interval
CTRS	Conners' Teacher Rating Scale
FACS	fetal anticonvulsant syndrome
FIQ	full intelligence quotient
IBE	International Bureau for Epilepsy
IQ	intelligence quotient
ILAE	International League Against Epilepsy
KUH	Kuopio University Hospital
LTG	lamotrigine
MCM	major congenital malformation
MRI	magnetic resonance imaging
NEPSY	developmental neuropsychological assessment
NI	neurological impairment
NS	non-significant
OR	odds ratio
OXC	oxcarbazepine
PB	phenobarbital
PCO	polycystic ovaries
PCOS	polycystic ovary syndrome
PHT	phenytoin
PGE	primary generalized epilepsy
PIQ	performance intelligence quotient
SD	standard deviation
SE	status epilepticus
SGA	small for gestational age
SHBG	sex-hormone binding globuline
SMR	standardised mortality ratio
SUDEP	sudden, unexpected death in epilepsy

TLE	temporal lobe epilepsy
VGB	vigabatrin
VIQ	verbal intelligence quotient
VPA	valproate, valproic acid
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for children
WWAE	women with active epilepsy

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are referred to in the text by the Roman numerals (**I-V**).

I Viinikainen K, Heinonen S, Eriksson K, Kälviäinen R. Fertility in women with epilepsy. Submitted

II Viinikainen K, Heinonen S, Eriksson KJ, Kälviäinen R. Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy. *Epilepsia* 2006;47(1):186-92

III Sorri I, Herrgård E, Viinikainen K, Pääkkönen A, Heinonen S, Kälviäinen R. Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero. *Epilepsy Research* 2005;65:117-120

IV Eriksson K, Viinikainen K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R. Children exposed to valproate in utero – Population based evaluation of risks and confounding factors for long-term neurocognitive development. *Epilepsy Research* 2005;65:189-200

V Viinikainen K, Eriksson K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R. The effects of valproate exposure in utero on behaviour and the need for educational support in school-aged children. *Epilepsy & Behavior* 2006;9(4):636-40

CONTENTS

1. INTRODUCTION

Epilepsy is a common neurological disorder, affecting approximately 0.5-1.0 percent of the population. It is characterized by recurrent epileptic seizures caused by abnormal excessive or synchronous neuronal activity in the brain. The incidence of epilepsy is highest in children and in elderly people. Epilepsy is not a specific disease or a single syndrome but rather a broad category of symptom complexes arising from disordered brain functions that themselves may be secondary to a variety of pathological processes. Recurrent epileptic seizures are a cause of severe morbidity and even mortality. In addition to social restrictions, seizures may cause injuries and even lead to death. Also, recurrent seizures may have a negative effect on a patient's cognitive abilities. Therefore the active and effective treatment of epilepsy is important. Freedom from seizures is the ultimate goal in treating patients with epilepsy.

In the majority of patients, epilepsy is well controlled with antiepileptic drugs (AEDs). Two thirds of the patients achieve seizure freedom with current antiepileptic medication. However, up to 30% of all epilepsy patients develop intractable epilepsy. The goal of the AED treatment is to achieve seizure control without causing any adverse effects to the patient. Nowadays over 20 different AEDs are available and an individualized treatment for every patient should be used. Some of intractable epilepsy patients can be also helped by epilepsy surgery.

Women of reproductive age with epilepsy represent a unique group of epilepsy patients due to the challenges of epilepsy treatment. Some of the aspects which need to be taken into consideration are the effects of AEDs on the female endocrine system, the impact of pregnancy on seizure control, the reported maternal and fetal complications and the risk not only of epilepsy but also of AED treatment to the developing child and also the long-term neurodevelopment of the offspring.

The present study was conducted to provide an overview of the women with epilepsy in Kuopio University Hospital area. This study addresses the issue of fertility and hormonal factors in women with epilepsy as well as pregnancy complications and the pregnancy

outcome. We also studied the long-term effect of AEDs on neurodevelopment in those school-aged children who had been exposed to AEDs in utero.

2. REVIEW OF THE LITERATURE

2.1. Epilepsy - definition

According to definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE), an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is not a specific disease or a single syndrome but rather a broad category of symptom complexes arising from disordered brain functions that themselves may be secondary to a variety of pathologic processes.

2.2. Epidemiology – prevalence, incidence and aetiology

In the Nordic countries, the prevalence rates of epilepsy vary between 3.6-5.3/1000 in children and 5.5-6.3/1000 in adults (Keränen et al. 1989; Forsgren 1992 and 2004, Eriksson and Koivikko 1997). Similar results have been reported in other developed countries (Hauser et al. 1991). In the less developed countries, the reported prevalence rates have a higher variation; in the reports from South and Central America, the prevalence rates tend to be higher than those found in the developed countries (Forsgren 2004).

It is still debatable whether epilepsy is more common in men than in women (Forsgren 2004). Keränen et al. (1989) and Forsgren (1992) found that the prevalence of epilepsy among men was slightly higher than in women. However, the opposite information is also available (Hauser et al. 1991). Overall, epilepsy is the most common serious neurological disorder affecting approximately 0.5 to 1.0 percent of the population with a slightly higher prevalence observed in men (Keränen et al. 1989; Forsgren 1992).

The annual incidence rates of epilepsy vary around 50/100 000 according to the studies from Sweden and United States (Hauser et al. 1993; Forsgren et al. 1996). In different age-groups, the incidence is highest in young children and in the elderly and lowest during young adulthood (Hauser et al. 1993; Forsgren et al. 1996; Sillanpää et al. 2006). In recent years, the incidence of epilepsy in young children has declined and correspondingly, an increase has been observed in the elderly (Forsgren 2004; Sillanpää et al. 2006). Incidence rates have also been reported to be higher in men than in women (Keränen et al. 1989; Hauser et al. 1993).

The cause of epilepsy is unknown in the majority of patients (Forsgren 1992; Hauser et al. 1993). The most common identified aetiology for epilepsy is stroke, accounting for approximately 11 % of epilepsy cases (Forsgren 1992; Hauser et al. 1993). Other common causes are head trauma 5-7 %, tumour 4-5 % and infection 2-3 %. Neurological deficits coexistent with epilepsy have been observed in 7-8% of patients with epilepsy (Forsgren 1992; Hauser et al. 1993). These epilepsies with a known cause are said to be 'remote symptomatic epilepsies'. It is evident that the more extensive the investigation, the more likely it is that etiological factors will be identified. Brain magnetic resonance imaging (MRI) identifies a high rate of abnormal findings in hospital based surveys (Li et al. 1995). However, no population-based epidemiological study with modern neuroimaging has been reported. Therefore, it is likely that the true incidence of symptomatic epilepsies is higher than that reported in previous studies, and that MRI will have an important impact on the diagnosis of previously undetectable structural abnormalities such as cortical dysplasias underlying epilepsy.

2.3. Classification of epilepsies

Epilepsy (or epileptic syndrome) affects all age-groups, has different type of aetiologies and manifestations. Therefore epilepsies can be subdivided into groups of characteristic clinical features related to e.g. family history of epilepsy, age at the onset of seizures, seizure type and associated neurological symptoms and signs. The epileptic syndromes can be divided into localization-related (or focal) and generalized epilepsies. According to this aetiology, these can be further categorized into idiopathic, symptomatic and probably symptomatic epilepsies. Idiopathic epilepsies are presumed to be genetic in origin, symptomatic epilepsies have

usually a known cause and probably symptomatic epilepsies are presumed to be symptomatic, even though no aetiology has been identified (Engel 2001; Dodson 2004).

Epileptic seizures are classified into two categories; partial seizures with or without secondary generalization in which the seizure originates from a focal region and generalized seizures, in which the epileptiform activity is present in both hemispheres at the onset of the seizure. The International League Against Epilepsy (ILAE) updates the classification of seizure types and epileptic syndromes according to the current knowledge (Engel 2001).

2.4. The impact of epilepsy for an individual

Epilepsy is a common, serious neurological disorder. It is described as a disorder of the anatomical and functional neuronal network of the brain and is characterised by an enduring predisposition to generate epileptic seizures. These seizures can vary in severity e.g. from mild subjective symptoms without any impairment of consciousness to automatisms with impaired consciousness and on to generalized tonic-clonic seizures with total loss of consciousness. Seizures, since they are the most prominent feature of epilepsy, have a serious impact on quality of life.

For the individual patient with epilepsy, epileptic seizures are not only socially restricting, but they also increase the risk of morbidity and mortality. Accidents and injuries have been reported more often in epileptic patients than in the general population (Tomson et al. 2004d). These injuries can take many forms e.g. fractures, burns, head traumas and drowning. In a recent review by Tomson (2004d) some of the injuries were related more commonly to recurrent seizures, especially to generalized tonic-clonic seizures.

An increased risk of unexpected death in patients with epilepsy has been reported in many studies (Olafsson et al. 1998c; Lindsten et al. 2000; Mohanraj et al. 2006). Standardised mortality ratios (SMR, the difference between observed and expected deaths) are found to be 2-3 times higher in patients with epilepsy compared to the general population (Lindsten et al. 2000; Duncan et al. 2006; Mohanraj et al. 2006). In the population-based study by Lindsten et al. (2000), an increased mortality rate was observed both in men and in women with epilepsy

and it was associated with both partial and generalized seizures. During a 30-year follow-up period, the overall survivorship of patients with epilepsy was decreased compared with the general population and the SMR was especially high in patients with remote symptomatic epilepsy (Olafsson et al. 1998c). In the recent study of patients with newly diagnosed epilepsy reported by Mohanraj et al. (2006), the SMR for all patients was 1.42 and for patients not responding to treatment 2.54 whereas it was normal, i.e 0.95, for those patients who achieved remission emphasizing the importance of seizure control on mortality.

The excess mortality may be due to the underlying aetiology leading to epilepsy, but an estimated proportion of 20% is thought to be due to epilepsy itself (Forsgren 2004). These epilepsy related deaths are most commonly associated with epileptic seizures e.g. status epilepticus and sudden unexpected death in epilepsy (SUDEP). SUDEP, where an otherwise healthy person with epilepsy dies unexpectedly with no cause found at autopsy, is the most important group of epilepsy related deaths (Nashef and Langan 2004; Tomson et al. 2004d). In patients with chronic epilepsy, the rate of SUDEP is higher than in patients with newly diagnosed epilepsy (Mohanraj et al. 2006). The increased risk of SUDEP is associated with high seizure frequency, early-onset epilepsy and concomitant use of multiple AEDs according to the study of Nilsson et al. (1999).

Status epilepticus (SE) is a neurological emergency, in which the epileptic seizure and epileptiform activity in the brain persists for over 30 minutes. Convulsive SE is extremely harmful to the patient and a recent survey from the United Kingdom (UK) reported that mortality during the first SE can be as high as 16% (Rossetti et al. 2006).

The possible effect of epilepsy on the cognitive abilities of the patient has also been addressed. People with epilepsy as a group show impaired intellectual performance compared with healthy subjects matched for age and education (Perrine and Kiolbasa 1999). Most of the studies of cognitive functioning in epilepsy are of patients with chronic epilepsy, but also newly diagnosed epilepsy patients have been shown to perform more poorly than control subjects in a number of cognitive tasks (Kälviäinen et al. 1992; Prevey et al. 1998; Pulliainen et al. 2000; Äikiä et al. 2001). A retrospective analysis of patients with epilepsy, who had undergone two evaluations of cognition over a time span of more than 10 years, was reported

by Thompson and Duncan (2005). A clear, cognitive decline was seen between the two evaluations, and this was associated with a high seizure frequency and the duration of epilepsy (Thompson and Duncan 2005).

In addition to epilepsy, many patients have another coexisting disease or disability which may have on additional impact on the individual and to the treatment of epilepsy (Jalava and Sillanpää 1996; Forsgren 2004; Gaitatzis et al. 2004). These co-morbidity rates are higher in patients with epilepsy than in the general population. The observed proportions of accompanying conditions in Swedish population are illustrated in Figure 1. Results from the Finnish populations of childhood-onset epilepsy as well as from the study of the United Kingdom have reported similar results (Jalava and Sillanpää 1996; Eriksson and Koivikko 1997; Gaitatzis et al. 2004).

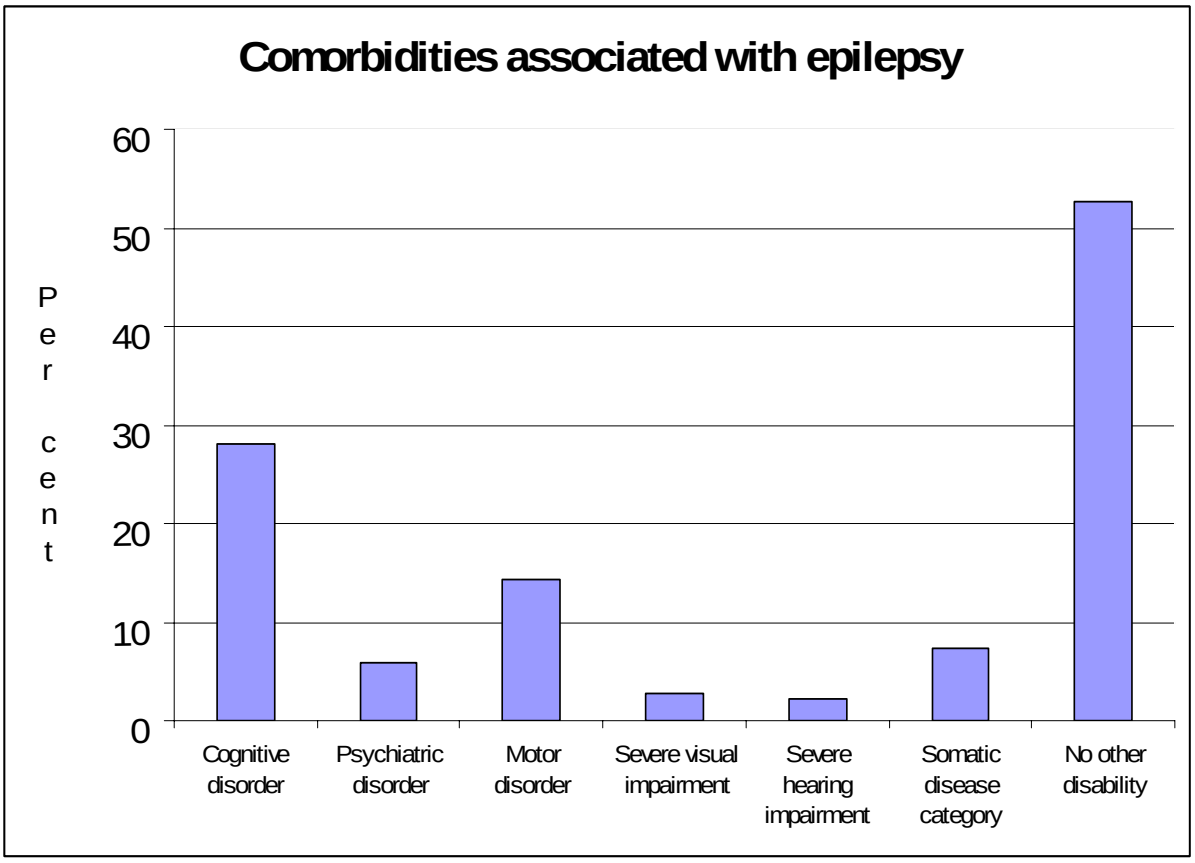

Figure 1. Results of the Swedish population-based prevalence study of adult epilepsy and coexisting disabilities (according to Forsgren 1992).

2.5. Antiepileptic drug treatment

The need for effective AED treatment is evident due to the detrimental effects of the epileptic seizures and their impact on the individual patient. The recent review of epilepsy-related injuries and mortality by Tomson et al. (2004d), concluded that effective treatment of epilepsy appears to decrease the injuries and mortality related to epilepsy, which further emphasizes the importance of effective epilepsy treatment. Also patients with epilepsy report seizure-freedom as one of the most important factors affecting their quality of life (Birbeck et al. 2002).

The first AED (potassium bromide) was introduced in 1857 and since that time the treatment of epilepsy as well as knowledge of the effects of AEDs have advanced significantly. Nowadays over 20 different AEDs are available. Two of the most commonly used AEDs are carbamazepine (CBZ) for partial epilepsies and valproate (VPA) for generalized epilepsies, which are described in detail in Table 1 below. The aim of the AED treatment is to achieve optimal seizure control without eliciting any adverse effects to the patient (Duncan et al. 2006). According to the current findings, seizure remission can be achieved in approximately two thirds of all patients. However, up to 30% of all epilepsy patients develop intractable epilepsy (Hauser and Hesdorffer 2001). Despite optimal treatment, these patients continue to experience seizures or other symptoms of epileptic syndrome, restricting their ability to lead a full life (Hauser and Hesdorffer 2001). Due to the different underlying aetiologies for epilepsy and individual variations of the patients, an individualised approach to the treatment of epilepsy is recommended (Duncan et al. 2006). Women with epilepsy represent one unique group of epilepsy patients whose treatment is challenging since so many aspects need to be considered.

Table 1. Comparison between the characteristics of carbamazepine and valproate

	Carbamazepine	Valproate
Mechanisms of action	Action on neuronal sodium-channel conductance Action also on monoamine, acetylcholine and NMDA receptors	Uncertain but may affect GABA glutaminergic activity, calcium conductance and potassium conductance
Primary indications	First-line or adjunct therapy in partial and generalized seizures (excluding absence and myoclonus). Also in Lennox-Gastaut syndrome and childhood epilepsy syndromes	First-line or adjunct therapy in generalized seizures (including myoclonus and absence) and also in partial seizures, Lennox-Gastaut syndrome and drug of first choice in the syndrome of primary generalized epilepsy. Also for childhood epilepsy syndromes and febrile seizures.
Route of elimination	Hepatic metabolism	Hepatic metabolism
Maintenance dosages in adults (mg/day)	400-1600 (maximum 2400)	500-2500
Drug interactions	Accelerates hepatic metabolism, has many interactions with antiepileptic and other drugs	Number of complex interactions with antiepileptic and other drugs
Some reported side-effects	Drowsiness, fatigue, dizziness, ataxia, diplopia, blurring of vision, sedation, headache, rash and other skin reactions, leucopenia, gastrointestinal disturbances, hepatic disturbances, endocrine effects	Weight gain, thinning or loss of hair, polycystic ovarian syndrome, nausea, vomiting, endocrine effects, drowsiness, tremor, weakness, thrombocytopenia
Comments	First choice drug in tonic-clonic and partial seizures in adults and children	Drug of choice in primary generalized epilepsy and useful in a variety of other epilepsies

(Modified from Shorvon S. In: Shorvon S, Perucca E, Fish D, Dodson E , Eds. The Treatment of Epilepsy. Oxford:Blackwell Publishing, 2004).

2.6. Epilepsy and female reproductive health

It has been estimated that 0.5 % of the childbearing population suffer from epilepsy and therefore it is one of the major neurological concerns also to be taken into consideration in fertile-aged women (Richmond et al. 2004). Many studies suggest that the fertility in women with epilepsy is decreased compared to the general population (Dansky et al. 1980; Webber et al. 1986; Artama et al. 2004). In the United States, in women with epilepsy the live birth rate was 0.85 of that expected during a 40-year period of time (Webber et al. 1986). The birth rate was lowest in the 1940's and has increased decade by decade so that by the 1970's no reduction was noted (Webber et al. 1986). In the United Kingdom, the fertility rate was found by Wallace et al. (1998) to be 33% lower in women with epilepsy compared to controls.

However, in a population-based study from Iceland, no reduction was noted in the fertility of women with epilepsy compared with controls (Olafsson et al. 1998b). In that study, 30% of women with epilepsy did not have children compared to 25% in the general population and only patients with remote symptomatic epilepsy and a severe co-morbidity (e.g. cerebral palsy or mental retardation) were childless more often than controls (odds ratio 22) (Olafsson et al. 1998b). In the study of Dansky et al. (1980), 58% of women with epilepsy had at least one pregnancy and 85% of married women had children, but the marriage rate was reduced in women with epilepsy compared to unaffected women. Schupf et al. (1996) reported that fertility was reduced in patients with epilepsy after the onset of epilepsy but not before its appearance. Jalava et al. (1997) reported that women with epilepsy may be disadvantaged in terms of marrying but when they are married, their fertility or pregnancies do not differ from controls according to a population-based follow-up study of patients with childhood-onset epilepsy.

A higher frequency of menstrual disturbances (e.g. anovulatory cycles, irregular menstrual cycles) have been reported in women with epilepsy than in unaffected women (Cummings et al. 1995; Svalheim et al. 2003; Herzog 2006) and this has been thought to be one of the most important factors explaining their reduced fertility. These changes have been associated with epilepsy itself and to the use of AEDs. In the retrospective cohort study of Svalheim et al. (2003), menstrual disturbances were associated with frequent seizures but not with the

epilepsy type. The association of epilepsy type and menstrual disturbances was studied by Cummings et al. (1995). They reported that 35.5 % of women with temporal-lobe epilepsy (TLE) had anovulatory cycles but this disturbance was not found in any of the women with primary generalized epilepsy (PGE). Irregular menstrual cycles and anovulation may also occur in association with polycystic ovarian syndrome (PCOS). In some studies, PCOS has, in addition to AEDs, been associated with epilepsy itself (Herzog 2006).

Of the individual AEDs, especially VPA has been associated with a high frequency of menstrual disturbances (Isojärvi et al. 1993 and 1996; Svalheim et al. 2003). Several mechanisms have been proposed e.g. changes in sex hormone levels and a higher prevalence of polycystic ovaries (PCO) and hyperandrogenism in women using VPA for epilepsy. Isojärvi et al. (1996) reported that PCO and/or hyperandrogenism were found in 64% of women using VPA compared to 19% in controls. These women had also a higher level of serum testosterone, dehydroepiandrosterone (DHEAS) and insulin levels and lower serum levels of sex-hormone binding globuline (SHBG). Accordingly, Rättyä et al. (2001) showed that after one month of VPA medication, the levels of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) increased. However, data in this area can be conflicting (Morrow and Craig 2003). Bauer et al. (2000) found no difference in the prevalence of PCOS in women using VPA or CBZ for epilepsy compared with untreated epileptic women.

Obesity is also more common in women using VPA (59 %) and obesity-associated PCOS has been thought to have an important role as a source of the menstrual disturbances in women using VPA (Isojärvi et al. 1993 and 1996). In the study of Isojärvi et al. (1993), the effects of VPA were more common in women who had received the AED medication before the age of 20.

Epilepsy, epileptic seizures and AEDs may have an effect on the hormones involved in endocrine regulation (Morrel 1998; Herzog 2006). These include an increase in prolactin levels after tonic-clonic seizures and direct effects on the hypothalamic-pituitary axis e.g. altered secretion of gonadotrophins. Conversely, these hormones may have an effect on the seizures – generally it has been considered that estrogens are proconvulsants whereas

progesterone has anticonvulsant properties (Tettenborn et al. 2002). This has been associated with a specific type of epilepsy, catamenial epilepsy, in which the seizure frequency seems to vary according to the cyclical hormonal changes during the menstrual cycle (Tettenborn et al. 2002).

CBZ and other enzyme-inducing AEDs (e.g. phenytoin (PHT) and oxcarbazepine (OXC)) which induce hepatic microsomal enzymes of the P-450 system, can evoke interactions with endogenous and exogenous hormones (Zupanc 2006). These AEDs increase steroid metabolism and affect protein binding and therefore by accelerating the metabolism of ethinyl estradiol, reduce the effectiveness of hormonal contraception. CBZ has also been reported to increase the level of SHBG in women with epilepsy which decreases the free progestin levels in the plasma (Isojärvi et al. 1996; Rättyä et al. 2001). Therefore the risk of contraceptive failure and breakthrough bleeding in women with epilepsy using AEDs is more common than in the general population and this needs to be taken into consideration when treating women with epilepsy (Tomson 2004a; Zupanc 2006).

The effects of epilepsy and AEDs on sexual functioning, have been studied in recent years. In these studies, women with epilepsy have reported sexual dysfunction more often than controls (Morrell et al. 2005). This is especially prevalent in women with localization related epilepsy (Morrell et al. 2005). In the study by Herzog et al. (2003), sexual dysfunction was more often present in women with TLE and especially right-sided TLE whereas no difference was found between women treated with and without AED treatment indicating an independent role of epilepsy in this respect. In terms of the specific AEDs, enzyme-inducers including PHT had a negative impact on sexual functioning (Morrel et al. 2005).

2.7. Epilepsy and pregnancy

2.7.1. Maternal outcome

Though the majority of the women with epilepsy enjoy uncomplicated pregnancies (Tomson and Battino 2005), women with epilepsy have been reported to have a greater risk of pregnancy complications than control women (Yerby et al. 1985; Sabers et al. 1998; Pilo et al.

2006). Some of the most frequently reported complications include toxaemia, bleeding in pregnancy, placental abruption; both induced and prolonged labour and an increase in the rate of caesarean sections. However, conflicting data concerning the adverse effects of epilepsy and AEDs on pregnancy outcome have been published, and in many of the later studies very few differences have been noted between women with epilepsy and controls with respect to pregnancy complications (Hiilesmaa et al. 1985; Yerby 1991; Morrow et al. 2003). In a Finnish study of pregnant women with epilepsy in an outpatient clinic material, pregnancy complications occurred as frequently in women with epilepsy as in controls (Hiilesmaa et al. 1985). In a recent study the rate of complications in pregnancy was increased only with respect to hypertension (not associated with pre-eclampsia) and induced delivery (Richmond et al. 2004).

Pregnancy may also have an effect on epilepsy since it may cause a change in seizure frequency, a decline in serum AED levels and changes in AED pharmacokinetics. In a recent report by the EURAP Study Group (2006) 58% of the women were seizure-free during pregnancy and the seizure frequency was unchanged in 63 % of the women. An increase in the number of seizures was observed in 17% of the women and the occurrence of seizures was independently associated with AED polytherapy and localization-related epilepsy. A similar increase in seizure frequency has been observed independently in a Swedish (Tomson et al. 1994) and an Italian study (Tanganelli and Regesta 1992), in which the increase in the seizure frequency was also associated with focal epilepsy and women with a higher frequency of seizures also in the pre-pregnancy period. In a review prepared by Tomson (1997a) it was noted that approximately 5% of women with epilepsy experience seizures during labour, delivery or immediately thereafter. Status epilepticus (SE) is of special concern at any time, but especially during pregnancy. However, SE does not occur more frequently during pregnancy and it is observed in less than one percent of pregnancies (Tomson 1997a).

Pregnancy alters many of the mechanisms associated with the pharmacokinetics of the AEDs. The serum levels of AEDs tend to decrease, most likely due to decreased protein binding, changes in the blood volume or changes in drug metabolism (Tomson 2004a). In some patients this decline of AED levels may affect the seizure frequency during pregnancy. In the study of Yerby et al. (1992), the total concentrations of several AEDs (CBZ, PHT, PB, VPA)

declined significantly during pregnancy, but the free concentrations of the drugs remained unchanged or even increased (VPA). Accordingly, Tomson et al. (1994) reported that though total plasma levels of CBZ decline during pregnancy, the free plasma levels stay the same or even increase due to decreased protein binding. The same study showed no association between plasma AED levels and seizure control during pregnancy (Tomson et al. 1994). A pronounced increase in the clearance of lamotrigine (LTG) during pregnancy has been demonstrated (de Haan et al. 2004). The fall in LTG plasma levels during pregnancy is considerably greater than that reported for other AEDs, and could result in an increase in seizure frequency thus necessitating dose adjustment. The active monohydroxy derivative of oxcarbazepine (OXC), which is mainly responsible for the drug's pharmacological effect, shares with LTG a primary route of elimination via glucuronidation and it seems to also undergo the same kind of pharmacokinetic alterations during pregnancy that are observed for LTG (Mazzucchelli et al. 2006).

In some women, the increased seizure frequency may be due to lack of compliance during pregnancy, usually due to fear of the teratogenic effects of AEDs (Tanganelli and Regesta 1992; Tomson 2004a). Although the absolute risk is low, maternal death has been estimated to be ten times higher for women with epilepsy than those in the general population (Adab et al. 2004b). Case histories suggest that these fatalities are a result of the seizures that are often associated with abrupt withdrawal of AEDs or with poor compliance. Also environmental factors e.g. sleep deprivation and anxiety during pregnancy, have been suggested as reasons for the increased seizure frequency. Adequate pre-pregnancy counseling is essential to increase the likelihood of maintained seizure control: a lack of such counseling has been identified as a major risk factor for an increase in seizure frequency during pregnancy (Lopes-Cendes et al. 1992).

2.7.2. Fetal outcome

Some of the reported fetal complications associated with maternal epilepsy are spontaneous abortion, intrauterine growth retardation, asphyxia, low Apgar scores and increased perinatal mortality, but data are often conflicting and complication rates vary between different studies (Yerby et al. 1985; Sabers 1997). In the prospective, multicenter study of Battino et al. (1999)

the overall proportion of children with low birth weight was not increased. However, the Danish prospective, cohort study of Hvas et al. (2000) reported that children exposed to AEDs were small for gestational age (SGA) and they had reduced body length and head circumference compared with unexposed children. A low birth weight was also reported by Yerby et al. (1985) in a large, population-based retrospective study. In the Swedish prospective study of Wide et al. (2000) a slight decrease in body weight was observed in infants exposed to polytherapy, in particular the head circumference was reduced in infants exposed to CBZ. Battino et al. (1999) reported that a small head circumference was associated with polytherapy and the use of PB and primidone. This smaller head circumference in a combination therapy of PB and PTH has also been reported in a retrospective analysis of Dessens et al. (2000). In the Finnish population- based prospective study published by Gaily et al. (1990a), a reduction in the head circumference was shown in children exposed to CBZ and a combination therapy of barbiturates with the difference persisting for up to five years. However, the paternal head circumference was also below the average in these two groups and the difference in the children disappeared after adjusting for paternal head circumference (Gaily et al. 1990a). Thus genetics may contribute, at least partially, to the head circumference of the AED exposed children. Pilo et al. (2006) reported that children exposed to AEDs suffer a higher frequency of respiratory distress syndrome.

Maternal seizures during pregnancy may have an adverse effect on the fetus. A decrease in fetal heart rate has been observed after maternal tonic-clonic seizures, and this has been considered to be due to changes in the blood circulation, transient lactic acidosis and asphyxia (Hiilesmaa et al. 1985). In addition, trauma caused by tonic-clonic seizure may harm the fetus. However, in the recent prospective study by Kaaja et al. (2003), maternal seizures during the first trimester were not associated with congenital malformations.

It has been thought previously that infants exposed to enzyme-inducing AEDs in utero are at a risk of having complications due to neonatal bleeding. This may be due to a deficiency of vitamin K_1 in the fetus induced by the AEDs. Therefore many guidelines have recommended vitamin K_1 supplementation (American Academy of Neurology 1998; Morrow and Craig 2003). However, in the first epidemiological study assessing the occurrence of bleeding complications in newborns, no difference was noted between controls and infants exposed to

AEDs (Kaaja et al. 2002). In a logistic regression analysis, the bleeding was associated with premature birth (<32 weeks) and alcohol abuse, but not to enzyme-inducing AEDs. Similarly, in another study from the United States, no haemorrhagic disease was observed in newborns exposed to AEDs (Choulika et al. 2004).

Perinatal mortality has been observed to be two to three times higher in infants of mothers with epilepsy compared to controls (Sabers 1997). In the study of Hiilesmaa et al. (1985), the rate of perinatal deaths was 5/150 (three stillbirths and two deaths during the first week of life). However, in the report of Annegers et al. (1988) no association was found between maternal epilepsy and the use of AEDs with any recognized foetal loss.

2.7.2.1 Major malformations

The increased risk in the rate of major congenital malformations (MCM) in children of mothers with epilepsy is well established (Samrén et al. 1997; Wide et al. 2004; Wyszynski et al. 2005). It has been related to the use of AEDs, especially to AED polytherapy during pregnancy (Kaneko et al. 1999; Richmond et al. 2004). No increase in the rate of malformations has been observed in children of mothers with epilepsy but without AED medication (Holmes et al. 2001). Also the type of maternal epilepsy has not been associated with different rates of malformations (Kaneko et al. 1988). In some AED regimens, a dose-dependent mechanism of teratogenesis has also been observed (Samrén et al. 1997).

In the prospective, multicenter study by Kaneko et al. (1999) MCMs were observed in 9.0 % of the AED exposed children compared to 3.1% of those without drug exposure. Pooled risks for MCMs in children exposed to AEDs vary from two to fourfold in different studies (Dravet et al. 1992; Olafsson et al. 1998; Canger et al. 1999; Artama et al. 2005). With respect to the individual drugs, PB, primidone and VPA, have been reported to have the highest association with malformations according to Kaneko et al. (1999). In a recent prospective Finnish study, the rate of MCMs was 3.8% compared to 0.8% in control population and the risk was independently associated with the use of CBZ, VPA, OXC, low serum folate concentration and a low maternal level of education (Kaaja et al. 2003).

Of the currently used AEDs, VPA has most often been associated with a higher frequency of malformations than other AEDs (Samrén et al. 1997; Canger et al. 1999; Wide et al. 2004). This risk of MCMs was four-fold compared to other AEDs according to the North American pregnancy registry and over 7- fold to women without AEDs (Wyszynski et al. 2005). The risk of MCMs was increased in women receiving VPA at doses of >1000mg/day compared with women receiving VPA <600mg/day indicating a dose-dependent teratogenic effect (Samrén et al. 1997). This teratogenic effect at high VPA doses (>1100 mg/day) has also been reported in the preliminary data of the Australian Pregnancy Registry (Vajda et al. 2006). However, data from the UK Register suggest that even low doses of VPA may be no worse in this respect than >200 mg/day doses of lamotrigine (Morrow et al. 2006) and suggest a dose-dependent effect of CBZ, LTG and VPA. A dose-dependent effect has been suggested also for PB in a retrospective analysis of birth register information (Samrén et al. 1999).

In a meta-analysis of the teratogenicity of CBZ, the malformation rate was 6.8 % compared to 2.34 % in controls in patients with CBZ monotherapy and this was increased up to 18.8% in polytherapy pregnancies (Matalon et al. 2002). This especially harmful effect of polytherapy has been reported in many studies (Kaneko et al. 1988; Holmes et al. 2001). In the prospective study of Kaneko et al. (1988), the frequency of MCMs was highest in the combination therapy of VPA and CBZ and/or PHT.

Perucca (2005) summarized the information of the recent malformation studies. The results of the MCM rates have varied several-fold between different studies though this is partially due to study designs and methodological differences (Perucca 2005). However, many studies have suggested that exposure to VPA is associated with a greater incidence of MCMs than other AEDs, especially at doses above 1000 mg/day (Samrén et al. 1997; Kaneko et al. 1999; Artama et al. 2005). The studies showed no consistent differences in the rate of MCMs between CBZ, PHT and PB. However, the difference in risk of MCM between VPA and CBZ was significant in three studies (Wide et al. 2004; Artama et al. 2005; Morrow et al. 2006). Figure 2 illustrates the results of five recent malformation studies and the MCM rates with different AEDs compared with CBZ.

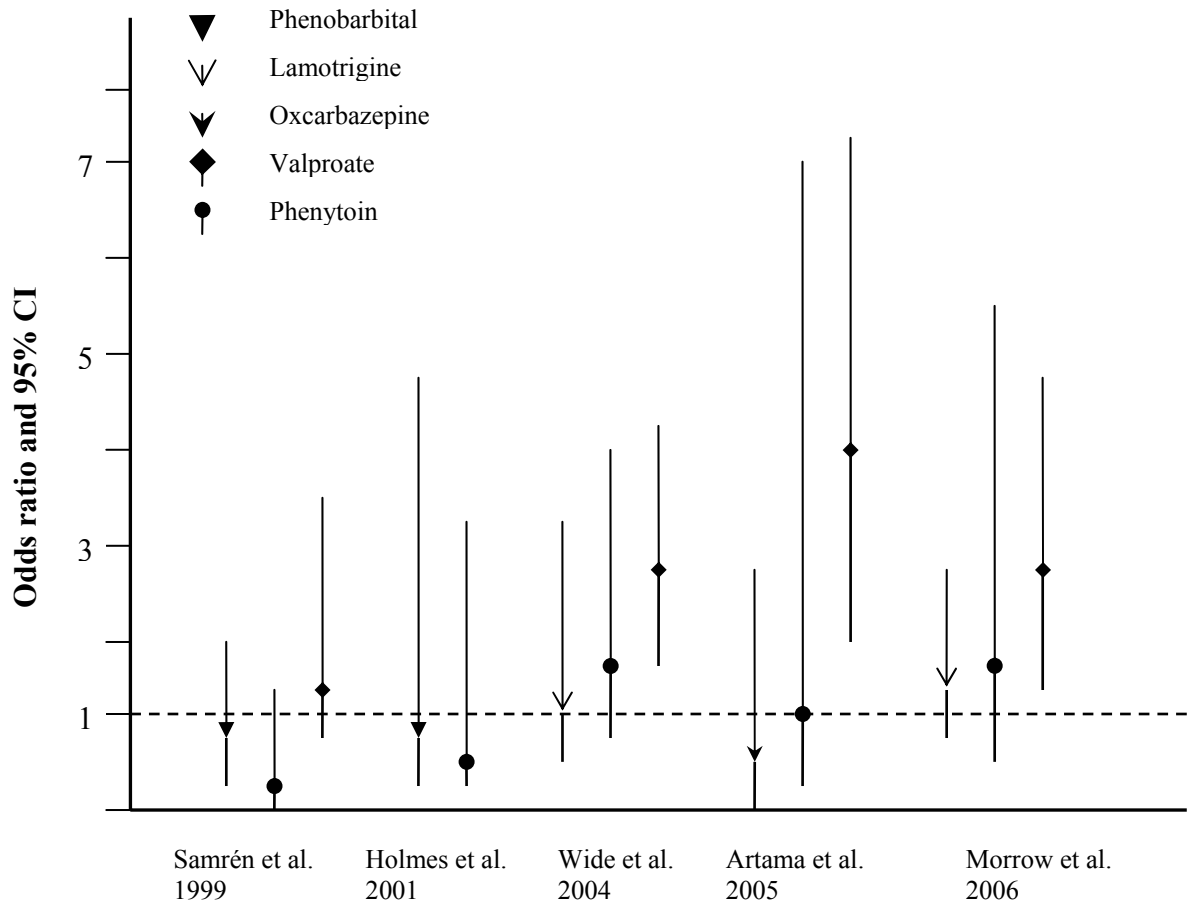

Figure 2. Odds ratios and 95% confidence intervals for major congenital malformations associated with prenatal exposure to antiepileptic drugs in monotherapy, relative to the odds ratio for malformations with carbamazepine exposure (Modified from Perucca 2005).

A variety of MCMs have been described in children exposed to AEDs e.g. spina bifida, cleft lip/palate, hypospadias, cardiac and circulatory malformations (e.g. persistent left superior vena cava), anomalies of the face and limb defects. In the international register study of Arpino et al. (2000), spina bifida was associated with VPA exposure (OR 5.7) but less often with CBZ exposure (OR 2.8). Neural tube defects were associated with the use of VPA and CBZ also in the study of Lindhout et al. (1992). PB was more commonly associated with cardiac (OR 2.2) and circulatory (OR 4.1) malformations (Arpino et al. 2000). In the meta-analysis of CBZ teratogenicity, the most frequent malformations were cardiac and urinary tract anomalies (Matalon et al. 2002).

As emphasized previously, neural tube defects e.g. spina bifida have been observed more commonly in women using AEDs (especially VPA and CBZ) compared to reference populations. A reduction in the rate of neural tube defects was noted after administration of folic acid supplementation preconceptually in the general population (Wald and Sneddon 1991). Also in normal pregnancies, without AEDs, the serum folate levels decline and in pregnant women with epilepsy the decline is even steeper (Dansky et al. 1992). Therefore, it has been recommended that women with epilepsy should receive adequate folic acid supplementation preconceptually until the end of the first trimester, though no clear association has been shown to support the belief that this strategy decreases the number of neural tube defects in infants of mothers with epilepsy (Morrow and Craig 2003; Tomson 2004b). It has also been suggested that high-dose folic acid substitution may even be seizure-provoking or may have an association with an increased risk of miscarriages but this information is still needing to be confirmed (Tomson 2004b). In a Swedish study reported by George et al. (2002), an association of low plasma folate levels and an increased risk of early spontaneous abortion was established but no association was found with high levels of folate.

When one wishes to assess the risk of MCMs in the children of epileptic mothers, AEDs (dosages and combinations) are not the only contributing factors. Genetic factors may also play a role in malformations. Malm et al. (2002) published a case report in which three sets of siblings born to mothers with epilepsy and exposed to VPA in utero were examined. All of the children in these three families exhibited fetal valproate syndrome, which strongly suggests that there is a hereditary susceptibility to valproate. Also it is likely that pharmacogenetics has an impact on the teratogenicity of AEDs. Finnell et al. (1992) studied phenytoin-induced teratogenesis. During the metabolism of PHT, oxidative metabolites are produced e.g. epoxides. Those children exposed to PHT and who developed a fetal hydantoin syndrome had lower epoxide hydrolase levels than children with PHT exposure but without malformations, emphasizing that individual genetic factors may be involved in the teratogenicity e.g. determining the activity of specific enzymes.

2.7.2.2. Minor malformations and fetal anticonvulsant syndrome

In addition to major malformations, minor malformations/anomalies (usually defined as unusual morphological features with no serious medical or cosmetic consequences to the patient) which become recognizable later in life have been found to be more common in AED exposed children (Yerby et al. 1992; Wide et al. 2000). In a prospective study by Koch et al. (1992) infants exposed to AEDs had a higher number of anomalies than children of mothers with epilepsy but without AED exposure (5.03 vs. 1.91). In children exposed to VPA, this value was even higher (8.0). However, children of fathers with epilepsy did not show more anomalies than control children (Koch et al. 1992). Also in a Swedish population-based prospective study, the number of minor anomalies was increased in children exposed to AEDs in utero, but the children had rarely more than one anomaly and no specific pattern of anomalies could be identified (Wide et al. 2000).

In a large retrospective analysis of Adab et al. (2004a), dysmorphic features were observed in 44 % of children exposed to VPA compared to 9% in children exposed to CBZ. Also in the retrospective study of Kini et al. (2006), children exposed to VPA exhibited a higher proportion of dysmorphic features compared with children exposed to CBZ and PHT. However, also 45% of the children with no AED exposure were found to have dysmorphic features indicating that single minor anomalies are common also in the general population (Kini et al. 2006). Dysmorphic features in AED exposed children have been associated with the cognitive outcome (Adab et al. 2004a; Holmes et al. 2005). In the studies of Adab et al. (2004a) and Kini et al. (2006), children with dysmorphic features and VPA exposure had lower VIQ scores than children without dysmorphic features.

In a population-based prospective study by Gaily et al. (1988a), the minor anomalies in AED exposed children were studied. The anomalies were subdivided into typical anomalies (epicanthus, hypertelorism, typical nose, long philtrum, abnormal ears, low hairline, nail hypoplasia, distal phalangeal hypoplasia, and three or more dermal arches) and other anomalies; no excess of the other anomalies were observed in these children (Gaily et al. 1988a). Some of the anomalies may also be genetically determined as they reported that also the mothers had more minor anomalies than control women. Of the many reported anomalies,

only the association between distal phalangeal hypoplasia and phenytoin has been well established (Gaily et al. 1990c).

Fetal anticonvulsant syndrome (FACS) term is often used when referring to children who have suffered adverse teratogenic effects due to AED exposure. FACS refers to a group of disorders in which malformations and developmental disorders occur in association with a characteristic facial appearance. Characteristic dysmorphic features as well as malformations have been described in children exposed to PHT, VPA and CBZ. However, the extent of developmental problems in these children is less known.

The term of fetal hydantoin syndrome was first introduced by Hanson and Smith (1975). It consisted of typical minor anomalies (e.g. epicanthus, hypertelorism and long philtrum) and included also mental deficiency, growth retardation and microcephaly. Also specific facial features have been associated with VPA exposure and a fetal valproate syndrome was described in 1984 by DiLiberti et al. In the retrospective cohort study of Kini et al. (2006), a large variety of dysmorphic features was recognized both in AED exposed children as well as in control children indicating that some of the typical FACS features are common also in the general population. However, features noted more often in valproate exposed children were medial deficiency of eyebrows, infraorbital grooves, broad nasal bridge, anteverted nose, abnormal philtrum and a thin upper lip (Kini et al. 2006). In CBZ exposed children, full cheeks with a small chin and an everted lower lip were more common (Kini et al. 2006). Moore et al. (2000) studied 57 children with FACS who were identified through the FACS Association and found that 33% of the exposed children had glue ear and up to 70% had a type of joint laxity. He also reported a similar facial dysmorphology in the exposed children as that described by Kini et al. (2006) though significant overlapping does seem to occur between different exposure groups and facial features. The study also reported a high frequency of autistic type behaviours and hyperactivity in children with FACS (Moore et al. 2000). Kini et al. (2006) reported also a correlation between valproate exposure, dysmorphic features and low verbal IQ in children with FACS. However, prospective population based studies have not revealed similar results. In the study of Gaily et al. (1988b), the majority of the AED exposed children were exposed to PHT, and no children with typical fetal hydantoin syndrome features could be identified.

Abnormal ophthalmologic findings have been reported to be more common in children with FACS (Glover et al. 2002). Of the 46 children with FACS 67% had ocular abnormalities, most commonly errors of refraction (41%). In particular myopia (50%) was common in VPA exposed children.

2.7.3. Cognitive and behavioural outcome

After the studies were published describing the immediate teratogenic effects of AEDs, the question of the long term effects of AED exposure in utero, was raised. The first systematic studies concerning the long term cognitive effects of AED exposure were conducted in the 1970´s and 1980´s. The prospective study by Gaily et al. (1988b) concluded that the children of mothers with epilepsy, most of whom had been exposed to AEDs in utero, had a lower mean intelligence quotient (IQ) than control children. Mental deficiency was observed in 1.4% of the children and borderline intelligence in 1.7% of the children (Gaily et al. 1988b). Overall, however, the prevalence of mental deficiency was the same or slightly increased in children of epileptic mothers compared with unexposed children (Gaily et al. 1988b). Koch al al. (1999) reported the results of a longitudinal prospective study. They also found that the intelligence scores were lower in AED exposed children. This deficit was associated mainly with polytherapy with primidone but the socio-economic status of the family also had an effect on the cognitive outcome of the children (Koch et al. 1999).

The effects of specific AED regimens have also been studied. In the prospective, population-based study of Gaily et al. (1988b) the majority of the children were exposed to PHT (103 children), which was also the case in the cohort study of Scolnik et al. (1994) (34 children). Gaily et al. (1988) found no association between low IQ and phenytoin exposure. Also the occurrence of brief maternal convulsions during pregnancy did not affect the cognitive outcome. In the smaller, prospective cohort study of Scolnik et al. (1994), children exposed to PHT had a lower global IQ as well as lower language developmental scores than unexposed controls. In the prospective, population-based study from Sweden, preschool-aged children with PHT exposure received lower scores in their locomotor development than control

children (Wide et al. 2004) although the number of children in PHT exposure group was rather small (N=15).

In addition to PHT, the effects of CBZ exposure on the cognitive development of the children have been studied. Gaily et al. (2004) reported the results of a large population-based prospective study of the cognitive development of CBZ exposed children at preschool- and school-age. Children with CBZ exposure did not differ from controls and they were reported to have normal intelligence. This normal intelligence in CBZ exposed children has also been reported in other studies (Gaily et al. 1988b; Scolnik et al. 1994). Wide et al. (2000) studied the AED exposed children at the age of 9 months and at that time point no difference was noted in the development of the AED exposed children (of which the majority had been exposed to CBZ) compared with unexposed controls. At preschool age the neurodevelopment of the CBZ exposed children was also reported to be normal (Wide et al. 2004).

During recent years, interest has mainly been focussed on the effects of prenatal VPA exposure on the cognitive development of the exposed children. In particular exposure to VPA was associated especially with a lower VIQ compared with other monotherapy exposures in the prospective study of Gaily et al. (2004) and also in the retrospective study of Adab et al. (2004a). A negative correlation of the VPA dose and VIQ was observed, but neither the type of maternal epilepsy nor the occurrence of generalized seizures during pregnancy, were associated with this deficiency (Gaily et al. 2004). Also in children exposed to VPA, even though the individual variation in performance has been great, a large proportion of these children have been reported to exhibit an especially low IQ (Adab et al. 2004a).

An increased risk of poorer cognitive performance has been observed in children exposed to polytherapy compared to monotherapy exposure (Koch et al. 1999; Gaily et al. 2004; Adab et al. 2004a). In the study of Koch et al. (1999), both the PIQ and the VIQ were lower in children exposed to polytherapy but in addition to AEDs, the socio-economic status of the family was also predictive of the cognitive outcome.

In addition to the effect of AEDs, many confounding factors affect the cognitive outcome of the children. Predictive factors for the low VIQ in children exposed to VPA were maternal IQ and frequent tonic-clonic seizures (Adab et al. 2004a). According to Gaily et al. (1990b) several factors were associated with the cognitive dysfunction observed in children exposed to AEDs, i.e. maternal seizures during pregnancy, partial seizures and paternal level of education. In the study of Holmes et al. (2005), a lower IQ was observed in children with AED exposure and microcephaly compared to children with AED exposure but normal head circumference. The IQ deficit was also more commonly seen in children with midface hypoplasia. The socio-economic status of the family has also been reported to affect the cognitive outcome of the children (Koch et al. 1999).

The cognitive and behavioural problems observed in children exposed to AEDs have been thought to lead to problems at school. Though the majority of the children with AED exposure attend mainstream school, a need for educational support and special arrangements regarding schooling have been reported (Adab et al. 2001). This reported risk has been especially prevalent in children with VPA exposure (Adab et al. 2001 and 2004a). Autism and related disorders as well as behavioural problems are also more common in children with AED exposure (VPA, CBZ and polytherapy) than in unexposed children (Dean et al. 2002). In the population-based, retrospective study from UK, disorders of the autistic spectrum or Asperger syndrome were diagnosed in 4.6 % (12/260) of the AED exposed children (Rasalam et al. 2005). These disorders were most common among VPA exposed children 8.9% (5/56). Dessens et al. (2000) found that adults who had been exposed to PB and PHT in utero exhibited more learning problems and mental retardation than controls. However, in this area, no true prospective, population-based studies have been conducted. The studies of Adab et al. (2001 and 2004a), Dean (2002) and Rasalam (2005) had a retrospective design and in the study of Dessens et al. (2000) the recruitment of subjects was retrospective with a subsequent prospective follow-up. These methodological shortcomings may have biased the reliability of the results.

2.8. Pregnancy management, recommendations and birth registers

Many guidelines have been given concerning the management of fertile-aged women with epilepsy. These recommendations have attempted to highlight the special concerns and provide answers to practitioners (ACOB 1997; Morrell 1998; Crawford 1999). The need of adequate pre-conception counselling for women with epilepsy is evident and emphasized also in the guidelines (Morrell 1998; Tomson 2004b). However, a prospective population based study analyzing the care of women with epilepsy reported that only 38% of the women had received pre-conceptional counselling and less than 50% of the women had planned their pregnancies (Fairgrieve et al. 2000). Therefore much work still needs to be done in order to optimize the treatment of women with epilepsy.

In order to enable rational decisions, women with epilepsy and their partners need to be counselled about conception, pregnancy, breast-feeding and caring for the infant. The avoidance of unplanned pregnancy requires the use of effective contraception. During counselling before conception, it is important to confirm the diagnosis of active epilepsy and reconsider the need for AED treatment (Kälviäinen and Tomson 2006). A woman who wishes to become pregnant and who has been seizure-free for two or more years may attempt to discontinue AEDs under supervision by her physician. The decision to withdraw medication gradually should follow the generally accepted principles for the treatment of adults with epilepsy. It will depend mainly on the level of risk that the individual patient is willing to accept. The risks include worsening of seizures, perhaps seizures that result in physical harm to the mother (and the fetus once the woman becomes pregnant). Although the risks are low, the possibility of status epilepticus and SUDEP should be discussed realistically before attempting drug withdrawal (Morrow and Craig 2003). If treatment is continued, the woman should use the most effective AED for her epilepsy type at the lowest possible dose to control seizures following the general principles for the treatment of epilepsy. The classification of the seizure and epilepsy syndrome should be re-evaluated and the appropriate medication adjusted accordingly (Kälviäinen and Tomson 2006).

The re-evaluation should be performed carefully for all patients, including those with difficult-to-treat epilepsies, to assess the possibility of improved seizure control with fewer AEDs. It is clear that some patients will still need polytherapy, but this should be limited to as few AEDs as possible. Epilepsy surgery may be an option in selected cases, e.g. in temporal lobe epilepsy, and this may eventually result in seizure control without drugs before the patient becomes pregnant (Kälviäinen and Tomson 2006). The treatment of new-onset epilepsy during pregnancy should follow the same principles as used in the non-pregnant woman.

Low folate concentrations within maternal erythrocytes have been correlated with neural tube defects in infants (anencephaly, spina bifida, and encephalocele) (Fishman 2000). Therefore, it has been recommended that women with epilepsy should have a daily intake of 0.4mg of folate from the time they commence trying to become pregnant until the twelfth gestational week (Tomson et al. 1997b). If the woman has previously given birth to a child with a neural tube defect, the recommended daily folate supplement is 4 mg for the above-mentioned period (Tomson et al. 1997b). Many guidelines recommend higher doses of folate (4-5mg/day) also for women being treated with valproate or carbamazepine (AAN guidelines 1998). However, in this population, the documentation for any benefit of high-dose folate supplementation is lacking and unknown adverse events of high-dose folate supplementation cannot be excluded. In Finland, therefore, 1 mg supplementation has been used, which is also convenient for patients, as they only have to take one tablet per day and because the duration of supplementation may last for as long as several years in some patients.

Ideally, drug levels should be obtained before pregnancy for comparison with the concentrations to be monitored during gestation. For highly protein bound AEDs, such as VPA and PHT, unbound levels are preferred. Drug level monitoring is most important for AEDs that may undergo major alterations in their active concentrations, e.g. PHT and in particular LTG, and for AEDs with unknown effects of pregnancy. Whether a decline in drug concentrations *per se* should prompt dosage adjustments is still controversial, but this kind of strategy appears to be justified, at least for LTG (Kälviäinen and Tomson 2006). Otherwise dose adjustments are made according to the level of seizure control.

All women with epilepsy who become pregnant should be referred to a specialist maternity unit and at least structural ultrasound should be performed. Most women will have a normal uncomplicated vaginal delivery, however, tonic-clonic seizures may result in fetal hypoxia. Therefore it is generally recommended that delivery takes place in a unit equipped with facilities for both maternal and neonatal resuscitation (Morrow and Craig 2003).

AED levels quickly revert to pre-pregnancy levels after the delivery. Hence, if the dose of an AED has been increased during pregnancy because of falling AED-levels or seizures during pregnancy, it may be useful to measure plasma levels at 2-4 weeks after the delivery and make any necessary dosage adjustments. All women with epilepsy should be encouraged to breastfeed their babies (Crawford 1999; Morrow and Craig 2003). The AED concentration profiled in breast milk follows the plasma concentration curve. The total amount of drug transferred to infants via breast milk is usually much smaller than the amount transferred via the placenta during pregnancy.

In Kuopio University Hospital, maternity and epilepsy clinics are jointly following up all women with epilepsy during their pregnancy with a pre-decided protocol (Table 2).

Table 2. Current follow-up protocol for pregnant women with epilepsy in the Kuopio University Hospital area (Kälviäinen 2004).

Pre-conceptional counselling	• Counselling for contraception until pregnancy is desired • Seizure-free patients - Discussing the possibility to withdraw AED treatment considering the risks • Most patients - Optimizing AED treatment according to seizure type and syndrome and counselling about teratogenicity • Prescription of folic acid before conception (1mg/day) until the end of 12th gestational week
Pregnancy	Visit both to epilepsy and maternity clinics (preferably on the same day)
1st trimester (~ week 11)	Information to the mother about pregnancy, delivery and breast-feeding Seizure control and AED medication, motivation for treatment Laboratory test – liver enzymes, blood count, AED plasma level measurements Ultrasound of the fetus (maternity clinic or personal physician)
2nd trimester (~ week 19)	Structural ultrasound of the fetus in the maternity clinic Seizure control and AED treatment Risks of AED treatment to the fetus Laboratory test (if needed)
3rd trimester (~ week 27)	Seizure control, AED treatment Laboratory test (if needed) Follow-up ultra-sound and examination in the maternity clinic
after week 36	Follow-up in the neurological clinic if needed Obstetric follow-up continues individually
After delivery	If seizure free during pregnancy – control visit 9-12 months after delivery If AED dosages change during pregnancy – adjustments of the AEDs according to plasma levels and clinical symptoms 2-4 weeks after delivery Review of AED treatment and contraception Encourage preconceptional care for future pregnancies

Optimal AED treatment is essential not only during pregnancy in view of the recognized adverse effects of AEDs but also the threat of seizures, if left untreated. The need for information on the effects of the older and newer AEDs is essential. To achieve this purpose many international birth registries have been established to gather details of the effects of AEDs (Beghi et al. 2001). Current registries include for example EURAP, the UK Epilepsy and Pregnancy Register, Australian Pregnancy Registry and North American Antiepileptic Drug Pregnancy Registry (Holmes et al. 2004; Russel et al. 2004; Tomson et al. 2004c; Vajda et al. 2004). In the majority of these registries, information has been gathered prospectively, which hopefully will provide a source of unbiased information on the adverse effects of AED treatment and will help to improve the future treatment of women with epilepsy.

3. AIMS OF THE STUDY

3.1. To determine the proportion of WWAE having children and to investigate factors related to fertility in women using VPA and CBZ

3.2. To compare the course of pregnancy, delivery and pregnancy outcome in WWAE and in the general pregnant population

3.3. To evaluate the possible effect of vigabatrin (VGB) treatment in utero to the visual function in the offspring

3.4. To investigate the cognitive performance of school-aged children exposed to VPA in utero compared to children exposed to CBZ as well as to children without AED exposure

3.5. To assess the neurological development, behavioural aspects and additional educational needs in children exposed to VPA in utero compared to children exposed to CBZ as well as to children without AED exposure.

4. SUBJECTS AND METHODS

4.1. Subjects

4.1.1. Study I

All pregnancies in the Kuopio University Hospital (KUH) area (population 250 000) since 1989 have been prospectively registered in the Birth Register of the Department of Obstetrics and Gynaecology. The term pregnancy is used when the gestational age is over 22 weeks or the birth weight over 500 gr. From this register, we retrieved all women who had a diagnosis of epilepsy in the data of the pregnancy registry and had been residents in the KUH area. Our study period was from January 1989 to October 2000 and during this period of time a total of 85 women with active epilepsy (WWAE, women who had epilepsy and had used AED medication during conception and throughout the pregnancy) had a singleton pregnancy (127 pregnancies) and 38 women who had a history of epilepsy but needed no AED medication during pregnancy (52 pregnancies). At the same time, 16505 women without epilepsy (24778 pregnancies) had given birth. In the study group of 85 WWAE, 20 subjects had used VPA monotherapy during their pregnancy and 49 had received CBZ monotherapy. When multiple pregnancies were included, the numbers were 87 WWAE and 18146 control women.

During same time period (1989-2000), 130 fertile-aged (18-40 years) women who had used VPA monotherapy and 316 women who had used CBZ monotherapy and were residents of the KUH area had visited the outpatient clinic of the Department of Neurology. To assess the fertility aspect more thoroughly, we reviewed the medical records of these 130 women with VPA monotherapy and selected 130 women with closest birth date and CBZ monotherapy as controls.

4.1.2. Study II

In study II we examined the pregnancy outcome of the 85 WWAE compared to the outcome of the 38 women with a history of epilepsy but without AEDs and also compared these to the general population. The WWAE had given birth to 127 children and the other 38 women to 52 children. Multiple pregnancies and major chromosomal anomalies were excluded from the pregnancy outcome analysis. As a control group we used all the pregnant women who had been registered to the Birth Register but who did not have epilepsy and had a singleton pregnancy (16505 women and 24778 pregnancies). See Figure 3 for study populations.

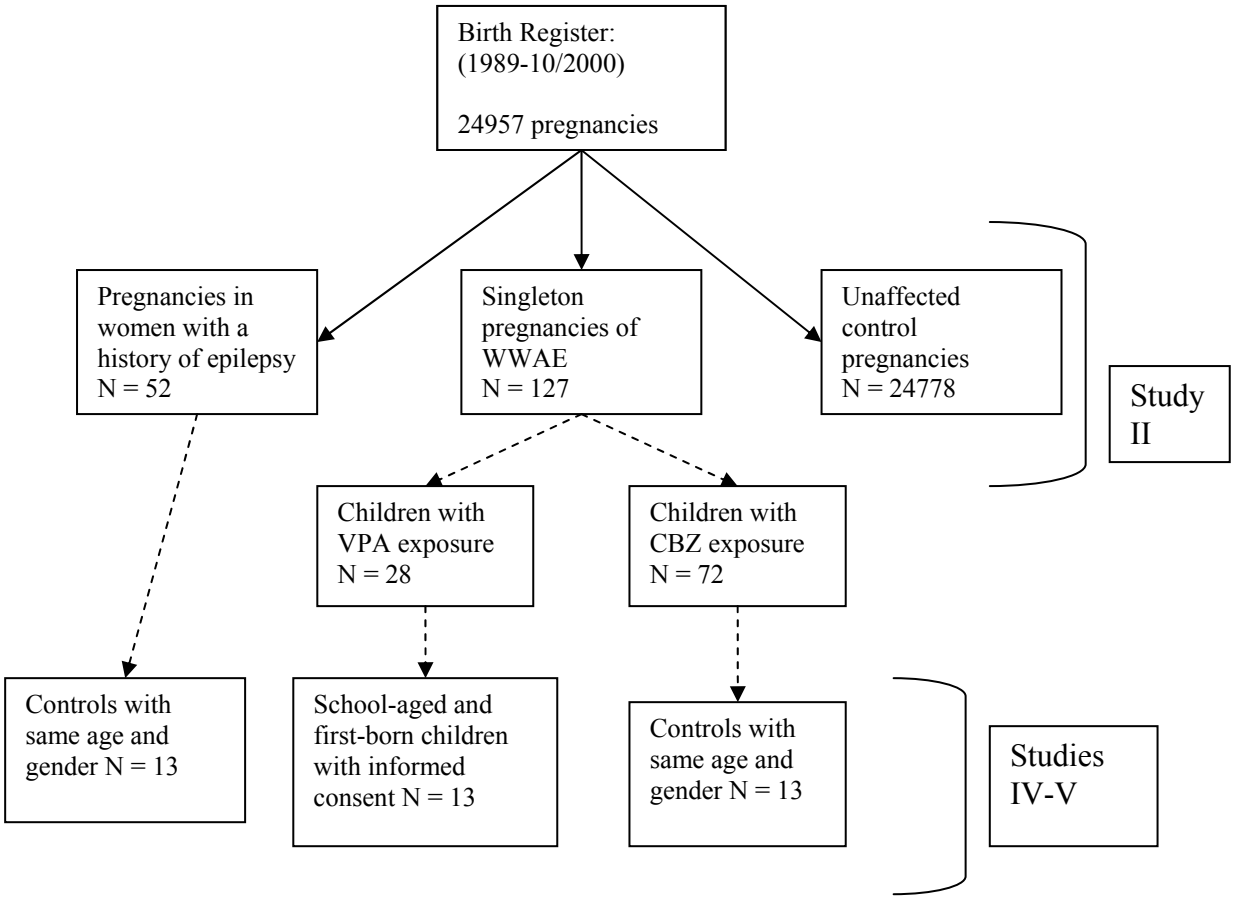

Figure 3. Study populations

4.1.3. Study III

From the Birth Register we were able to identify three women who had used VGB during pregnancy and four children who had been exposed to the drug. Of the four children exposed, we were able to examine two at school age to search for possible structural malformations and visual dysfunction.

4.1.4. Studies IV-V

All women who had epilepsy and had used VPA monotherapy during pregnancy were identified from the Birth Register. To investigate the effect of VPA exposure on the children, we examined the children at school age (≥ 6 years old). Out of the 28 VPA exposed children, 16 were school-aged and first born during the study year (2003). Thirteen children participated in this controlled study, and also their mothers were examined. The controls were selected from the Birth Register children with the closest birth date and the same gender as the VPA exposed children. Thirteen control children were exposed to CBZ and 13 children had no AED exposure, but their mothers had a history of epilepsy.

4.2. Methods

4.2.1. Kuopio University Hospital Birth Register and register data used for fertility assessment (Studies I-II)

The Kuopio University Hospital Birth Register contains comprehensive information regarding the background of the mother, risk factors, course of the pregnancy and pregnancy outcome. This information has been gathered to the register by questionnaires, which are sent to every mother during their pregnancy. These questionnaires are returned to the maternity clinic of KUH before the delivery and supplemented with information from the follow-up of the pregnancy, delivery and pregnancy outcome at the delivery unit of KUH. From this register, we obtained demographic data of the mothers and the information about the management and course of the pregnancy as well as the data of the outcome of the pregnancy. Also the medical records of the WWAE were reviewed and Birth Register information was supplemented with

the neurological data retrieved from medical records (e.g. the type of epilepsy, onset of epilepsy, frequency of seizures, AED medication). The WWAE had been followed up according to the pre-decided protocol (Table 2) jointly by the epilepsy and maternity clinics in KUH.

To assess the overall fertility among women with epilepsy, we reviewed the medical records of our Neurology outpatient clinic between years 1989 and 2000. We reviewed the medical records of the 130 women with VPA monotherapy and of 130 women with CBZ monotherapy with the closest birth date. From the medical records, we obtained information concerning the number of children, hormonal disturbances (if any noted) and co-morbidities. We also looked for any available reasons for not having children. No structured interview for the women was used.

In addition to information obtained from the Birth Register and medical records of the women studied, we retrieved epidemiological information from the Statistics Finland and from STAKES (National Research and Development Centre for Welfare and Health). According to Statistics Finland, 23% of Finnish women did not have children in the year 2000. To confirm the number of women having active epilepsy and using AED medication in KUH area, we assessed information obtained from the Social Insurance Institution of Finland (KELA). Overall, 286 women (16-39 years) in KUH area had active epilepsy in year 2000. The registry of STAKES provided information of fertile-aged women (16-39 years) (N = 36261) living in the same hospital area at the same time (in the year 2000).

Premature delivery was defined as delivery before gestational week 37, and prolonged pregnancy as lasting longer than week 42. Small-for-gestational-age newborns were below the tenth percentile according to the normal tables of our population when adjusted for the gestational age and sex. Infants with birth weight less than 2500g were considered to have low birth weight. Fetal distress term was used when fetal venous pH was <7.15 and/or Apgar scores at 5 minutes were <7 after birth. Major malformations were defined as structural abnormalities with surgical, medical or cosmetic importance identified by a pediatrician at birth and at discharge from hospital.

4.2.2. Assessment of the AED exposed children

4.2.2.1 Study III

The medical records of the mother and children exposed to VGB were reviewed with respect to medication, seizures and neonatal information. A paediatric neurologist performed a thorough examination of the children and an ophthalmologist examined both the mothers and the children for any visual dysfunction. Visual acuity as well as visual fields were examined. A standard ophthalmologic evaluation was performed to exclude other eye diseases. The ophthalmologic examination consisted of a history of visual symptoms, testing the best corrected visual acuity, phorias and tropias, biomicroscopy, and indirect ophthalmoscopy with the aid of tropicamide 0.8% + phenylephrine 5% drops. Intraocular tension was measured with the Goldmann applanation tonometer. Visual fields were examined with the kinetic Goldmann perimeter.

4.2.2.2 Studies IV-V

The 13 children exposed to VPA *in utero* and their age- and gender matched controls were examined and interviewed in the facilities of Clinical Research Center of Kuopio University. They were first examined by a pediatric neurologist and then underwent a detailed evaluation of neuropsychological functioning supervised by a psychologist lasting for 2 hours. Both the pediatric neurologist and psychologist were blinded to the medical history and the drug exposure of the children and mothers. The medical records of the children and their mothers were reviewed and all relevant information concerning e.g. pregnancy and delivery, the type of epilepsy and the use of AEDs and/or other medications, seizures before and during the pregnancy, the pre-, peri- and postnatal details of growth and possible problems in neurological development of the child were all recorded. The medical information was combined with the information from the Birth Register and with the data from the clinical and neuropsychological examinations.

4.2.2.2.1 Neurological evaluation

The neurological functioning of the children was assessed by using Touwen's test (Touwen 1979). This standardized examination was used to detect any possible minor neurological dysfunctions of the child and to exclude other neurological diseases that could influence the results of the cognitive and neuropsychological evaluation. The results of the examination in Touwen's test are represented in six subsystems: sensorimotor function, posture, balance, physical coordination, fine-finger dexterity and dyskinesia. Mild neurological dysfunction is determined to be present if there are deficits in one or two of the categories and severe (neurological impairment) if deficits are seen in over two categories. Minor dysmorphic features were evaluated during the neurological evaluation from a checklist for dysmorphic features and the results were based on blinded, but individual, non-controlled clinical evaluation by a paediatric neurologist. Dysmorphic features were defined as unusual morphological features with no medical importance of cosmetic consequence to the patient. We individually sought facial anomalies (epicanthal folds, hypertelorism, flat nasal bridge, long philtrum, midface hypoplasia, cleft lip or palate and other noted abnormalities of the face) and abnormalities of the hand (finger and nail hypoplasia). Other observed anomalies e.g. of the skin and joints, were also recorded if noted.

4.2.2.2.2 Neuropsychological evaluation

The general cognitive function of all mothers was evaluated with the Wechsler Adult Intelligence Scale (WAIS, Wechsler 1955) or WAIS- Revised (Wechsler 1981). Full scale intelligence Quotient (FIQ), verbal IQ (VIQ) and performance IQ (PIQ) were estimated on the basis of six subtests: Information, Similarities, Digit Span, Digit Symbol, Picture Completion and Block Design.

The children underwent individual neuropsychological assessments using the Wechsler Intelligence Scale for Children III (WISC-III; Wechsler 1991) and the NEPSY, a Developmental Neuropsychological Assessment (Korkman, Kirk and Kemp, 1998). Scores for FIQ, for VIQ and for PIQ were estimated in the same way as WAIS. Low intelligence was determined to be present if the FIQ score was less than 80 and exceptionally low intelligence

if the score was <70. Eight subtests of the NEPSY evaluating five cognitive domains were administered: the Tower from Attention and Executive functions; Comprehension of Instructions and Verbal Fluency from the Language domain; Visuomotor Precision from the Sensorimotor domain, and Arrows from the Visuospatial domain. In addition, from the Memory and Learning subtests, Memory for Faces, Narrative Memory and List Learning were administered.

4.2.2.2.3 Behavioural assessment

The Conners' Teacher Rating Scale – questionnaire (CTRS) was sent to every family and after it was completed by teachers it was sent back for a further analysis of the behavior of the child. The rating scale consists of (56) individual questions scored from zero (definitely not) to three (definitely true). These individual questions were further categorized into 13 different domains according to the Conners' manual. These categories are Oppositional, Cognitive Problems/Inattention, Hyperactivity, Anxious-Shy, Perfectionism, Social Problems, Conners' ADHD Index, Conners' Global Index: Restless-Impulsive, Conners' Global Index: Total, DSM-IV: Inattentive, DSM-IV: Hyperactive-Impulsive and DSM-IV: Total. The raw scores of the rating scale were then transformed into standard points, which permitted a comparison between children of different ages and sexes.

4.2.3. Statistical analysis

The SPSS statistical package (Ver. 9.0-13.0) was used for statistical analysis. In all of the studies, t-test was used for normally distributed continuous variables and chi-square for dichotomous variables. Fischer's exact test was applied when the expected count was less than five. Confidence intervals of 95% were used and P-values <0.05 were considered as being statistically significant. Multiple logistic regression analysis, BMDP, was used to evaluate the effect of maternal risk factors on the pregnancy outcome in Study II. The pregnancy outcome variables were adjusted for all significant or nearly significant maternal risk factors ($p<0.1$). In study IV for the comparison of the cognitive level of mother-child pairs, the IQs were classified into categories of cognitive ability levels according to standard

deviation units above and below the mean. In studies IV-V, Kruskall-Wallis test was used for continuous variables.

4.2.4. Ethics

This study was approved by the ethics committee of the Kuopio University Hospital and Kuopio University. Informed consent was obtained in study III-V from the mothers and those children who could understand the meaning of consent.

5. RESULTS

5.1. Epilepsy and female fertility (Study I)

The average number of children in WWAE was 2.1 ± 1.3 and in healthy pregnant population 2.2 ± 1.2 (p=0.6, NS). In KUH area, 4.7 per 1000 pregnancies (0.47%) involved a mother with active epilepsy. At the same time, 0.79 percent of the fertile-aged population in KUH area had active epilepsy and according to these numbers (0.47/0.79) 60% of women with active epilepsy had given birth to a child. In Finland, 77 % of women have children according to Statistics Finland (2005).

The menstruation cycle was regular in 85 % of controls and in 83 % of WWAE. No difference was noted in the time needed to become pregnant between WWAE and controls (4.7 months vs. 5.4 months, median 2 months in both groups). Overall 7.6 % of the control women had used some form of fertility treatment, in WWAE, the equivalent figure was 4.7% (NS) and none of the women in valproate group had used treatment for infertility.

Of the 118 women with VPA monotherapy attending the neurology outpatient clinic, 61 women (52 %) had given birth to a child with the respective figures for those with CBZ medication being 66 and 58 %. Figure 4 shows the stated reasons for not having children for WWAE with the most frequently used monotherapies (data for CBZ and VPA patients combined). No significant differences were noted between women using VPA and CBZ in the studied variables.

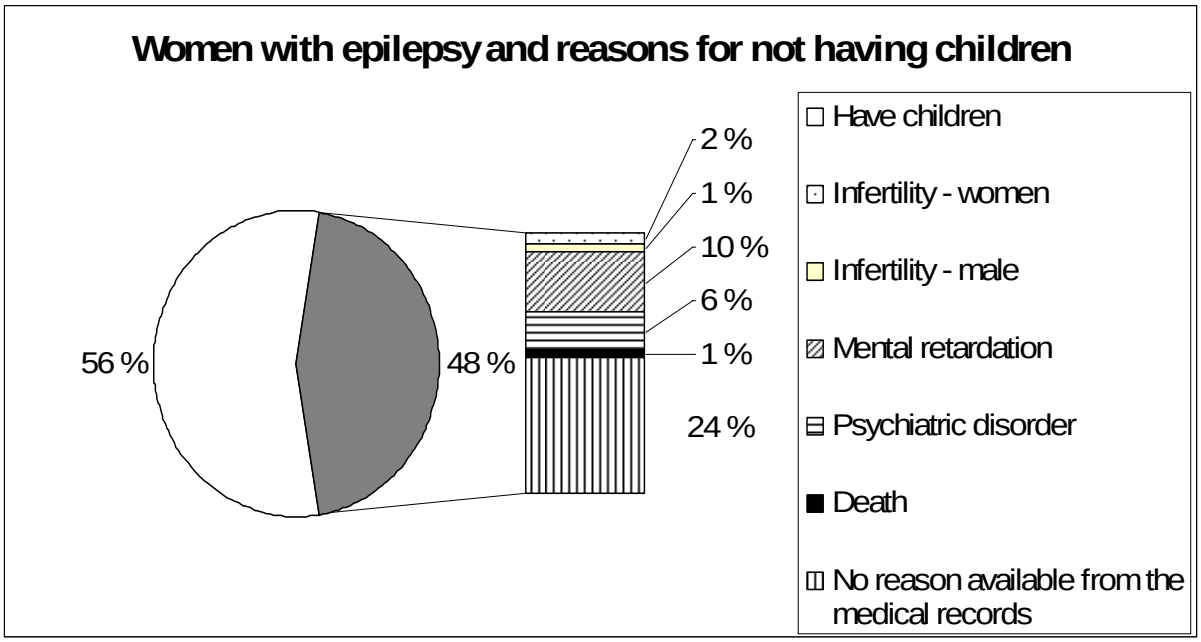

Figure 4. Women with active epilepsy with monotherapy on either carbamazepine or valproate, and stated reasons for not having children.

5.2. Epilepsy and pregnancy (Study II)

Women with active epilepsy gave birth at the age of 29 ± 5 years as did the controls. Monotherapy was in use in most pregnancies (104/127, 82%), duotherapy in 20 cases (16 %) and polytherapy with 3 drugs in 3 cases (2%). In the majority of the pregnancies, CBZ (72/127) 57% and VPA (28/127) 22% monotherapies were in use. Adequate folic acid substitution was used in 26 pregnancies (20%).

The seizure type was partial with and without secondary generalization in most patients (68%) and generalized (e.g. absence or myoclonic seizures) in 14% of cases, and the exact type of seizures could not be determined in a minority of the (15%) cases.

The majority of the mothers were seizure-free during the pregnancy (80/127, 63%) and 47/127 (37%) experienced seizures during pregnancy. In all, 56% of the patients did not experience any change in their seizure frequency and 27% had encountered a change for better (83% no change or change for better). A change for the worse in seizure control

occurred in 18% of the pregnancies but no specific reason, which could explain this exacerbation of seizures, was found. One woman had a status epilepticus (SE) during both her pregnancies and another woman experienced a flurry of seizures and a cesarean section was performed during the premonitory phase of SE.

The study populations were similar with regard to the maternal risk factors and pregnancy complications. There were no statistically significant difference in the duration of the pregnancy in WWAE 280 ± 14 days, in women with non-active epilepsy 280 ± 13 days and in the control group 278 ± 16 days.

The odds ratios for selected pregnancy outcome variables between study groups are presented in Figure 5. A significant number of the children of WWAE were found to be small for gestational age (SGA), but no differences were found in the number of newborns with low birth weight. No difference was noted in the AED medication or seizure frequency during pregnancy in the mothers of SGA children. However, the mothers with SGA children seemed to be shorter than mothers without SGA children (161.4 ± 6.4 cm vs. 164.9 ± 5.7 cm, $p<0.05$). Apgar scores at 1 minute in children of WWAE were low, but no longer at the age of 5 minutes. Accordingly, the admissions for neonatal intensive unit or to neonatal ward were significantly ($p=0.01$) more prevalent in children of WWAE (N=17, OR 1.98, 95% CI 1.17-3.34).

In the VPA group, 11/20 (55%) deliveries were induced compared to 16.7 % of the control women, $p<0.0001$. The CBZ group did not differ from controls in this respect. Identified reasons for the induction were postmaturity (3 pregnancies), pre-eclampsia (2), abnormal fetal cardiotocography (2), absent or uncoordinated contractions (2) and social reasons (2).

The frequency of major malformations was 4.8% (95% CI -0.6-10.2) in the children of WWAE, while no major malformations were found in the children of women with a history of epilepsy but who were not using AEDs during pregnancy. The malformations are described in detail in study II. All children with the malformations had been exposed to polytherapy or high-dose monotherapy with VPA or CBZ.

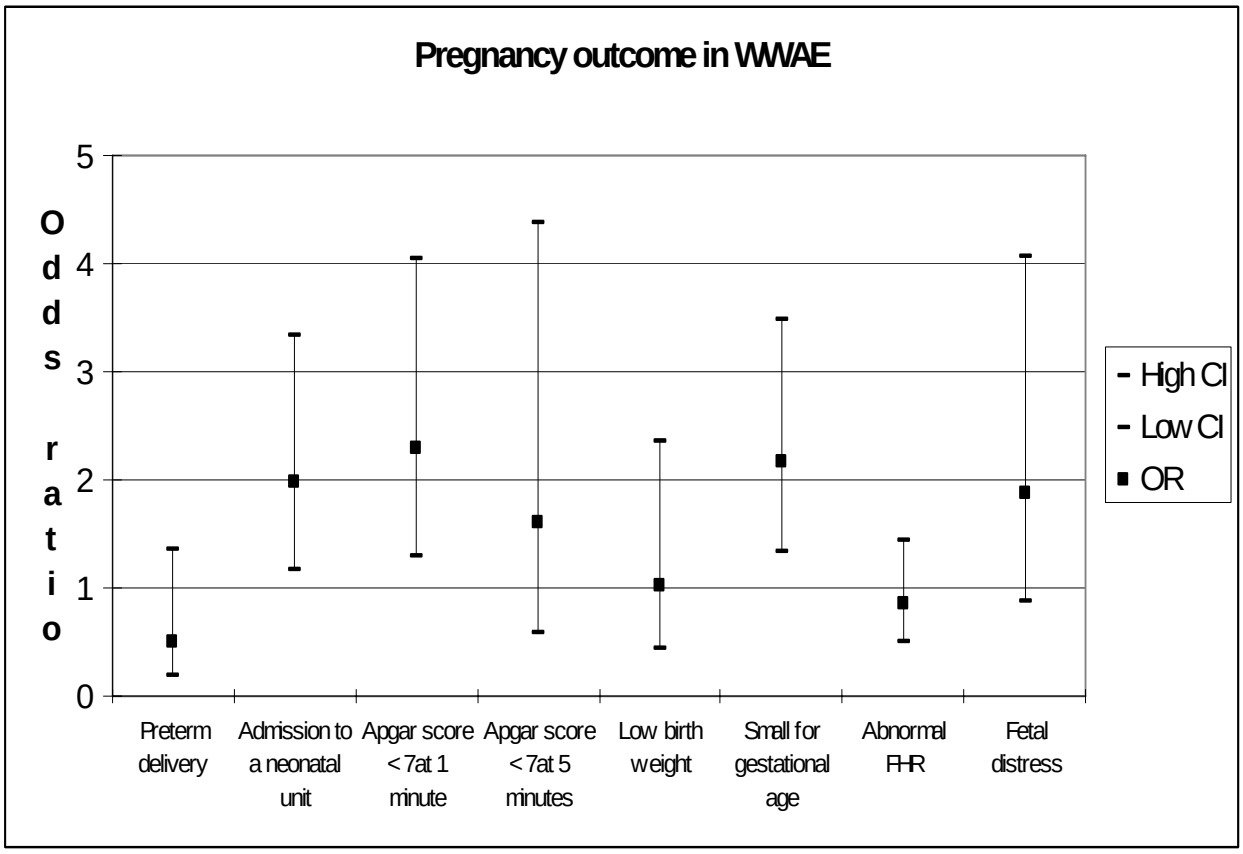

Figure 5. Pregnancy outcome variables of women with active epilepsy (adjusted for maternal age >35 years, pregravid body mass index >25kg/m^2 and unemployment of the mother).
(FHR = fetal heart rate, CI = confidence interval, OR = odds ratio)

5.3. Children and mothers exposed to vigabatrin (Study III)

There were two mothers who had used polytherapy (CBZ and CBZ + VPA) with VGB during pregnancy. The total dose of VGB in the first mother 190g was during the pregnancy and 370g in the second mother. In the two exposed children, no ophthalmologic structural abnormalities were detected. Visual field testing was unreliable and therefore visual dysfunction could not be assessed.

5.4. Neurological assessment of the exposed children at school-age (Studies IV-V)

In the standardized neurological evaluation of the Touwen's test, neurological dysfunction was found in 8/39 (20.5%) of the studied children (5 VPA, 1 CBZ and 2 no AED). Two of the VPA exposed children had autistic and regressive behavioral features which were suggestive of low intelligence and three had developmental verbal dysfunction and one of them had also difficulties in tasks related to co-ordination of extremities and fine motor functions. The one CBZ exposed child had learning difficulties. In the group of no AED exposure, one child had delayed development of expressive speech and the other exhibited dysfunction in fine motor, balance and co-ordination.

Both the need of additional educational support in school and the need for rehabilitation (e.g. speech therapy) were increased in children exposed to VPA compared to either those with CBZ exposure or those with no AED group. In all, 5/8 (63%) of the children in VPA group needing additional educational support had subnormal intelligence whereas the other 3/8 (37%) had average intelligence. A summary of the neurological findings of the children are described in Table 3.

Table 3. Summary of the neurological findings of the AED exposed children at school-age.

	Touwen's test N (%)		Minor dysmorphology N (%)		FIQ N (%)			Rehabilitation N (%)		Educational support N (%)	
	normal	NI	+	-	normal	<1 SD	<2 SD	+	-	+	-
VPA	8(62)	5(38)	8(62)	5(38)	8(62)	3(23)	2(15)	4(32)	9(69)	8(62)	5(38)
CBZ	12(92)	1(8)	3(23)	10(77)	11(85)	2(15)	0	0	13(100)	2(15)	11(85)
No AED	11(85)	2(15)	3(23)	10(77)	13(100)	0	0	1(8)	12(92)	2(15)	11(85)

NI = neurological impairment, FIQ = full intelligence quotient, SD = standard deviation, Minor dysmorphology ≥ 1 minor anomalies

5.5. Neuropsychological assessment of the exposed children (Studies IV-V)

In the neuropsychological evaluation of the children, all children with no AED exposure and almost all of the children exposed to CBZ could perform adequately in the subtest of NEPSY and scored within one S.D. from the mean. Two to four children of the VPA group could not perform all of the NEPSY subtests. Those children who could perform adequately scored statistically significantly lower in the subtest of Memory for Faces ($p= 0.016$ compared to CBZ) and in the List Learning subtest ($p= 0.008$ compared to no AED exposure group). The scores of the neuropsychological tests are reported in study IV.

Table 4 shows the results of the WISC scores in children and WAIS scores of the mothers. Mothers with VPA had a significantly lower IQ and educational level than women using CBZ and women without AED exposure. Also children exposed to VPA had a trend towards lower IQ scores than the other children, though this difference did not reach statistical significance. Also in the different WISC subtests, the VPA exposed children scored lower than the other children. Two of the children with VPA exposure had exceptionally low intelligence (FIQ<80) while their mothers had average intelligence. Children with CBZ exposure did not differ from controls and had normal intelligence. Also the mothers using CBZ had IQ scores similar to controls. The values of the WISC subtest scores are reported in detail in study IV.

Table 4. Intelligence quotients of the mothers and children not exposed to antiepileptic drugs (No AED), exposed to carbamazepine (CBZ monotherapy) and exposed to valproate (VPA monotherapy) and level of education (years) in mothers

AED groups	**No AED** (N=13)	**CBZ monotherapy** (N=13)	**VPA monotherapy** (N=13)	**All** (N = 39)	**p-values**
WAIS IQs, education					
Mean maternal FIQ (95% CI)	108.8 (105.0-112.5)	109.2 (102.0-116.4)	95.6* (89.5-101.8)	104.5 (100.8-108.2)	0.003**
Mean maternal VIQ (95% CI)	107.5 (101.3-113.8)	105.1 (96.8-113.4)	92.9* (85.8-100.1)	101.1 (97.5-106.2)	0.012*
Mean maternal PIQ (95% CI)	109.5 (105.1-113.9)	112.5 (105.1-119.9)	99.5* (92.4-106.7)	107.2 (103.3-111.0)	0.022*
Maternal education years (S.D.)	14.2 (2.3)	14.8 (2.2)	12.5* (1.9)	13.8 (2.3)	0.035*
AED exposure groups	**No AED** (N=13)	**CBZ (**N = 13)	**VPA** (N = 13)	**All** (N = 39)	p-values
WISC-III IQs					
Mean FIQ children (95% CI)	99.6 (95.0-104.3)	98.9 (91.2-106.5)	84.5 (69.4-99.7)	94.3 (88.6-100.1)	0.157 NS
Mean VIQ children (95% CI)	98.2 (91.2 -105.2)	96.5 (86.9-106.0)	85.1 (70.2-99.9)	93.7 (87.2-99.3)	0.269 NS
Mean PIQ children (95% CI)	102.1 (94.1-110.0)	102.5 (93.7-11.4)	84.7 (68.4-101.0)	96.4 (89.8-103.1)	0.071 NS

5.6. Behavioural assessment (Study V)

Conners' Teacher Rating Scale was used to detect possible behavioural problems in these school-aged children. Children exposed to VPA received generally higher scores in all of the analysed domains but due to small number of patients, these differences did not reach statistical significance. However, in two of the categories (social problems, p=0.07 and cognitive problems/inattention, p=0.09) the VPA-exposed children showed a tendency towards more behavioural problems. Children with CBZ and no AED exposure had very similar scores and no statistical differences were noted between these two groups.

5.7. Dysmorphic features and the overall neurocognitive development

Dysmorphic features were seen in 8 children (62%) exposed to VPA and in three children (23%) in both the CBZ and the no exposure group ($p = 0.085$). Four of the thirteen VPA exposed children (31%) had 2 or more of these features. All the children in CBZ group had only one minor dysmorphic feature and one child in the no exposure group had two features. If the AED exposed children were summed together (VPA + CBZ) 11/26 (42 %) had dysmorphic features compared to 23 % (3/13) in children with no AED exposure. The most frequently observed features were flat nasal bridge, long philtrum and thin upper lip, epicanthal folds and short fingers.

The overall performance of the AED exposed children was evaluated to obtain a comprehensive view of their neurodevelopment. The results of the Touwen's test, FIQ, dysmorphic features, additional educational support, need for therapies and Conners' Global Index scores were grouped together. If all of the results fell in the normal range, the children were categorized as having normal neurodevelopment, minor dysfunction if performance in one or two of the categories was abnormal and as neurologically impaired if problems were seen in more than two categories. All of the children exposed to VPA had minor or major neurological/cognitive problems. The majority of the children exposed to CBZ and without AED exposure had normal performance or only minor problems.

6. DISCUSSION

This study consists of five individual scientific papers which focus on (1) the fertility of WWAE in the area of Kuopio University Hospital and the effects of co-morbidities and AEDs on fertility, (2) the management and outcome of the pregnancies of WWAE, (3) the effect of VGB exposure on visual function, (4) the long-term cognitive and (5) behavioral development of the AED exposed children. Information of WWAE was obtained from the Birth Register of KUH and from the records of the Neurology Outpatient Clinic covering the hospital district providing a population-based, comprehensive data of the pregnancies. This prospective, population-based study of the AED exposed children has provided valuable information for the monitoring of the cognitive effects of AEDs.

6.1. Fertility

In our population, 60% of women with epilepsy had children compared to 77 % of unaffected women. We believe that the most important factor explaining this 22% difference is the higher number of co-morbidities (mental retardation and psychiatric disorders) observed in women with epilepsy; they accounted for 15 to 18 percent in our study in monotherapy population with well-controlled epilepsy and up to 29 % in the study of Forsgren (1992). In our study, approximately 20% of women did not have any recognized or reported reason for not having children. This number was identified from the medical records and therefore may include a bias in that the women may not have told the physician the real reason for not having children. However, we believe that this bias is not significant because these women were mainly seen in our hospital at regular intervals and any infertility problems would be treated mainly at KUH. Also the proportion of women not having children is fairly close to that found in the general population (23% of women not having children) when the influence of co-morbidities is excluded.

The majority of the studies concerning fertility in women with epilepsy have reported a decreased fertility (Webber et al. 1986; Wallace et al. 1998). In these studies however, the higher prevalence of severe co-morbidities in women with epilepsy compared to controls was not taken into consideration. Severe co-morbidities e.g. mental retardation will independently

affect the patient's social environment and her possibility to have children. In the population-based study by Olafsson et al. (1998b), the fertility rate was the same in women with epilepsy and controls and the fertility was reduced only in women with epilepsy together with a severe co-morbidity e.g. cerebral palsy or mental retardation. These co-morbidity rates have been studied by Forsgren (1992) showing that in both women and men with epilepsy, the percentage of coexisting diseases/disabilities is as high as 47%, with contribution of mental retardation being 23% and severe psychiatric condition being 6%.

Our findings are in concordance with the results of Olafsson et al. (1998b) and the research of Artama et al. (2004) where the fertility rate in women with epilepsy was 0.88 of the reference population. In addition, we found no difference in the time needed to become pregnant or in the need for fertility treatments between WWAE and controls. No significant changes were observed in the regularity of menstrual cycles, in the marriage rate or in the mean number of infants. Also, no significant differences were noted between women using VPA those using CBZ in terms of fertility or menstrual disturbances. Tettenborn et al. (2002) also concluded that there are misconceptions in relation to fertility in women with epilepsy and that these women do not have markedly reduced fertility compared to controls.

6.2. Pregnancy outcome

In our carefully monitored population with its pre-decided follow-up protocol, no significant differences were found between WWAE and controls in the frequently reported pregnancy complications. This result was consistent with the prospective results of Hiilesmaa et al. (1985) and with the recent obstetric study of Richmond et al. (2004). However, the rate of small for gestational age (SGA) infants was significantly higher in WWAE than in the reference group, as was also observed in the prospective study by Hvas et al. (2000). This increase in the number of small-for-date infants could not be explained by preterm delivery or low birth weight because their number was not increased. Furthermore, neither the epilepsy type nor the AED medication differed between mothers with SGA children and those giving birth to normal weight infants. Also no increase was noted in the number of SGA children in mothers with epilepsy but without AED medication. The mothers with SGA children, however, were shorter which partially could have contributed to the outcome.

Apgar scores at 1 minute after birth were lower in infants of WWAE but no longer reduced at the age of 5 minutes and accordingly the need of neonatal care after birth was increased when compared to controls. Over half (55%) of the deliveries of women using VPA had to be induced. This need for induced delivery has been observed before in women with epilepsy but not associated so clearly with women using VPA (Yerby et al. 1985). There were many different reasons for induction; no dominating reason could be identified. This finding needs to be confirmed in further studies.

The overall rate of major malformations is 4.8% in our study. The malformations were identified by a pediatrician at birth and at discharge from hospital. No reference group examined with a similar method for identifying malformations was available. However, according to information from STAKES, the mean malformation rate is 2.9% (1993-2000) among all newborns, indicating an approximately two-fold increase in the rate of malformations seen here, which is in concordance with previous studies (Olafsson et al. 1998; Canger et al. 1999; Artama et al. 2005). The malformations occurred in children exposed to either polytherapy or high-dose monotherapy (either CBZ or VPA) and were similar to those reported in literature. No association between specific AEDs and malformations could be drawn from this material. In previous prospective studies, the higher rate of malformations has also been associated with polytherapy or high-dose monotherapy, especially with VPA (Kaneko et al. 1988; Wide et al. 2004).

These findings underline the importance of careful pregnancy monitoring in WWAE. Furthermore, the deliveries should take place in a hospital equipped and prepared for neonatal intensive care.

6.3. Ophthalmologic findings of the offspring exposed to vigabatrin

In our case-report of the effects of AED polytherapy with VGB, no structural abnormalities were found in the two VGB exposed children. However, visual fields could not be measured reliably and no conclusions of the possible visual dysfunction can be drawn. It is, however, well established that patients using VGB are at an increased risk of having bilateral, absolute

concentric constriction of the visual field, with varying degrees of severity (Kälviäinen and Nousiainen 2001). Also in the first, controlled and systematic evaluation of the ocular outcome in children exposed to AEDs during pregnancy, no serious defects were associated with AED exposure (Fahnehjelm et al. 1999). However, none of the children in the study of Fahnehjelm et al. (1999) had been exposed to VGB and therefore it is important to gather information from the possible adverse effects also from these case-report studies.

6.4. Neurodevelopmental outcome and dysmorphic features

We evaluated the neurodevelopment of AED exposed children in a prospective, population-based study. Only a few studies with prospective and population-based design have been conducted previously (Gaily et al. 1988; Wide et al. 2002). In the VPA exposed children, the scores of FIQ, VIQ and PIQ were lower than in other groups, though due to the small group size, the difference did not reach statistical significance. In the VPA group the prevalence of low intelligence (FIQ <80) was 38% and exceptionally low (FIQ <70) intelligence was detected in 15% of the children. In previous population-based studies, VPA exposed children have been reported to have lower VIQ than control children (Gaily et al. 2004). This specific influence on verbal performance was not observed in our study. In the retrospective study of Adab et al. (2004a), the lower VIQ in VPA exposed children was independently associated with maternal IQ, VPA exposure and five or more tonic-clonic seizures during pregnancy. In our study, the mothers using valproate scored significantly lower than women with CBZ and those without AED medication in FIQ, VIQ and PIQ tests, though most of the results fell within the normal range. Also their level of education, measured in years, was significantly lower than that of the controls. However, only one mother in each group experienced tonic-clonic seizures during pregnancy and each had only one seizure. Therefore it is evident that many confounding factors can influence the cognitive outcome of the AED exposed children. In our study, the lower level of schooling and cognitive performance of the mothers using VPA could have contributed to the unfavourable neurocognitive outcome of their children. Also in the study of Gaily et al. (2004), the mothers of children with VPA exposure had had lower maternal education.

In the study by Gaily et al. (2004), a negative trend of VPA dose and VIQ score was found. Adab et al. (2004a) reported also a dose-dependent relationship of VPA and VIQ – children exposed to VPA doses >800mg/day during the first trimester had lower VIQ but no relationship was found in doses <800mg/day. In our study, the average dose of VPA was 1182 mg/day and the women with CBZ medication were taking 751mg /day. Due to the small sample size, no association could be detected between the VPA dose and possible cognitive effects derived from this drug.

The children with CBZ exposure did not differ from control children and had average intelligence. This finding is in agreement with the previous population-based studies (Gaily et al. 2004; Wide et al. 2004), in which normal intelligence has been observed in children prenatally exposed to CBZ.

The scores of the IQ tests of the mothers and the children cannot be compared directly as the tests used are different (WAIS and WISC, respectively) and the tests have been standardized for different kinds of populations and age-groups. The mean FIQ scores were higher in mothers (WAIS) compared with the FIQ scores of WISC in children, reflecting perhaps this difference between the IQ tests.

When assessing the AED exposed children at school age, 42% exhibited dysmorphic features; this value rose to 62% if only children exposed to VPA were taken into account. These children had one or more dysmorphic features. These have been associated with intelligence scores in the retrospective study of Adab et al. (2004a). In our study, 14% (2/14) of children with dysmorphic features had also subnormal intelligence. However, single dysmorphic features are common also in the general population (Kini et al. 2006) and therefore the significance of these features in AED exposed children needs to be interpreted cautiously. In this respect, our numbers are similar to those reported by Wide et al. (2000).

Eight (62%) children with VPA exposure and 15 % of children with CBZ or those without AED exposure needed additional educational support. The need was clearly increased in VPA exposed children compared to that in general Finnish population (appr. 18%) (Michelsson and Stenman 2001). This is in concordance with the results of Adab et al. (2001). These findings

indicate that the cognitive problems observed in these children in the neuropsychological test have clinical significance and accordingly, their need for educational support is elevated. No other prospective population-based studies examining the need for additional educational support have been reported.

Children exposed to VPA scored also higher than the other children in Conners' Teacher Rating Scale indicating behavioural problems, although this difference did not reach statistical significance. The high scores seem to focus on areas of social problems and cognitive problems/inattention. The increased need of special education reported by Adab et al. (2001) could reflect this increase in behavioural problems. The possible behavioural problems in AED exposed children, is a field which has rarely been studied since it is difficult to study objectively and it has a susceptibility to bias. These findings are preliminary and need to be confirmed in further prospective, large-scale studies.

When the performance of each child studied at school-age was analysed, it showed that all of the children exposed to VPA had at least minor and some of them exhibited major neurological or cognitive problems. This finding is of special concern. Although the study population is small, it is population-based, prospective and comprehensive. However, many significant confounding factors, e.g. genetic traits, environmental variables, control of mothers; epilepsy after delivery, and parenting habits and abilities are very difficult to control in this kind of study setting and probably have also influenced the outcome.

7. CONCLUSIONS

1. There is no significant difference between the fertility rates in WWAE and the general population when severe co-morbid factors are excluded. Clinically relevant hormonal disturbances or treatments for fertility problems did not seem to be more common in WWAE compared with controls.

2. The majority of women with epilepsy enjoy uncomplicated pregnancies and good obstetric outcome, when a pre-decided protocol is used for both obstetrical and neurological follow-up in antenatal care. However, the increased number of small for gestational age infants as well as the need for neonatal intensive care underline the importance of careful pregnancy and delivery monitoring. Major congenital malformations were observed in 4.8 % of the pregnancies.

3. In the ophthalmologic examination, no structural abnormalities were found in the two children exposed to VGB in utero.

4. Though many confounding factors influence the cognitive outcome of the AED exposed children, an unfavourable impact of VPA exposure on cognition cannot be excluded. However, children exposed to CBZ do seem to have normal intelligence.

5. All of the children exposed to VPA had at least minor and some of them suffered from major neurological or cognitive problems. The frequency of behavioural problems and the need for additional educational support were increased in VPA exposed children.

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APPENDIX: ORIGINAL PUBLICATIONS (I-V)

I

Fertility in women with active epilepsy

Viinikainen K, Heinonen S, Eriksson K, Kälviäinen R

Submitted for publication

II

Community-based, prospective, controlled study of obstetric and neonatal outcome of 179 pregnancies in women with epilepsy.

Viinikainen K, Heinonen S, Eriksson KJ, Kälviäinen R.

Epilepsia 2006;47(1):186-192

III

Ophthalmologic and neurologic findings in two children exposed to vigabatrin in utero.

Sorri I, Herrgård E, Viinikainen K, Pääkkönen A, Heinonen S, Kälviäinen R.

Epilepsy Research 2005;65:117-120

IV

Children exposed to valproate in utero – Population based evaluation of risks and confounding factors for long-term neurocognitive development.

Eriksson K, Viinikainen K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R.
Epilepsy Research 2005;65:189-200

V

The effects of valproate exposure in utero on behaviour and need for educational support in school-aged children.

Viinikainen K, Eriksson K, Mönkkönen A, Äikiä M, Nieminen P, Heinonen S, Kälviäinen R.

Epilepsy & Behavior 2006;9(4):636-40

PUBLICATIONS
SERIES OF REPORTS, DEPARTMENT OF NEUROLOGY

1. **Juhani Partanen (1978):** Time-locked phenomena of human motor unit potentials. An electromyographic study of satellites and doubles.
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