MIIA ARTAMA

Reproductive Health of Patients with Epilepsy

Birthrate and Malformations in Offspring

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ACADEMIC DISSERTATION
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Public Health, Medisiinarinkatu 3, Tampere,
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Supervised by
Professor Anssi Auvinen
University of Tampere
Docent Jouko Isojärvi
University of Oulu

Reviewed by
Professor Rolv Terje Lie
University of Bergen
Professor emeritus Matti Sillanpää
University of Turku

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 3551 6055
Fax +358 3 3551 7685
taju@uta.fi
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Contents

List of Original Publications

This study consists of the following original publications referred to in the text by the Roman numerals (I–IV).

I Artama M, Isojärvi JIT, Raitanen J, Auvinen A (2004): Birth rate among patients with epilepsy: A nationwide population-based cohort study in Finland. Am J Epidemiol 159:1057–1063.

II Artama M, Isojärvi JIT, Auvinen A (2006): Antiepileptic drug purchases and birth rate in patients with epilepsy: A Nationwide population-based cohort study in Finland. Hum Reprod 21:2290–2295.

III Artama M, Ritvanen A, Gissler M, Isojärvi J, Auvinen A (2006): Congenital structural anomalies in offspring of women with epilepsy: A population-based cohort study in Finland. Int J Epidemiol 35:280–287.

IV Artama M, Auvinen A, Raudaskoski T, Isojärvi I, Isojärvi J (2005): Antiepileptic drug use of women with epilepsy and congenital malformations in offspring. Neurology 64:1874–1878.

Abbreviations

AED = Antiepileptic Drug
CBZ = Carbamazepine
CI = Confidence Interval
CNS = Central Nervous System
GABA = Gamma-Aminobutyric Acid
HR = Hazard Ratio
ILAE = International League Against Epilepsy
ICD-9 = International Classification of Diseases, ninth revision
MBR = Medical Birth Register
RR = Rate Ratio
OR = Odds Ratio
OXC = Oxcarbazepine
PHT = Phenytoin
RCM = Register of Congenital Malformations
SII = Social Insurance Institution
STAKES = National Research and Development Centre for Welfare and Health
SUDEP = Sudden Unexpected Death in Epilepsy
VNS = Vagal Nerve Stimulation
VPA = Valproate
WHO = World Health Organization

Tiivistelmä

Tämän tutkimuksen tarkoituksena oli arvioida syntyvyyttä ja jälkeläisten epämuodostumariskiä epilepsiapotilasryhmässä suhteessa epilepsiaa sairastamattomaan vertailuryhmään, sekä selvittää epilepsialääkkeiden käytön vaikutusta näihin vastetapahtumiin.

Tutkimus perustui pääosin rekisteripohjaiseen tietoon. Kaikki 1985–1994 välisenä aikana epilepsian vuoksi epilepsialääkkeisiin erityiskorvattavuuden ensimmäistä kertaa saaneiden henkilöiden tiedot poimittiin Kansaneläkelaitoksen (KELA) ylläpitämästä erityiskorvausoikeusrekisteristä ja nämä henkilöt valittiin tutkimukseen. Näille henkilöille poimittiin väestöpohjainen iän suhteen ryhmäkaltaistettu vertailuryhmä epilepsiaa sairastamattomia henkilöitä väestörekisteristä. Ryhmille syntyneiden lasten henkilötiedot saatiin väestörekisteristä. Yksityiskohtaisemmat, syntynyttä lasta ja epämuodostumia koskevat tiedot poimittiin STAKESin ylläpitämistä syntyneiden lasten rekisteristä ja epämuodostumarekisteristä. Epilepsialääkeostoja koskevat tiedot poimittiin KELAn tietokannasta. Lisäksi yhdessä osatutkimuksessa epilepsiaa sairastavien äitien raskaudenaikaista lääkkeidenkäyttöä ja syntyneiden lasten diagnooseja koskevat tiedot poimittiin äitien sairauskertomuksista 45:stä eri sairaalasta.

Tutkimuksessa todettiin epilepsiapotilailla muuta väestöä alempi syntyvyys, erityisesti miehillä ja yli 20-vuotiailla. Kun vertailut tehtiin lääkittyjen ja lääkkeitä käyttämättömien epilepsiapotilaiden kesken, ainoastaan okskarbatsepiiniä käyttäneillä miehillä havaittiin tilastollisesti merkitsevästi alentunut syntyvyys. Naisilla vastaavaa eroa ei havaittu missään lääkeryhmässä. Tässä tutkimuksessa syntyvyyttä käytettiin fertiliteetin mittarina. Meillä ei ollut tietoa ehkäisyn käytöstä tai tietoisen lapsettomuuden vallitsevuudesta. Tutkimuksemme tueksi tarvitaan erityisesti uudempien epilepsialääkkeiden käytön lisääntymisjärjestelmään kohdistuneiden vaikutusten selvitystä.

Riski merkittäviin epämuodostumiin oli kaksinkertainen epilepsiapotilaiden jälkeläisillä (kokonaisesiintyvyys 54/1,000 syntynyttä lasta) suhteessa epilepsiaa sairastamattoman vertailuryhmän jälkeläisiin (kokonaisesiintyvyys 28/1,000 syntynyttä lasta). Eri elinryhmien merkittävistä epämuodostumista epilepsiapotilaiden jälkeläisillä havaittiin selvästi kohonnut riski selkärankahalkioon (OR = 11.3; 95% CI = 2.34–108) ja sukuelinten synnynnäisiin epämuodostumiin (OR = 8.38; 95% CI = 2.15–47.4). Lisäksi havaittiin kohonnut riski muun verenkiertoelimistön synnynnäisiin epämuodostumiin (OR = 4.19; 95% CI = 1.38–14.0), muihin synnynnäisiin epämuodostumiin (OR = 3.20; 95% CI = 1.35–7.80) ja muihin raajojen synnynnäisiin epämuodostumiin (OR = 2.66; 95% CI = 1.29–5.51).

Raskauden ensimmäisen kolmanneksen aikana epilepsialääkkeitä käyttäneille naisille syntyi enemmän epämuodostuneita lapsia suhteessa epilepsiaa sairastaviin lääkitsemättömiin äiteihin (65/1,411; 4.6% ja 26/939; 2.8%). Yhtä epilepsialääkettä (mitä tahansa tutkituista valmisteista) käyttäneiden epilepsiapotilaiden lapsilla ei havaittu tilastollisesti merkittävästi kohonnutta riskiä epämuodostumiin suhteessa lääkitsemättömien naisten lapsiin (OR = 1.55; 95% CI = 0.94–2.60). Yksittäisistä lääkeaineista vain valproaatille altistuneiden lasten riski epämuodostumiin oli selvästi koholla (OR = 4.18; 95% CI = 2.31–7.57). Kahta tai useampaa lääkettä käyttäneiden naisten jälkeläisillä epämuodostumariski oli kohonnut (OR = 2.73; 95% CI = 1.26–5.64). Myös yhdistelmälääkityksen vaikutus katosi, kun valproaatille altistuneet jätettiin ryhmän ulkopuolelle. Epilepsialääkkeitä ensimmäisen raskauskolmanneksen aikana käyttäneiden naisten epämuodostuneina syntyneistä lapsista yli puolet (37/65; 57%) oli altistunut valproaatille. Lisäksi valproaatin käytön ja epämuodostumariskin välillä havaittiin selvä annos-vaste suhde ($P < 0.0001$).

Vaikka tiettyjen epilepsialääkkeiden raskaudenaikaiseen käyttöön näyttää liittyvän lisääntynyt epämuodostumariski, on epilepsialääkkeisiin liittyvää epämuodostumariskiä kuitenkin arvioitava suhteessa eri hoitovaihtoehtoihin, niiden tehokkuuteen ja teratogeenisyyteen. Erityisesti uudempien epilepsialääkkeiden raskaudenaikaisen käytön vaikutuksista sikiöön tarvitaan lisätietoa.

Abstract

The purpose of this study was to evaluate birthrate and the risk for congenital malformations in the offspring of a population-based cohort of epilepsy patients in relation to a reference cohort of persons without epilepsy. The purpose was moreover to estimate the effect of antiepileptic drug (AED) use on these study outcomes.

This study was mainly based on information from registers. Information on all patients with epilepsy who were approved as eligible for full reimbursement for the purchases of AEDs by the Social Insurance Institution (SII) of Finland for the first time 1985–1994 was obtained from the SII database. A population-based reference cohort of persons without epilepsy was identified from the Population Register Centre of Finland with frequency-matching by age. Information on the dates of birth of liveborn children was also obtained from the Population Register Centre. More detailed information on liveborn and stillborn children and congenital malformations was obtained from the Medical Birth Register (MBR) and the Finnish Register of Congenital Malformations (RCM), both maintained by the National Research and Development Centre for Welfare and Health (STAKES). Information on antiepileptic drug purchases was obtained from the SII database. In addition, information on AED use during pregnancy and on diagnoses of children was abstracted from the medical records of 45 hospitals on mothers with epilepsy (IV).

The birthrate was lower among patients with epilepsy than in the reference cohort without epilepsy, especially in men and both genders aged 20 years or more. When the birthrate was compared between patients on AED and patients not using AED, the birthrate was decreased only in men on OXC. In women, no similar decrease was observed in any AED group in relation to the patients not using AED. Birthrate was used as a measure of fertility in this study. We did not have information on intention to conceive or contraceptive use. More information on the effects of AED use on the reproductive system is needed, especially regarding the effects of the newer AEDs.

The risk for congenital malformations was two-fold in the offspring of women with epilepsy (overall prevalence 54/1,000 births) in relation to the offspring of the reference cohort without epilepsy (overall prevalence 28/1,000 births). The risk for spina bifida (OR = 11.3; 95% CI = 2.34–108) and congenital anomalies of the genital organs (OR = 8.38; 95% CI = 2.15–47.4) was substantially higher in the offspring of women with epilepsy than in the offspring of women without epilepsy, likewise the risk for other congenital anomalies of the circulatory system (OR = 4.19; 95%

CI = 1.38–14.0), other congenital anomalies (OR = 3.20; 95% CI = 1.35–7.80), and other congenital anomalies of limbs (OR = 2.66; 95% CI = 1.29–5.51).

More children with malformations were born to women using AED during the 1st trimester of pregnancy than to women with epilepsy not using AED (65/1,411; 4.6% vs 26/939; 2.8%). Overall, the risk of congenital malformations was not significantly elevated in the offspring of women on monotherapy in comparison with untreated women with epilepsy (OR = 1.55; 95% CI = 0.94–2.60) when all AEDs used as monotherapy were pooled together, but the risk was elevated for the offspring exposed to valproate as monotherapy (OR = 4.18; 95% CI = 2.31–7.57). The offspring of women on polytherapy had clearly increased risk for congenital malformations (OR = 2.73; 95% CI = 1.26–5.64). The effect of polytherapy use disappeared when the use of VPA was excluded from the polytherapy group. More than half of the malformed children born to mothers on AED were exposed to VPA. In addition, a clear dose-dependent relationship was found between the use of valproate and the risk for congenital malformation in the offspring (p for trend < 0.0001). However, AED related risk of malformations should be considered in relation to different treatment alternatives in terms of efficacy and teratogenicity.

1 Introduction

Epilepsy is one of the most common chronic neurological diseases. In Finland, approximately 50,000 persons (1% of the population) are diagnosed with epilepsy. The incidence of epilepsy is highest in young children, lowest in adults and increases in the elderly (Stefan et al. 2001, Forsgren et al. 2005a).

Pharmacotherapy is the mainstay of epilepsy treatment, the primary goal being seizure control without side effects (Brodie and French 2000, Perucca et al. 2000). However, epilepsy itself and the use of AEDs may affect reproductive endocrine function in both women (Herzog et al. 1986b, Isojärvi et al. 1993) and men with epilepsy (Herzog et al. 1986a, Isojärvi et al. 1990, Rättyä et al. 2001). Some AEDs may affect serum concentrations of sex steroid hormones (Morrell and Montouris 2004).

In women, use of AEDs is known to increase the risk for menstrual disturbances (Svalheim et al. 2003). Endocrine disorders are more common in women with epilepsy than in other women (Isojärvi et al. 1993, Isojärvi et al. 1996, Morrell et al. 2002). Furthermore, women with epilepsy have an increased risk of ovulatory dysfunction, ovulatory failure, and polycystic ovaries (Isojärvi et al. 1993, Isojärvi et al. 1996, Morrell et al. 2002).

The risk of reproductive endocrine disorders is higher in men with epilepsy than in the general population, especially among those treated with AEDs (Herzog et al. 1986a, Isojärvi et al. 1990, Isojärvi et al. 1995, Rättyä et al. 2001). Men on AEDs have been reported to have more sperm abnormalities and lower sperm motility than men without epilepsy (Chen et al. 1992, Yerby and McCoy 1999, Røste et al. 2003, Isojärvi et al. 2004). These patophysiological factors may reduce fertility in men with epilepsy (Isojärvi et al. 2005).

Fertility is reduced in patients with epilepsy (Schupf and Ottman 1994, Jalava and Sillanpää 1997, Wallace et al. 1998). One fourth of epilepsy patients are women in fertile age, and approximately 3–4 per 1,000 pregnancies occur in women with epilepsy (Dansky and Finnell 1991, Olafsson et al. 1998b). The use of certain AEDs during pregnancy elevates the risk for congenital malformations in the offspring of women with epilepsy. However, the use of AEDs can seldom be stopped during pregnancy because of the risk of seizures, which may be detrimental to both the mother and the child (Canger et al. 1999).

Population-based studies on birthrate in patients with epilepsy are rare, and most earlier studies have been based on clinical materials with a few hundred patients. Furthermore, few studies have evaluated the effect of AED use on birthrate in epilepsy patients. Most earlier studies on malformations in the offspring of epilepsy patients have been based on small and selective clinical materials including patients with complicated epilepsy. Furthermore, few studies have been conducted with detailed analysis by type of malformation.

This large population-based study was conducted to obtain valid and accurate estimates of the birthrate among subjects with epilepsy and the prevalence of congenital malformations in the offspring of women with epilepsy in relation to the reference cohort of subjects without epilepsy. Comprehensive registry based information on offspring and congenital malformations was used for these analyses. Furthermore, it was possible to evaluate the effect of commonly used AEDs on these outcomes.

2 Review of the literature

The present study focuses on adult epilepsy patients.

2.1 Epilepsy

Epilepsy is rather a group of multiform neurological disorders more than a single disease. It is a diverse brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function: epileptic seizures. Many different conditions with several causes and outcomes share the common feature of epileptic seizures. Diagnosis of epilepsy requires at least one seizure, the presence of persistent alteration in the brain and possible associated neurobiological, cognitive, psychological and social disturbances. (Fisher et al. 2005.) Although these newer criteria with a minimum requirement of one seizure due to an persistent alteration in the brain has been introduced, the older definition with a requirement of two seizures is also used in practice in certain situations.

2.1.1 Classification of epileptic seizures, epilepsies and epileptic syndromes

The International League Against Epilepsy (ILAE) classification of epileptic seizures (Commission on Classification and Terminology of the ILAE 1981) is based on the clinical form and the EEG abnormality of seizures (Table 1). Epileptic seizures are divided into two categories: generalized and partial. Generalized seizures arise from large areas of cortex in both hemispheres and the patient´s consciousness is always lost. Partial seizures arise in certain, often small loci of the cortex in one hemisphere. (Commission on the Classification and Terminology of the ILAE 1981, Shorvon 2005.)

The ILAE classification of epilepsies and epileptic syndromes defines epileptic syndrome as an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together. The classification of epilepsies and epileptic syndromes is based on type and etiology of epileptic seizures (Table 2). (Commission on the Classification and Terminology of the ILAE 1989.)

Table 1. ILAE classification of seizure types (Commission on the Classification and Terminology of the ILAE, 1981).

1. Partial (focal) seizures

A Simple partial seizures
(consciousness not impaired)
1. With motor symptoms
2. With somatosensory or special sensory symptoms
3. With autonomic symptoms or signs
4. With psychic symptoms

B Complex partial seizures
(with impairment of consciousness; may sometimes begin with simple symptomatology)
1. Simple partial onset followed by impairment of consciousness
2. With impairment of consciousness at onset

C Partial seizures evolving to secondary generalised (maybe generalised tonic-clonic, tonic or clonic)
1. Simple partial seizures (A) evolving to generalised seizures
2. Complex partial seizures (B) evolving to generalised seizures
3. Simple partial seizures evolving to complex partial seizures evolving to generalised seizures

2. Generalised seizures

A Absence seizures
B Myoclonic seizures
C Clonic seizures
D Tonic seizures
E Tonic-clonic seizures
F Atonic seizures

3. Unclassified epileptic seizures

Table 2. International Classification of Epilepsies and Epileptic Syndromes (Commission on the Classification and Terminology of the ILAE, 1989) (adapted).

Epilepsy / Epileptic syndromes

1. Localization-related (focal, local, partial)
Idiopathic
Symptomatic
Cryptogenic

2. Generalized epilepsies and syndromes
Idiopathic, with age-related onset, in order of age
Cryptogenic or symptomatic, in order of age
Symptomatic
Non-specific etiology
Specific syndromes

3. Epilepsies and syndromes undetermined as to focal or generalized
With both generalized and focal seizures

4. Special syndromes

2.1.2 Etiology and occurrence

In approximately half of epilepsy patients, the etiology of epileptic seizures is unknown (Sander and Shorvon, 1996). Aetiologies of epilepsies vary between age groups. Head trauma, infections and tumours are known causes for epilepsy at any age. (Sander and Shorvon 1996.) In children, adolescents and in young adults, epilepsy is usually due to unknown, genetic, developmental or congenital origin (Brodie et al. 2003). In later life, the most common etiologies of epilepsies are cerebrovascular diseases, especially ischemic stroke in addition to tumours, head trauma and infections (Hauser et al. 1993). However, the etiology of epilepsy may be multifactorial. Furthermore, the contributors to each of known cause for the etiology of epilepsies have not been formally ascertained. (Sander and Shorvon 1996.)

The incidence rate of epilepsy varies in developed countries between 40 and 70 per 100,000 person-years (Sander and Shorvon 1996). Higher incidence rates have been reported in the developing countries, where the risk of a condition which can lead to permanent brain damage (malaria, pre and perinatal complications and malnutrition), and therefore epilepsy, is high. The incidence of epilepsy is higher in men than in women. (World Health Organization, WHO 2005.) The age-specific incidence of epilepsy is U-shaped: it is highest in young children, lowest in adults and increases again in the elderly (Stefan et al. 2001, Forsgren et al. 2005a, Sillanpää et al. 2006). In Finland, the incidence of epilepsy has been similar to that of the other developed countries. However, the incidence in the total population decreased in the period 1986-2002 from 72 per 100,000 persons to 53 per 100,000 persons. The incidence of epilepsy has decreased in children and in adults, but increased in the elderly during this period in Finland. (Sillanpää et al. 2006.)

Overall, the prevalence of epilepsy is 9 per 1,000 persons in the world, from 5 to 9 per 1,000 persons in the developed countries, and from 3 to 8 per 1,000 persons in European countries (Forsgren et al. 2005a, WHO 2005). In Finland, a total of 54,000 people were eligible for 100% reimbursement for antiepileptic drugs (AEDs) due to epilepsy in 2005 (Social Insurance Institution (SII) of Finland 2006). The prevalence of active epilepsy has been from 3 to 4 per 1,000 children aged 0–15 years (Sillanpää 1973, Eriksson and Koivikko 1997), and 6 per 1,000 adults (Keränen et al. 1989) in Finland.

2.1.3 Treatment of epilepsy

2.1.3.1 Pharmacotherapy

Pharmacotherapy is the mainstay of epilepsy treatment with the primary goal of seizure control without side effects (Brodie and French 2000, Perucca et al. 2000). Moreover, controlled epilepsy improves quality of life, reduces mortality and morbidity, and avoids the social consequences of epilepsy and secondary handicap (Shorvon 2005).

The medical basis for a decision as to whether and how the AED treatment is initiated depends on the epilepsy syndrome and seizure type (Bazil and Pedley 1998). Also, etiology, age at onset, severity, chronicity, and prognosis of epilepsy influence the medical basis for the decision on AED treatment (Perucca et al. 2000, Sander 2004). Other important factors affecting the choice of AED treatment include mechanism of action, pharmacokinetics, ease of use, efficacy, tolerability, safety, interaction profile and "comfort factor" (i.e. doctors prescribe AEDs with which they are familiar) (Brodie and Kwan 2001). Therefore, the choice of AED treatment is always based on individual patient characteristics (Brodie and Kwan 2001, Perucca 2003).

AEDs can be categorized into general categories according to their main mechanisms of action: a) potentiation of gamma-aminobutyric acid $(GABA)_A$-mediated postsynaptic inhibition (e.g. benzodiazepines, barbiturates, tiagabine and vigabatrin) b) inhibition of repetitive, high-frequency neuronal firing by blocking voltage-dependent sodium channels (e.g. carbamazepine (CBZ) and oxcarbazepine (OXC), phenytoin (PHT), and lamotrigine) c) blockage of T-type calcium channels (ethosuximide). However, the mechanism of action is not fully known for all AEDs and some AEDs have several modes of action (e.g. valproate (VPA), topiramate). (Bazil and Bedley 1998, Duncan et al. 2006.)

AED treatment options have improved significantly during the last two decades (Beghi and Perucca 1995). Older AEDs include drugs introduced before the 1990's (Duncan et al. 2006). Some of these drugs are still widely used as a primary medical treatment for epilepsy, but many new AEDs have been introduced since 1990 (Bazil and Pedley 1998). These newer AEDs are mainly for the treatment of partial epilepsy, and most of them are used as adjuvant medication with the older AEDs. However, some of them (lamotrigine, levetiracetam, gabapentin and OXC) are also licensed as monotherapy. (Brodie and Kwan 2001.)

Phenobarbital was introduced in 1912. It has been a widely used first choice AED in the treatment of partial and generalized seizures (Mattson et al. 1985). Phenobarbital was the most commonly prescribed AED of the 20th century, and it is still among the essential AEDs in the world (WHO 2005). It is licensed both for monotherapy and

adjuvant therapy, but is no longer widely used in western European countries any more. Phenobarbital affects $GABA_A$ receptor as well as sodium, potassium and calcium conductance (Shorvon 2005).

Phenytoin was introduced in 1938 and is still one of the most commonly used AEDs in the treatment of partial and primary and secondarily generalized seizures (Shorvon 2005, WHO 2005, Duncan et al. 2006). However, because of side-effects to the central nervous system (CNS), systemic side-effects and drug interactions, it has been increasingly relegated to a second-choice therapy (Shorvon 2005). Phenytoin affects the sodium channels (Duncan et al. 2006).

Primidone has been a first-line drug in the treatment of partial and primary and secondarily generalized seizures (Shorvon 2005), but due to CNS side-effects (sedation, cognitive impairment), its use in Europe has decreased substantially (Loiseau 1999).

CBZ was introduced in 1963 and is still an essential first-line AED in the treatment of partial and generalized seizures, excluding absence and myoclonus seizures (WHO 2005, Duncan et al. 2006). It is the most commonly prescribed AED in Europe. CBZ is used as monotherapy and adjuvant therapy. It mainly binds to the neuronal sodium channel, which results in voltage and use-dependent blockage of the channel. CBZ is metabolized in the liver. It is a hepatic enzyme inducer. CBZ is itself also highly susceptible to enzyme induction and the levels of CBZ can be affected by other hepatic enzyme inducers. Therefore, CBZ has pharmacokinetic interactions with several AEDs and also with other drugs (e.g. contraceptive pills) when used as polytherapy. It is usually well tolerated, but 30 to 50% of patients on CBZ experience some mild side effects. CBZ can induce changes in endocrine function, e.g. changes in circulating pituitary and sex hormone concentrations. Use of CBZ may also contribute to the development of osteoporosis by altering bone metabolism. CBZ is discontinued in less than 5% of patients, the medication is changed due to the side effects. (Shorvon 2005.)

VPA was introduced in Europe in the early 1960´s. It is a mainstay therapy in the treatment of primarily generalized seizures, but it is also effective therapy in partial and secondarily generalized seizures (Shorvon 2005). VPA is used as monotherapy and add-on therapy. Its mechanism of action is not fully known. The main effect of VPA is through the $GABA_A$ -receptor, but it also has some other modes of action (McLean and Macdonald 1986, Macdonald and Kelly 1993). It inhibits hepatic enzymes and therefore may have interactions with some other AEDs when used as polytherapy. VPA seems to be fairly well tolerated in short-term use. However, it has several long-term side effects including weight gain, endocrine effects and development of polycystic ovaries, which may limit its use. (Shorvon 2005.)

Ethosuximide was introduced in 1958 for the treatment of generalized absence seizures. It is licensed both for monotherapy and adjuvant therapy use. Ethosuximide affects calcium T-channel conductance. (Shorvon 2005.)

OXC is an analogue of CBZ. It is used as monotherapy or adjuvant therapy in the treatment of partial epilepsy with or without secondary generalization (Duncan et al. 2006). Its mechanism of action is very similar to that of CBZ. However, in addition to blocking of voltage-sensitive sodium channels, it also affects calcium channel activity. OXC is metabolized in the liver, but it does not induce hepatic enzymes to such a degree as CBZ, and therefore it has fewer pharmacokinetic interactions with other AEDs than CBZ. However, it also interacts with contraceptives. (Shorvon 2005.) OXC is as effective as CBZ, but it may be better tolerated (LaRoche and Helmers 2004).

Vigabatrin is used as adjuvant therapy in partial and secondarily generalized seizures. It acts through the GABAergic system. (Shorvon 2005.) Its use is limited due to the visual field defects associated with its use (Kälviäinen et al. 1998, Duncan et al. 2006).

Lamotrigine is the most commonly used newer AED. It is effective both as monotherapy and add-on therapy for partial and generalized epilepsies. It affects sodium channels (Duncan et al. 2006).

Gabapentin is used as adjuvant therapy for refractory partial and secondarily generalized epilepsies. Its mechanism of action is unknown. (Sander 2004.) It is well tolerated and its potential for interactions is low.

Topiramate is used as an adjuvant AED for partial and secondarily generalized epilepsies. It acts through the sodium and calcium channels. (Duncan et al. 2006.) Topiramate has several side effects and therefore its use is limited. Undesirable cognitive effects are among the most important side effects of topiramate.

Tiagabine is used as an adjunctive AED in the treatment of partial and secondarily generalized seizures (Shorvon 2005). It has a certain mechanism of action through the GABAergic system; it is a GABA uptake inhibitor and thereby increases the effects of GABA (Sander 2004).

Levetiracetam is used as monotherapy or as an adjuvant AED for partial and generalized seizures in adults. It has a certain mechanism of action of synaptic vesicle protein modulation. (Duncan et al. 2006.) It is efficacious, well tolerated and has a low potential for interactions. Therefore, its use is rapidly increasing.

There are also other drugs used in the treatment of epilepsy (e.g. acetazolamide, benzodiazepines) which are not solely licensed for the medical treatment of epilepsy and which are not considered here (Shorvon 2005).

2.1.3.2 Other treatment options

A ketogenic diet can be used as an additional treatment of medically intractable epilepsy (Maydell et al. 2001). This is a high-fat, low carbohydrate, adequate protein diet, which has been shown to decrease seizure frequency in patients with both generalized and partial seizures (Freeman et al. 1998, Maydell et al. 2001). However, it is more effective in children than in adults with epilepsy (Maydell et al. 2001).

Vagal nerve stimulation (VNS) is an adjuvant palliative treatment alternative especially for patients with refractory partial seizures, and also for patients with generalized seizures on whom ablative epilepsy surgery cannot be used. Vagal nerve stimulation desynchronises the electroencephalography (EEG) and involves synaptic and neuro-chemical mechanisms (Schachter and Schmidt 2001). However, the exact mechanism of action of VNS is not known (George et al. 2002). The effectiveness of VNS in terms of seizure reduction has been reported to be from 30% to 50% over the first year of treatment (Salinsky et al. 1996, Morris et al. 1999, DeGiorgio et al. 2000, Schachter and Schmidt 2001), although most patients still need to continue their antiepileptic medication (Schachter and Schmidt 2001).

Epilepsy surgery may be an effective treatment alternative for a limited group (from 2 to 5%) of patients with medically refractory partial epilepsy (Kwan and Brodie 2000, Shorvon 2005). The risk of at least one seizure after epilepsy surgery is high, but the rate of recurrent seizures is low (Schwartz et al. 2006). The first year after the surgery is an important predictive factor for long term seizure freedom (Jutila et al. 2002).

2.1.4 Prognosis of epilepsy

Overall, the prognosis of epilepsy differs between the epilepsy syndromes and depends on etiology, age at onset, number of seizures at onset, and the efficacy of treatment (MacDonald et al. 2000, Bell and Sander 2001, Stefan et al. 2001). Approximately 80% of subjects, who have had a seizure, will have a recurrent seizure. The risk of subsequent seizure is highest during the first six months after the initial seizure (Stefan et al. 2001). Furthermore, the number of seizures within the first six months after the first seizure is an important predictive factor for remission of seizures (MacDonald et al. 2000). If a second seizure has not occurred within 18 months after the first one, the risk of subsequent seizures decreases to less than 20%. Approximately 70% of patients with epilepsy diagnosis will become seizure-free within five years of diagnosis (Stefan et al. 2001).

Approximately half of newly diagnosed epilepsy patients become seizure free with the first AED. Of the remaining patients, 10% have their seizures controlled with another AED used as monotherapy. (Kwan and Brodie 2000.) If a patient has seizures after two alternative monotherapy treatments, polytherapy treatment is usually started (Brodie and Dichter 1997, Kwan and Brodie 2000). 30% to 40% of the epilepsy patients do not achieve seizure control with AED treatment (Brodie and Dichter 1997, Kwan and Brodie 2000).

The main goal of epilepsy treatment is remission. Epilepsy can be considered as being in remission after freedom from seizures lasting 5 years with or without antiepileptic medication (Commission on Epidemiology and Prognosis of the ILAE 1993). However, when the antiepileptic medication is discontinued in seizure-free patients, seizure relapse occurs in approximately one third (Sillanpää and Schmidt 2006).

Patients with epilepsy in developed countries have two to three times higher mortality in relation to general population (Cockerell et al. 1994, Nilsson et al. 1997, Olafsson et al. 1998a, Shackleton et al. 1999). Mortality is considerably more common in patients with symptomatic epilepsy than in patients with idiopathic epilepsy. This may be explained by an underlying disorder causing epilepsy (e.g. cerebrovascular disease or neoplastic disorders) and contributing to the increased risk of death in some patients with symptomatic epilepsy. (Tomson 2000, Forsgren et al. 2005b.) Sudden, unexpected death in epilepsy (SUDEP) is the most common seizure-related cause of death in young adolescents and young adults with epilepsy. The risk for SUDEP is more than 20 times higher in these age-groups than the risk for sudden unexpected death in general population. (Forsgren et al. 2005b.)

2.1.5 Other factors related to epilepsy

Epilepsy may affect not only a person´s health-related quality of life but also psychosocial life (Leidy et al. 1999). Patients with epilepsy have lower socio-economic status than those without epilepsy (Hesdorffer et al. 2005). Also, they are likely to have lower educational level (Sillanpää et al. 1998) and higher rate of unemployment than population in general (Sillanpää et al. 2004). The frequency of driver´s license holders is lower among epilepsy patients than among subjects without epilepsy (Sillanpää and Shinnar 2005). However, some studies have not found differences in socio-economic background among patients with epilepsy and those without epilepsy (Schupf and Ottman 1994).

Subjects with epilepsy report less social and leisure time activity than other population (Steinhoff et al. 1996). The proportion of singles is higher among the patients with epilepsy than among the rest of the population and the rate of marriages is lower among epilepsy patients (Dansky et al. 1980, Schupf and Ottman 1994, Jalava and Sillanpää 1997).

2.2 Epilepsy and reproductive health

2.2.1 Endocrine function

2.2.1.1 Women with epilepsy

Epilepsy itself and the use of AEDs may affect reproductive endocrine function in women with epilepsy (Herzog et al. 1986a, Isojärvi et al. 1993). Epilepsy and seizures are known to affect the secretion of pituitary hormones (Pritchard 1991). Moreover, some AEDs may affect serum concentrations of sex steroid hormones (Morrell and Montouris 2004). Fluctuation of sex hormone levels or variations in AED concentrations during the menstrual cycle may increase seizure frequency in women with epilepsy (Foldvary-Schaefer et al. 2004).

High seizure frequency and AED use, especially in polytherapy, are known to increase the risk for menstrual disturbances (Svalheim et al. 2003). Endocrine disorders are more common in women with epilepsy than in other women, especially in women with partial seizures of temporal lobe origin (Herzog et al.1986a, Isojärvi et al. 1993, Isojärvi et al. 1996, Herzog et al. 2003), but also in women with primary generalized epilepsy (Bilo et al. 1988, Morrell et al. 2002). Women with epilepsy have an increased risk of ovulatory dysfunction and ovulatory failure, especially those with idiopathic generalized epilepsy on VPA (Morrell et al. 2002). The risk of polycystic ovaries and hyperandrogenism is elevated in women treated with VPA in monotherapy or in combination with CBZ (Isojärvi et al. 1993, Isojärvi et al. 1996). Elevated serum testosterone concentration with (Betts et al. 2003) or without (Isojärvi et al. 1993) polycystic ovaries has been shown to be more common among women treated with VPA in monotherapy or in combination with CBZ than in control women. Furthermore, high frequency of sexual dysfunction in terms of interest or libido and disorders in sexual arousal have been reported among women with epilepsy (Morrell and Guldner 1996). These pathophysiological factors may reduce fertility, and birthrate in women with epilepsy.

2.2.1.2 Men with epilepsy

Epilepsy and the use of antiepileptic medication also affect reproductive endocrine function in men with epilepsy (Herzog et al. 1986b, Isojärvi et al. 1990, Rättyä et al. 2001). Epilepsy itself may affect reproductive physiology (Herzog et al. 1986b, Røste et al. 2005), but enzyme inducing AEDs, such as CBZ, phenobarbital or phenytoin may also be associated with increased serum sex hormone binding globulin levels, and thus reduce the bioactivity of testosterone and estradiol (Isojärvi et al. 1995, Isojärvi et al. 2005). Also, use of VPA may increase serum androstenedione levels (Rättyä et al. 2001).

Reproductive endocrine disorders are more common in men with epilepsy than in the general population, especially among those treated with AEDs (Herzog et al. 1986b, Isojärvi et al. 1990, Isojärvi et al. 1995, Rättyä et al. 2001). Men on AEDs, especially CBZ, OXC or VPA, have also been reported to have more sperm abnormalities and lower sperm motility than men without epilepsy (Chen et al. 1992, Yerby and McCoy 1999, Røste et al. 2003, Isojärvi et al. 2004). These pathophysiological factors may reduce fertility in men with epilepsy (Isojärvi et al. 2005).

2.2.2 Fertility

One fourth of epilepsy patients are women in fertile age, and as a result, approximately 3–4 per 1000 pregnancies occur in women with epilepsy (Dansky and Finnell 1991, Olafsson et al. 1998b). Most earlier studies have reported reduced fertility in epilepsy patients (Schupf and Ottman 1994, Jalava and Sillanpää 1997, Wallace et al. 1998) (Table 3). Several studies have shown lower fertility among men than among women with epilepsy (Dansky et al. 1980, Webber et al. 1986, Schupf and Ottman 1994). However, Olafsson et al. (1998b) did found no difference in the average number of children born to patients with epilepsy and controls without epilepsy, either men or women. However, children who were born before and after the parent's diagnosis of epilepsy were not distinguished in that study.

Patients with epilepsy appear to have lower fertility after, but not before diagnosis of epilepsy (Schupf and Ottman 1996). Some of the earlier studies have found that age at diagnosis of epilepsy influences the number of offspring. Schupf and Ottman (1994) found that early age at diagnosis was associated in men with reduced likelihood of fathering a pregnancy. No similar association between early age at diagnosis and reduced likelihood of pregnancy was found in women with epilepsy in the study by

Schupf and Ottman (1994). Other studies report no association between age at diagnosis and likelihood of having children (Jalava and Sillanpää 1997, Olafsson et al. 1998b).

Lower fertility in epilepsy patients is partly explained by the lower rate of marriages and higher proportion of singles, but fertility is also decreased in married epilepsy patients (Schupf and Ottman 1996). Dansky et al. (1980) found that fertility decreased in married men, but not in married women with epilepsy. However, the results of some other studies have been contrary to the finding of Dansky et al. (1980) (Schupf and Ottman 1994, 1996). Among married epilepsy patients, fertility has been found to be lower in those diagnosed when young than in those with late onset of epilepsy (Dansky et al. 1980, Schupf and Ottman 1996).

The effect of pre-pregnancy seizure frequency on fertility has not been well established. In a Finnish study, no clear association between seizure frequency during the previous 5 years and likelihood of pregnancy was found (Jalava and Sillanpää 1997). Findings regarding the effect of epilepsy type on fertility have been contradictory. Some earlier studies have found that patients with partial seizures have had lower fertility than those with generalized seizures (Webber et al. 1986, Schupf and Ottman 1996), whereas other studies have found no association between type of epilepsy and likelihood of having children (Jalava and Sillanpää 1997, Olafsson et al. 1998b).

The effect of AED use on the number of children born has not been widely studied. In a Finnish study, the number of children was lower in patients on AEDs than in untreated patients, or subjects without epilepsy. Childlessness was four times more common in patients on polytherapy in relation to those without epilepsy. (Jalava and Sillanpää 1997.) However, more detailed information on the types of AEDs used was not included in that study.

2.2.3 Congenital malformations in the offspring of women with epilepsy

Congenital malformation is a synonym for birth defect, congenital abnormality and congenital anomaly. All these conditions refer to structural, behavioural, functional or metabolic disorder present at birth (Sadler 2000). Congenital malformations have been classified mostly according to etiology, pathogenesis or outcome (Kalter 2003). One of the most comprehensive classifications of congenital malformations is the International Classification of Diseases, ninth revision (ICD-9) (WHO 1977), where congenital malformations have been categorized according to system, body part, and organ.

Table 3. Selected studies on birthrate in patients with epilepsy.

Study	Study population patients/controls	Control group	Rate/risk		
			F&M	F	M
Wallace et al. UK, 1998	7,626/ NA[§)]	General population	NA	0.75 0.68-0.83[1)]	NA
Webber et al. USA, 1986	NA	Sample of general population	NA	0.92 0.78-1.1[1)]	[1)] 0.71 0.57-0.89
Schupf and Ottman USA, 1994	1,558/316	Siblings without epilepsy	NA	**OR 0.37[2)], 0.23-0.56*[)]**	**OR 0.36[2)], 0.22, 0.59*[)]**
Jalava and Sillanpää Finland, 1997	100/ 99[†)]+ 100[‡)]	Sample of general population[†)] employee controls[‡)]	3.6 2.1-6.3[3,†)] 3.2 1.9-5.5 [3, ‡)]	NA	NA
Olafsson et al. Iceland, 1998b	209/418	Sample of general population	**OR 1.3 0.9-1.9[2)]**	NA	NA

[1)] Fertility ratio Observed/Expected
[2)] Likelihood of pregnancy
[3)] Rate of childlessness
[§)] Number of patient-years
[*)] OR and 95% CI adjusted for age, sibship size, education, and ethnicity
[†)] Reference: random controls from the Finnish general population
[‡)] Reference: employee controls

Congenital malformations have also been classified to minor and major, according to severity and functional disturbance related to the anomaly. Major congenital malformations are abnormalities that require surgical or medical treatment, are physically handicapping, or have serious cosmetic consequences (Holmes et al. 2001, Kalter 2003). Minor congenital malformations are those with little or no medical or cosmetic significance. Minor congenital malformations may also be a component of certain malformation syndromes (Kalter 2003).

In 65 to 70% of congenital anomalies the cause is unknown. One fifth of the cases have genetic etiology, and 3% to 5% have a chromosomal or cytogenic basis. Maternal infections with viral agents account for 2% to 3% of all congenital anomalies. Only 2% to 3% of birth defects are caused by environmental or iatrogenic exposures. (Finnell 1999).

Effects of maternal AED use on congenital malformations

In most earlier studies, the risk of congenital anomalies has been 2–3 times higher among the offspring of women with epilepsy than in children born to women without epilepsy (Table 4). The risk has been higher in the offspring exposed to AEDs than in the offspring of mothers without AED treatment during pregnancy (Olafsson et al. 1998b, Nulman et al. 1999, Samren et al. 1999, Holmes et al. 2001, Matalon et al. 2002, Fried et al. 2004), and it has increased with the number of AEDs in use (Olafsson et al. 1998b, Holmes et al. 2001, Pennell 2003, Wide et al. 2004, Morrow et al. 2006). However, antiepileptic medication cannot usually be discontinued because of risk of seizures during pregnancy, which may be a disadvantage for both the mother and the child (Canger et al. 1999).

Table 4. Summary of the results from selected earlier studies on congenital anomalies in the offspring of mothers with epilepsy.

Publication	Number of births	Overall result	Confirmation of patients with epilepsy	Inclusion of terminations (t) /stillbirths (s)	Information on AED use	
					Yes/No	Yes/No
Olafsson et al. Iceland, 1998	221/82,217 [a] 42/82,217 [b]	**SMR** [a] **SMR** [b]	**2.7 (1.4-4.5)** **2.2 (0.3-0.8)**	Hospital records	No	Yes
Fairgrieve et al. UK, 2000	400/65,478 [a]	**OR** [a]	**2.2 (1.3-3.4)**	Maternity clinic records	Yes (t,s)	Yes
Fonager et al. Denmark, 2000	235/17,259 [a]	**OR** [a]	**2.2 (1.3-3.8)**	Pharmacoepidemiological Prescription Database	Not reported	Yes
Kaneko et al. Japan, 1999	885/98 [e]	**OR** [e]	**3.1 (unknown)**	Hospital records	No	Yes
Wide et al. Sweden, 2004	1,398/581,258 [a]	**OR** [a]	**1.9 (1.4-2.4)**	National Birth Registry	Not reported	Yes
Holmes et al. USA, 2001	316/98/508 [c]	**OR** [b] **OR** [d]	**0.4 (0.0-7.0)** **3.3 (0.9-8.3)**	Hospital records	No	Yes
Dean et al. UK, 2002	261/38	**RR** [e]	**2.6 (0.7-10.4)**	Hospital records	[*]	Yes
Dravet et al. France, 1992	229/117,183 [f]	**RR** [f]	**6.9 (4.5-12.4)**	Hospital records	No	Yes
Jick and Terris USA, 1997	297/594 [d]	**RR** [d]	**3.3 (1.2-9.2)**	General practice records	No (t,s)	Yes
Samrén et al. The Netherlands, 1997	192/158 [d]	**RR** [d]	**2.3 (1.2-4.7)**	Hospital records	Yes (s, 2 centrse)	Yes

[a] Offspring of patient on AED / offspring of general population, [b] Offspring of patients without AED / offspring of general population,
[c] Offspring of patients on AED / patients without AED / control women, [d] Offspring of patients on AED / control women,
[e] Offspring of patients on AED / patients without AED [f] Offspring of patients on AED + without AED / offspring of general population
[*] Included all pregnancies continuing into 2nd trimester

Several studies have found that the offspring of epilepsy patients without AED treatment during pregnancy have similar risk of congenital malformations to those of subjects without epilepsy (Holmes et al. 2001, Fried et al. 2004). This supports the assumption that teratogenicity is more related to AEDs than to epilepsy itself. However, according to some earlier studies, the elevated risk of malformations attributed to AEDs may in fact be due to epilepsy per se (Gaily and Granström 1992) i.e. the genetic background of epilepsy (Koch et al. 1992). Some studies have found that subjects with one child with phenytoin embryopathy had a higher risk of having a second child with a similar condition (Smith 1980, Van Dyke et al. 1988, Moore et al. 2000). Yet women with epilepsy on different treatments, and without treatment also differ regarding the type or severity of the disease and therefore, the teratogenic effect of epilepsy and antiepileptic treatment cannot be distinguished (Kaneko et al. 1999, Dean et al. 2000, Dolk and Elhatton 2002).

Carbamazepine

According to the meta-analysis by Matalon et al. (2002), the risk of congenital malformations in the offspring exposed to CBZ during fetal development has been two to three-fold to general population. Most of the earlier studies have not reported dose-dependency in teratogenicity of CBZ. The risk of congenital malformations is higher among children exposed to CBZ as polytherapy than as monotherapy. This is the case especially if the polytherapy regimen is with VPA or PHT (Matalon et al. 2002). On the other hand, the risk of malformations is lower among offspring exposed to CBZ as monotherapy than in those exposed to VPA as monotherapy (Wide et al. 2004).

Maternal use of CBZ is associated with the risk of neural tube defects (NTD) in the offspring (Rosa 1991, Lindhout and Omtzigt 1994, Canger et al. 1999, Hernández-Díaz et al. 2000, 2001). Hernández-Díaz et al. (2001) found a seven-fold risk of NTDs in the offspring exposed to CBZ during pregnancy. An elevated risk of cardiovascular anomalies (Canger et al. 1999, Arpino et al. 2000, Diav-Citrin et al. 2001), urinary tract anomalies, and cleft palate has also been reported in the offspring exposed to CBZ during pregnancy (Matalon et al. 2002).

Jones et al. (1989) first described a pattern of minor anomalies associated with the maternal use of CBZ as monotherapy during pregnancy. This carbamazepine syndrome consists of craniofacial defects, hypoplastic nails, and microcephaly. This finding has later been confirmed by several other studies (Ornoy and Cohen 1996, Nulman et al. 1997). However, the clinical significance of this syndrome is not known. Overall, the diagnostic criteria for antiepileptic drug syndromes are still unclear and abnormal facial

features and other minor anomalies are also difficult to quantify (Yerby et al. 1992, Dean et al. 2000). Furthermore, a child with a pattern of anomalies may have been exposed to more than one AED during pregnancy (Dean et al. 2000).

Valproate

Several studies have reported that the use of VPA during pregnancy clearly increases the risk of congenital malformations (Kaneko et al. 1988, Battino et al. 1992, Omtzigt et al. 1992, Lindhout and Omtzigt 1994, Samrén et al. 1997, Canger et al. 1999, Sabers et al. 2004, Vajda et al. 2004, Wyszynski et al. 2005). The teratogenicity of VPA has been reported to be dose dependent in some studies. Maternal daily doses of VPA exceeding 1000–1400 mg during pregnancy have been found to significantly increase the risk of congenital malformations in the offspring. (Samrén et al. 1997, Kaneko et al. 1999, Samrén et al. 1999, Vajda et al. 2004, Vajda and Eadie 2005.) Furthermore, the risk of congenital malformations has been 2–3 times higher in the offspring exposed to AED polytherapy combination including VPA than in the offspring exposed to polytherapy combination without VPA (Morrow et al. 2006).

The use of VPA during pregnancy has especially been found to elevate the risk of neural tube defects and spina bifida (Dalens et al. 1980, Bjerkedal et al. 1982, Robert and Guibaud 1982, Lindhout and Schmidt 1986). The risk of hypospadias, cleft palate, congenital heart defects, skeletal and limb defects has also been elevated in studies on the offspring exposed to VPA during pregnancy (Samrén et al. 1997, Canger et al. 1999, Samrén et al. 1999, Arpino et al. 2000, Vajda and Eadie 2005, Morrow et al. 2006).

A specific fetal valproate syndrome has been reported in the offspring exposed to VPA during pregnancy (DiLiberti et al. 1984, Clayton-Smith and Donnai 1995, Moore et al. 2000). Certain facial features, such as broad, flat nasal bridge, trigonocephaly, epicanthic folds, median deficiency of eyebrows, long upper lip, thick lower lip and small, downturned mouth are characteristics of fetal valproate syndrome (DiLiberti et al. 1984, Clayton-Smith and Donnai 1995). The most common malformations associated with fetal valproate syndrome include neural tube defects, congenital heart defects, oral clefts, genital abnormalities, and limb defects (Clayton-Smith and Donnai 1995, Moore et al. 2000).

Oxcarbazepine

Few studies have evaluated the teratogenic effects of OXC in humans (Kaaja et al. 2003, Meinguisher et al. 2004, Sabers et al. 2004). Meinguisher et al. (2004) found no malformations in the offspring of 35 patients treated with OXC monotherapy during pregnancy and found one malformation in 20 children born to mothers treated with OXC polytherapy. In another study one malformation was found in children exposed to OXC monotherapy and one in children exposed to OXC polytherapy (Sabers et al. 2004). In a Finnish study conducted by Kaaja et al. (2003), one child out of nine with OXC exposure was found to have a major malformation. However, all these studies included only a small number of pregnancies with OXC exposure, and therefore, no further conclusions on teratogenicity of OXC can be made based on these results.

3 Objectives

Overall objective of this study was to assess the effect of epilepsy on reproductive health.

The specific aims of present study were:

I To estimate overall birthrate among patients with epilepsy in relation to a reference cohort without epilepsy.

II To compare the birthrate in patients with epilepsy on AEDs with that in untreated epilepsy patients and a reference cohort without epilepsy.

III To assess the prevalence and risk of congenital malformations in the offspring of women with epilepsy in relation to reference cohort without epilepsy.

IV To estimate the prevalence and risk of congenital malformations in the offspring of patients with epilepsy on AED during the 1st trimester of pregnancy in relation to the offspring of untreated epilepsy patients.

4 Study format and procedures, study populations and methods

This chapter is an overview of the study populations and methods of the present study and the original publications. More detailed information is available in the original publications (I–IV).

4.1 Study format and procedures

This is a cohort study based on information obtained from five Finnish registers of population statistics and health: The Finnish Population Register, (maintained by the Population Register Centre of Finland), the Special Refund Entitlement Register and the Drug Prescription Register (both maintained by the SII of Finland), the MBR and the RCM (both maintained by STAKES). In addition, information on maternal drug use during pregnancy and diagnoses of the children born was abstracted from maternal medical records reviewed in 45 hospitals (IV). The registry linkages were done using the unique identification number assigned to all residents in Finland as the key. The study protocol was approved by the ethics committees of the Northern Ostrobothnia and Pirkanmaa Hospital Districts. Register linkages were conducted with permission from STAKES, SII of Finland, and the Population Register Centre of Finland. Information included in the medical records was obtained with permission from the Ministry of Social Affairs and Health, Finland. As the study subjects were not contacted, informed consent to participate was not required.

4.2 Study populations

4.2.1 Patients with epilepsy (I–IV)

The entire Finnish population is entitled to national health insurance, which is maintained by the state and is organized through the SII of Finland. This insurance includes a pharmaceutical reimbursement system, which covers part of the costs of the prescription medicines. The reimbursement is calculated as a percentage of surplus costs after a fixed price. As of 2006, the reimbursement system included three categories:

basic (fixed price 10 euros, reimbursement 42% per payment), special (fixed price 5 euros, reimbursement 72% per payment) and complete (fixed price 5 euros, reimbursement 100% per payment). As of 2006, the complete reimbursement category comprised approximately 40 diseases, including epilepsy (SII of Finland 2006). The reimbursement is based on diagnosis and antiepileptic drugs prescribed for other indications than epilepsy are not included in the epilepsy reimbursement category.

In this study, the epilepsy patient cohort consisted of all epilepsy patients who were eligible for complete (100%) reimbursement for antiepileptic medication due to epilepsy between 1985 and 1994 and who were alive and residing in Finland on January 1, 1990 (N = 20,101). The patient cohort consisted of those born between 1920 and 1979. The information was obtained from the Special Refund Entitlement Register maintained by SII of Finland. The information included the unique personal identification number and type of reimbursement (perpetual or temporary) (I–IV).

Persons who had died before 1 January 1990 were removed from the SII database. Therefore, no information on them was available, nor was Information on type of epilepsy or antiepileptic medication available.

4.2.2 Reference cohort (I–III)

The reference cohort without epilepsy was identified through the Population Register Centre of Finland, with frequency-matching to the patient cohort by 5-year age (I–III). The cohort consisted of a stratified random sample of all those alive and resident in Finland on 1 January 1990. Those included in the patient cohort were excluded from the reference cohort. Figures 1 and 2 show the procedures of the present study in more detail.

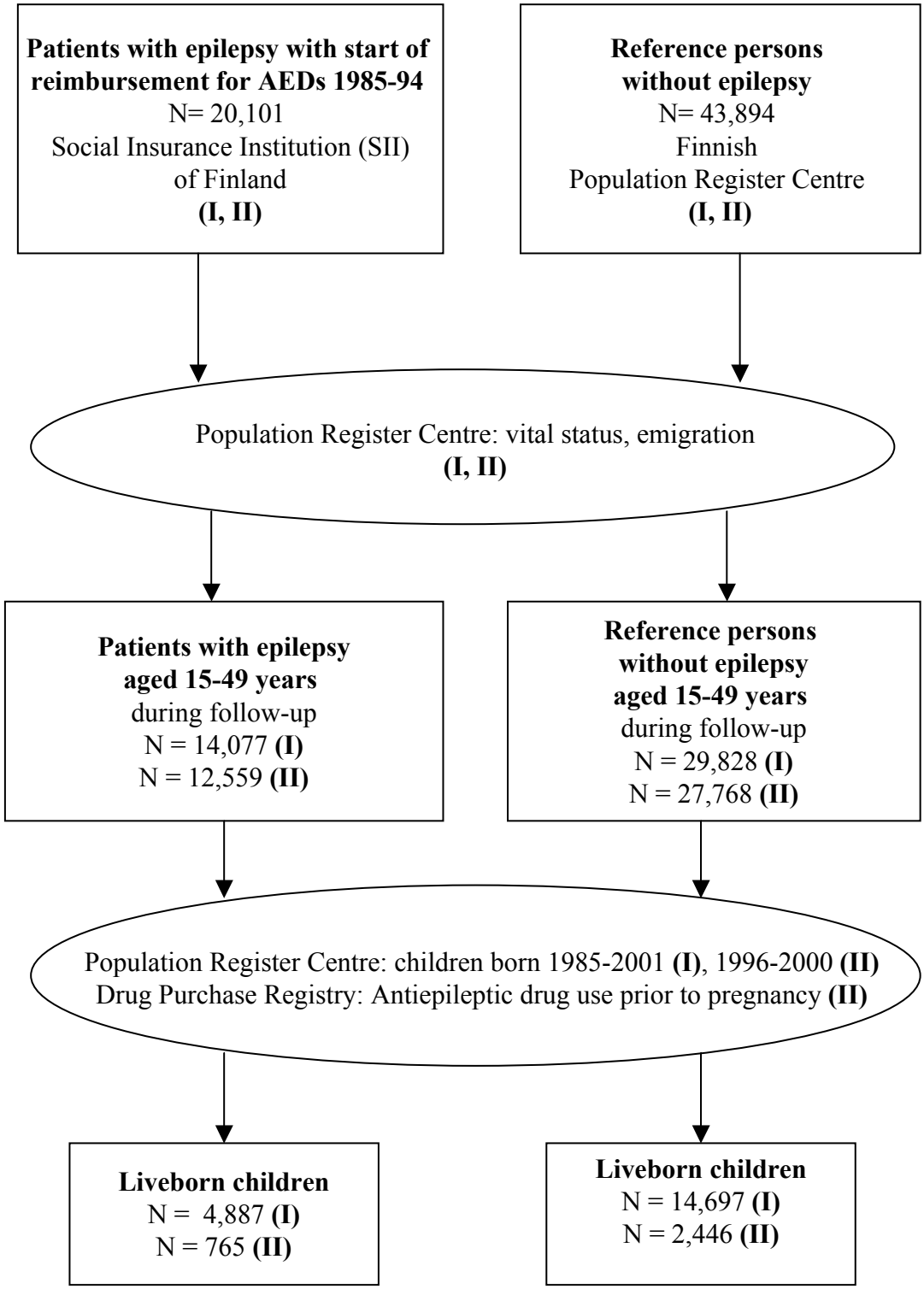

Fig. 1. The procedures and material for the studies I and II.

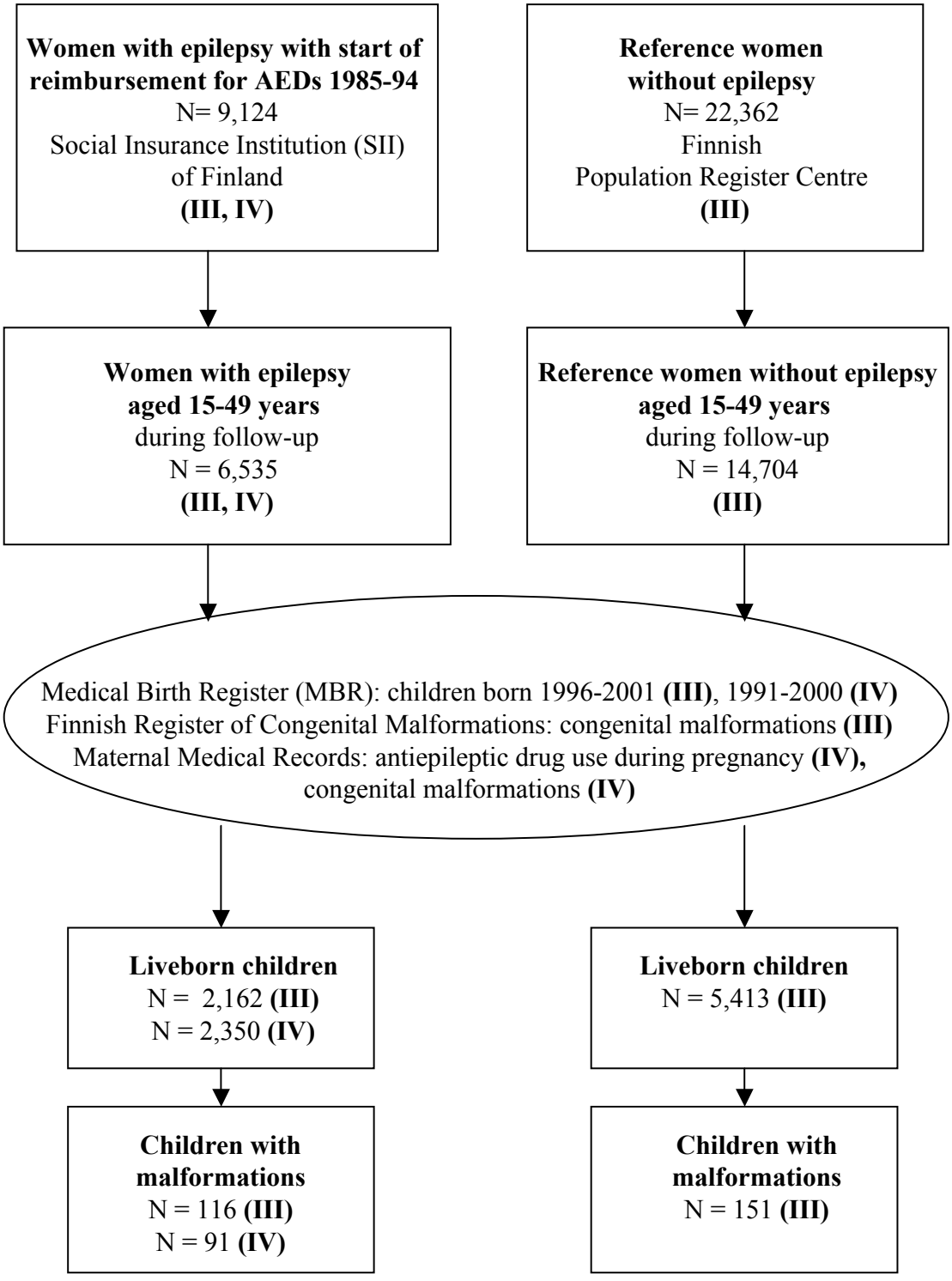

Fig. 2. The procedure and material for the studies III and IV.

4.3 Methods (I–IV)

4.3.1 Information on covariates and follow-up status

Information on vital status, marital status and emigration was obtained through the Population Register Centre of Finland. The information covered vital status and marital status at the end of follow-up (March 28, 2001), date of first marriage, date of possible emigration, and date of possible death. Information on maternal age at delivery and number of previous parities was obtained from the MBR maintained by STAKES.

Information on antiepileptic drug purchases for epilepsy from 1 January 1996 to 31 December 2000, was obtained from the Drug Purchase Register, maintained by the SII of Finland (II). Information included personal identification number, anatomic therapeutic chemical (ATC) code of the drug and the date of purchase.

Information on maternal AED use during pregnancy from 1 January 1991 to 31 December 2000 was abstracted from the medical records of women with epilepsy from 45 hospitals (IV). Information covered use, type, and dose of antiepileptic medication through the three trimesters of pregnancy.

4.3.2 Outcomes

Information on liveborn children was obtained from the Population Register Centre of Finland including information on the number and dates of births of liveborn children and dates of possible deaths (I, II). More detailed information on children born was obtained from the MBR maintained by STAKES. Information included the personal identification numbers of mothers and their liveborn or stillborn children, information on previous pregnancies, stillbirths (fetal weight of at least 500 g or gestational age at least 22 weeks), and deliveries (III, IV).

Information on congenital malformations was obtained from the Finnish RCM, maintained by STAKES (III). Information covered the personal identification numbers of mothers, and of their liveborn or stillborn children, as well as diagnosis of congenital anomaly according to ICD-9. Only major congenital structural anomalies are included in the register. However, if a child has a major anomaly, information on minor anomalies is also included in the register. A major congenital anomaly is defined in the register as a major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism at birth, selective termination of pregnancy or spontaneous abortion with congenital anomalies. Hereditary diseases and other diseases not associated with

congenital anomalies, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated dysmorphic features, normal variation and common less significant congenital anomalies are excluded from the register according to the exclusion list of the European Surveillance of Congenital Anomalies (EUROCAT) (http://www.eurocat.ulster.ac.uk). The RCM obtains information from hospitals, health-care professionals, cytogenetic laboratories and several nationwide registers on health and population statistics. Information on congenital malformations in the register is updated during the first year of life. Because the RCM was revised in 1993, information from before and after 1993 is not directly comparable. Therefore, only births between 1 January 1993 and 31 December 2000 were included. Information included the personal identification numbers of mothers, and of their liveborn or stillborn children and ICD-9 code of malformation.

Information on congenital malformations was abstracted from maternal obstetric records (IV). Information included the personal identification numbers of mothers, and liveborn children, also diagnosis according to ICD-9. As detailed information on congenital malformations was not always available in the medical records, minor and major anomalies could not be distinguished (IV).

4.3.3 Statistical methods

The live birthrates were estimated in terms of live births per person-years and the outcome was the first liveborn child after the start of follow-up (I). The data analyses were carried out using Cox proportional hazard modelling (Cox and Oakes 1984) in Stata 7.0 (StataCorp, 2001). The proportionality assumption was evaluated using Kaplan Meier graphics. Analyses were performed separately for men and women. Subjects contributed person-years only at fertile ages (15–49 years).

For patients with epilepsy, the follow-up started with reimbursement of AED costs or the 15th birthday, whichever was later (I). In the reference cohort without epilepsy, the start of follow-up (the index date) was the later of the 15th birthday or the mean starting date of reimbursement in patients with epilepsy in the corresponding five-year age group. The follow-up ended at live birth. Study subjects were censored on their 50th birthday, on emigration, at death, or the common closing date (28 March 2001), whichever was earliest, if they did not experience a live birth.

Analyses were performed for the first liveborn child, for the second liveborn child, for the third liveborn child, and for the fourth liveborn child separately (I). Similar analyses were performed by start of reimbursement, where the start of follow-up was divided into two periods for the epilepsy patients (1985–1989 and 1990–1994). For the reference cohort without epilepsy, follow-up was subdivided into two groups regarding

the start of reimbursement in every five-year birth category and the starting date of follow-up was July 1, 1987, or July 1, 1992. Separate analyses were performed for the five years preceding the index date (for the patient cohort: starting date of reimbursement for antiepileptic medication and for the reference cohort: the mean starting date of reimbursement in the patient cohort in that five-year birth category). Analyses were performed for each of the years, with the start of the follow-up on the date 1–5 years before the index date (or the 15th birthday if it was later).

Factors considered potential confounders and modifiers were sex, age, marital status, and previous live births (I). Analyses were stratified according to age at start of follow-up, age during observation, year of start of follow-up, follow-up period ($\leq$ 4 years, $\geq$ 5 years), marital status (never married, ever married) and number of children at start of follow-up.

Poisson regression modelling was used in the analyses of the effect of certain AEDs on birthrate (II). This method was used as the proportionality assumption was not fulfilled in the Cox proportional hazard model. Analyses were performed in Stata 8.2 (StataCorp, 2004). Analyses were performed separately for men and women with the first liveborn child as an outcome. Subjects contributed person-years only at fertile ages (15–49 years).

For patients on AEDs, the start of the follow-up was the first purchase of the AED, as all the patients were of fertile age (over 15 years old) at the start of the follow-up (II). The epilepsy patients not using AEDs and the reference cohort without epilepsy were used as comparison groups and the start of the follow-up was defined separately for each AED. For these groups, the start of the follow-up was set as the mean starting date of AED use among the patients with the medication in the corresponding five-year age group.

For patients on AEDs, the closing date of follow-up was the end of the medication use, the 50th birthday, emigration, death, the common closing date (28 March 2001), or the first pregnancy, whichever was the earliest (II). Start of the first pregnancy was estimated by subtracting nine months from the birth date of the first liveborn child, as information on time of conception was not available for this study. As the prescription of medicines is limited to three-month batches in Finland, the end of drug exposure was defined as three months after the last purchasing date.

For epilepsy patients not on AED and the reference cohort without epilepsy, the closing date was the 50th birthday, emigration, death, the common closing date (28 March 2001), or start of the first pregnancy, whichever was earliest.

Analyses were conducted separately for the use of CBZ, OXC and VPA (II). The number of subjects with other AEDs was too small for meaningful analysis. Patients who were on more than one AED during the follow-up contributed person-years to each

AED (overall use (monotherapy or polytherapy) and monotherapy). Those who did not have any antiepileptic medication during follow-up constituted the untreated epilepsy patient group.

Comparisons were made separately between the patients on AED and patients not taking any AED during the study period, and between patients on AED and the reference cohort without epilepsy (II). Analyses were conducted for each of the three AEDs, separately for overall use (monotherapy or polytherapy) and monotherapy use. Factors considered to be potential confounders and modifiers were sex, age and marital status at start of follow-up. Analyses were conducted separately for men and women. Age and marital status at start of follow-up were adjusted in the analyses.

The occurrence of major congenital malformations in the offspring of women with epilepsy was estimated in terms of prevalence proportion (number of malformations in offspring per 1,000 births) (III, IV). The analyses of major congenital malformations were performed using exact logistic regression in LogXact 4.1 (Cytel Software Corporation, 1999) with a major congenital malformation as the outcome (III). This exact logistic method was used as it yields more reliable results than regular asymptotic methods for rare outcome such as malformation. In this study, several children of the same mother may have been included in the analyses. As the exact method was used, correlation between the offspring of the same mother could not be accounted for in the analyses.

Overall odds ratio was estimated and separate analyses were conducted by organ systems according to ICD-9 (WHO 1977) (III). If a child had more than one major malformation of one organ system, these were treated as one outcome. Minor anomalies were excluded according to the definitions of the European Surveillance of Congenital Anomalies (EUROCAT, 2005) (III). Only children born after the epilepsy diagnosis were included in the analyses.

Factors considered to be potential confounders were maternal age at delivery and number of previous parities (III). Analyses with adjustment for each of these factors were conducted separately. Maternal age at reimbursement for antiepileptic medication and at delivery were considered as potential effect modifiers. Stratified analyses were conducted by maternal age at start of reimbursement and at delivery, time since reimbursement/index date and number of previous parities.

The effect of AED use was assessed by comparing the prevalence of congenital structural anomalies in the offspring of women with epilepsy being treated with AEDs during the 1st trimester of pregnancy (from zero to 12 weeks from the last menstrual period) and patients who had discontinued their antiepileptic medication prior to pregnancy in terms of prevalence proportion (number of malformations in offspring per 1,000 births) (IV). Odds ratios for congenital anomalies were performed using exact

logistic regression in LogXact 4.1 (Cytel Software Corporation, 1999) with congenital anomaly as an outcome. Stata 7.0 (StataCorp, 2001) was used for calculating significance for differences in prevalence proportions.

Separate comparisons were made pertaining to the use of CBZ, OXC, PHT and VPA (IV). The number of patients and live births was not sufficient to allow meaningful analyses of other medications (acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, phenobarbital, primidone, tiagabine, or vigabatrin). These drugs were combined into "the other medication" group. Monotherapies and polytherapies were analysed separately. CBZ, OXC, PHT and VPA were included in polytherapy combinations of "the other medication" group.

Major and minor congenital structural anomalies could not be separated, as detailed information on the type of anomaly was not always available (IV). Therefore, only main categories according to the organ systems of ICD-9 were included in the analyses. Bulbus cordis anomalies and anomalies of septal closure, other congenital anomalies of the heart, and other congenital anomalies of the circulatory system were classified as congenital anomalies of the cardiovascular system. If a child had more than one anomaly of one organ system, those anomalies were considered as a single outcome of the organ system. In the analyses, factors considered to be potential confounders were maternal age at delivery and number of previous births.

5 Results

5.1 Live birthrate (I, II)

Overall live birthrate was lower among both men and women with epilepsy (men: Hazard Ratio (HR) = 0.58, 95% Confidence Interval (CI) = 0.54–0.62; women: HR = 0.88, 95% CI = 0.83–0.93) in relation to the reference cohort without epilepsy (Table 5). In both genders, the birthrate was also lower before epilepsy diagnosis for the 5-year period prior to diagnosis (men: HR = 0.76, 95% CI = 0.72–0.80; women: HR = 0.79, 95% CI = 0.76–0.83). A negative trend was found with increasing age on observation for birthrate in men with epilepsy, but no clear differences between the age groups during the follow-up were observed in women with epilepsy.

Furthermore, in men, the birthrate was decreased regardless of the number of previous children. In women, the birthrate was slightly decreased for the first live birth (HR = 0.84, 95% CI = 0.75–0.90) and for the second live birth (HR = 0.89, 95% CI = 0.76–1.04), but not for the subsequent live births. Year of diagnosis (1985–89, 1990–94) or follow-up period (0–4 years, $\geq$ 5 years) did not modify the birthrate in epilepsy patients. Marital status did not affect the effect of epilepsy in stratified analyses, but when it was considered as a time-dependent covariate, effect of epilepsy decreased in both genders with epilepsy (men HR = 0.69, 95% CI = 0.65–0.74; women HR = 0.94, 95% CI = 0.89–1.00). Birthrates for the first liveborn children were also lower both in men (HR = 0.76, 95% CI = 0.72–0.80) and in women with epilepsy (HR = 0.79, 95% CI = 0.76–0.83) for the five-year period preceding the epilepsy diagnosis.

Table 5. Chance (hazard ratios (HR) with 95 percent confidence intervals (CI)) of a subsequent child among patients with epilepsy in relation to the reference cohort without epilepsy according to demographic factors and factors related to follow-up and gender, by gender, 1985–2001.

	Men	Women
	HR (CI)	HR (CI)
Total	0.58 (0.54–0.62)	0.88 (0.83–0.93)
Age (years) at diagnosis		
0–9	1.20 (0.55–2.63)	1.13 (0.75–1.72)
10–19	0.69 (0.61–0.79)	1.02 (0.94–1.12)
20–29	0.55 (0.50–0.61)	0.73 (0.67–0.79)
30–39	0.49 (0.42–0.56)	0.64 (0.54–0.76)
40–49	0.61 (0.40–0.91)	0.62 (0.26–1.52)
Age (years) at observation		
15–19	0.77 (0.46–1.28)	1.26 (1.01–1.57)
20–29	0.66 (0.60–0.72)	0.88 (0.82–0.94)
30–39	0.52 (0.48–0.57)	0.74 (0.68–0.81)
40–49	0.45 (0.35–0.56)	0.78 (0.55–1.11)
Year of start of follow-up		
1985–1989	0.67 (0.61–0.73)	1.03 (0.96–1.12)
1990–1994	0.57 (0.51–0.63)	0.83 (0.75–0.90)
Marital status		
Never married	0.56 (0.52–0.61)	0.85 (0.79–0.90)
Ever married	0.63 (0.56–0.72)	0.87 (0.77–0.98)
No. of children at start of follow-up		
0	0.54 (0.50–0.59)	0.84 (0.79–0.90)
1	0.59 (0.50–0.70)	0.89 (0.76–1.04)
2	0.77 (0.62–0.96)	0.75 (0.61–0.94)
≥3	0.59 (0.42–0.83)	0.80 (0.57–1.12)

5.1.2 Antiepileptic drugs and live birthrate (II)

The birthrate was lower in both patients with epilepsy on AEDs and not using AEDs than in the reference cohort without epilepsy (Table 6) (II). Birthrates were lower in men with epilepsy than in women with epilepsy on CBZ or OXC (interaction CBZ:

Table 6. Number of live births, total follow-up time (person-years, pyrs) and birthrate (per 1,000 person-years) in patients with epilepsy on antiepileptic medication, patients without antiepileptic medication and the reference cohort without epilepsy according to AEDs, 1996–2000.

AED	Patients on therapy			Untreated patients			Referents		
	births N	pyrs total	birth rate	births N	pyrs total	birth rate	births N	pyrs total	birth rate
Carbamazepine									
All users									
Female	130	3591	36.2	201	1211	44.6	1302	6151	57.2
Male	101	5834	17.3	151	1574	24.8	1147	7538	39.6
Monotherapy									
Female	98	2847	34.4	195	1205	44.2	1279	6125	57.4
Male	77	4743	16.2	151	1570	25.3	1131	7521	39.8
Oxcarbazepine									
All users									
Female	41	1215	33.7	172	1169	41.7	1165	5987	56.3
Male	18	1412	12.7	144	1545	25.8	1030	7528	39.2
Monotherapy									
Female	28	778	36.0	172	1168	41.9	1172	5992	56.8
Male	10	941	10.6	145	1546	26.1	1034	7385	39.3
Valproate									
All users									
Female	99	2431	40.7	186	1182	43.8	1222	6054	57.1
Male	58	2715	21.4	150	1552	26.3	1077	7441	39.7
Monotherapy									
Female	62	1616	38.4	180	1177	43.2	1196	6020	57.1
Male	36	1586	22.7	147	1546	26.2	1060	7414	39.8

overall $p < 0.05$; monotherapy $p < 0.05$; OXC: overall $p = 0.05$; monotherapy $p < 0.05$). In comparison with untreated epilepsy patients, women on any of the three AEDs had non-significantly lower birthrates. In men, however, birthrate was significantly decreased only in those on OXC (Rate ratio (RR) = 0.52, 95% CI = 0.32–0.84).

Adjustment for marital status and age at start of follow-up decreased the effect of CBZ both in men (unadjusted RR = 0.70, 95% CI = 0.54–0.90; adjusted RR = 0.86, 95% CI = 0.66–1.13) and in women (unadjusted RR = 0.81, 95% CI = 0.65–1.01; adjusted RR = 1.01, 95% CI = 0.80–1.27) (Table 7) (II). Adjustment did not, however, affect the results regarding the effects of other AEDs (OXC, VPA).

Table 7. Adjusted rate ratios (RR) with 95% confidence intervals (CI) for the first liveborn child among female and male epilepsy patients on AED (monotherapy or polytherapy) in relation to patients without AEDs and the reference cohort without epilepsy, Finland 1996–2000

Study group	Women All users *	Men All users *
	RR (CI)	RR (CI)
Epilepsy patients without AED	1.00 Ref	1.00 Ref
Epilepsy patients on AED		
Carbamazepine	1.01 (0.80–1.27)	0.86 (0.66–1.13)
Oxcarbazepine	0.83 (0.59–1.17)	0.52 (0.32–0.84)
Valproate	0.87 (0.66–1.15)	0.78 (0.55–1.11)
Reference cohort without epilepsy	1.00 Ref	1.00 Ref
Epilepsy patients on AED		
Carbamazepine	0.69 (0.58–0.83)	0.47 (0.38–0.58)
Oxcarbazepine	0.60 (0.44–0.82)	0.34 (0.21–0.54)
Valproate	0.65 (0.51–0.83)	0.52 (0.38–0.72)

AED, antiepileptic drug; RR, rate ratio; Ref, reference
*) AED use in monotherapy or polytherapy

5.2 Prevalence of congenital malformations (III, IV)

5.2.1 Overall occurrence of major congenital malformations (III)

The prevalence of major malformations was 54/1,000 births among women with epilepsy and 28/1,000 among women without epilepsy (Table 8). The offspring of women with epilepsy had a two-fold (Odds ratio (OR) = 1.98, 95% CI = 1.53–2.55) risk for major congenital malformations in relation to the reference cohort without epilepsy. A substantial increase in the risk for spina bifida (OR = 11.3, 95% CI = 2.34–108) and congenital malformations of the genital organs (OR = 8.38, 95% CI = 2.15–47.4) was found in the offspring of mothers with epilepsy in relation to the offspring of the reference cohort without epilepsy. Also, higher risk for congenital anomalies of the circulatory system (OR = 4.19, 95% CI = 1.38–14.0), other congenital anomalies (OR = 3.20, 95% CI = 1.35–7.80), and other congenital anomalies of the limbs (OR = 2.66, 95% CI = 1.29–5.51) was observed in the offspring of women with epilepsy than in the offspring of the mothers without epilepsy. Six confirmed and two suspected valproate syndromes were observed in the offspring of women with epilepsy.

Adjustment for maternal age at delivery did not alter the effect of epilepsy. Adjustment for previous parities did not affect any other results except those related to other congenital anomalies of the nervous system (unadjusted OR = 2.93, 95% CI = 0.84–10.6; adjusted OR = 3.48, 95% CI = 1.10–11.0). No clear trend for maternal age at delivery was observed in the risk for major malformations (p for trend = 0.07). However, the risk increased with time since reimbursement for antiepileptic medication (p for trend = 0.02).

Table 8. Prevalence (per 1,000 births), number (N) of major congenital malformations and crude odds ratios with 95% confidence intervals (CI) for major congenital malformation in offspring of patients with epilepsy in relation to offspring of the reference mothers by type of malformation, 1993–2000.

Type of malformation (ICD-9 code)	Prevalence/1000 births				OR	CI
	Patients		Referents			
Spina bifida	4.2	(9)	0.4	(2)	11.10	(2.38–108)
Other congenital anomalies of the nervous system (742)	3.2	(7)	1.1	(6)	2.93	(0.84–10.6)
Congenital anomalies of the eye (743)	2.8	(6)	1.3	(7)	2.15	(0.60–7.48)
Congenital anomalies of the ear, face, and neck (744)	3.7	(8)	1.1	(6)	3.35	(1.02–11.7)
Bulbus cordis anomalies and anomalies of cardiac septal closure (745)	15.7	(34)	8.7	(47)	1.82	(1.13–2.91)
Other congenital anomalies of the heart (746)	3.2	(7)	3.0	(16)	1.10	(0.38–1.00)
Other congenital anomalies of the circulatory system (747)	4.6	(10)	1.1	(6)	4.19	(1.38–14.0)
Congenital anomalies of the respiratory system (748)	5.1	(11)	3.0	(16)	1.72	(0.72–3.96)
Cleft palate and cleft lip (749)	5.1	(11)	3.1	(17)	1.62	(0.69–3.68)
Other anomalies of the upper alimentary tract (750)	1.4	(3)	0.9	(5)	1.50	(0.23–7.73)
Other congenital anomalies of the digestive system (751)	1.9	(4)	2.2	(12)	0.83	(0.23–2.76)
Congenital anomalies of the genital organs (752)	4.6	(10)	0.6	(3)	8.38	(2.15–47.4)
Congenital anomalies of the urinary system (753)	8.8	(19)	3.3	(18)	2.66	(1.32–5.38)
Certain congenital musculoskeletal deformities (754)	5.1	(11)	2.2	(12)	2.30	(0.92–5.71)
Other congenital anomalies of the limbs (755)	2.3	(5)	0.4	(2)	6.27	(1.03–65.9)
Other congenital musculoskeletal anomalies (756)	1.9	(4)	2.4	(13)	0.77	(0.18–2.50)
Congenital anomalies of the skin, hair, and nails (757)	6.5	(14)	2.0	(11)	3.20	(1.35–7.80)
Chromosomal anomalies (758)	1.9	(4)	2.4	(13)	0.77	(0.18–2.50)
Other congenital anomalies (759)	6.5	(14)	2.0	(11)	3.20	(1.35–7.80)
Overall	54.0	(116)	28.0	(151)	1.98	(1.53–2.55)

5.2.2 Antiepileptic drug use during pregnancy and congenital malformations (IV)

The most frequent types of congenital malformations were anomalies of the cardiovascular system, cleft lip and palate, anomalies of the genital organs, certain musculoskeletal deformities, and other anomalies of the limbs in the children of both the untreated epilepsy patients and the epilepsy patients on AED during the first trimester of pregnancy. The overall proportion of children with congenital malformations was higher in women on AEDs (65/1,411, 4.6%) than in untreated women with epilepsy (26/939, 2.8%) (Table 9). The proportion of children with congenital malformation was lower in women on monotherapy (52/1,231, 4.2%) than in women on polytherapy (13/180, 7.2%). Among women on AED, more than half of the children with congenital malformations were born to women on VPA (37/65, 57%).

In relation to the offspring of the untreated patients, the OR for congenital malformations was slightly higher in the offspring of women on any AED during the first trimester of pregnancy (OR = 1.70, 95% CI = 1.05–2.81) (Table 9). No significantly increased OR was found for congenital malformations in the offspring of patients on AED monotherapy (OR = 1.55, 95% CI = 0.94–2.60), but a clearly elevated OR was found for the congenital malformations in the offspring of patients on polytherapy (OR = 2.73, 95% CI = 1.26–5.64) in relation to offspring of patients not using AED.

Exposure to VPA during the first trimester of pregnancy substantially increased the OR for congenital malformations in the offspring compared to the children of the untreated patients, regardless of type of VPA use (monotherapy or in combination with other AEDs) (Table 9). The offspring exposed to any other AED used as monotherapy, or in combination with other AEDs, did not have significantly higher OR for congenital malformations in relation to the offspring of the patients not using AED.

No significantly higher OR for congenital malformations was found for the offspring of mothers on any CBZ therapy (either as monotherapy or polytherapy), (OR = 1.27, 95% CI = 0.72–2.23) in relation to the offspring of the women not using AED (Table 9). However, a significantly higher OR for congenital malformations was found in the offspring of mothers on CBZ polytherapy (OR = 3.43, 95% CI = 1.44–7.61).

Table 9. Prevalence (per 1,000 births) and number (N) of births with congenital malformation in women with epilepsy on AED during the first trimester of pregnancy, and odds ratios (OR) with 95% confidence intervals (CI) for congenital malformation in offspring in relation to offspring of women with epilepsy without AED during the first trimester of pregnancy, by type of antiepileptic medication, 1991–2000.

	Prevalence	Number	OR	CI
No AED	28	26	1.00	Reference
Carbamazepine	35	32	1.27	(0.72–2.23)
Monotherapy	27	22	0.99	(0.53–1.83)
Polytherapy	88	10	3.43	(1.44–7.61)
Excluding VPA	69	4	2.60	(0.64–7.88)
Oxcarbazepine	23	3	0.83	(0.16–2.77)
Monotherapy	10	1	0.36	(0.01–2.23)
Polytherapy	65	2	2.42	(0.27–10.5)
Excluding VPA	59	1	2.19	(0.05–15.2)
Valproate	102	37	4.01	(2.32–7.01)
Monotherapy	107	28	4.18	(2.31–7.57)
Polytherapy	92	9	3.54	(1.42–8.11)
Other Medication *	38	5	1.37	(0.40–3.72)
Monotherapy	–	0	–	(0.00–5.73)
Polytherapy	47	5	1.75	(0.51–4.77)
Excluding VPA	41	3	1.48	(0.28–5.02)
Total therapy	46	65	1.70	(1.05–2.81)
Excluding VPA	36	38	0.96	(0.54–1.72)
Total monotherapy	42	52	1.55	(0.94–2.60)
Excluding VPA	25	24	0.89	(0.49–1.63)
Total polytherapy	72	13	2.73	(1.26–5.64)
Excluding VPA	49	4	1.80	(0.45–5.38)

AED, antiepileptic drug; VPA, valproate

* Other medication: acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, phenobarbital, primidone, tiagabine, topiramate, or vigabatrin.

However, when CBZ polytherapy combinations with VPA were excluded, the risk of congenital malformations was not significantly higher (OR = 2.60, 95% CI = 0.64–7.88) in relation to the offspring of the patients not using AED.

A significant dose-dependent relationship was found for VPA monotherapy ($p < 0.0001$), but not for CBZ monotherapy. Adjustment for maternal age at delivery, or number of previous births did not affect the effect of use of different AEDs on the risk of congenital malformations in the offspring.

6 Discussion

6.1 Birthrate

In most studies, the birthrate has been lower in epilepsy patients (Webber et al. 1986, Schupf and Ottman 1996). However, Olafsson and colleagues (1998b) in their population-based study in Iceland did not find a difference in birthrate between patients with epilepsy and the reference cohort. In our study, birthrate was decreased in both sexes, especially in men after epilepsy diagnosis.

In our study, the birthrate was decreased both in treated and untreated women with epilepsy. A difference in birthrate between women on different AEDs was not observed in this study (II). This finding is unexpected, as some studies have suggested that in women use of VPA is more commonly associated with reproductive disorders than some other AEDs (Morrell et al. 2002, Betts et al. 2003).

Men with epilepsy had a decreased birthrate regardless of the number of previous live births, but number of earlier children modified the birthrate in women with epilepsy (I). Female patients without children or with one earlier child had lower birthrate than women without epilepsy. Among women with more than one child, no difference between the patients and the reference cohort was observed.

A low birthrate has been reported among married epilepsy patients (Dansky et al. 1980, Schupf and Ottman 1994, 1996, Jalava and Sillanpää 1997). Complete information on marital status was not available, but only information on the date of first marriage. The effect of epilepsy did not differ between never and ever married subjects, but adjustment for marital status decreased the difference between epilepsy patients and the reference cohort, especially when marital status was used as a time-dependent covariate (I). Adjustment for marital status decreased the difference in birthrate between the patients on CBZ and the patients not using AED, but it did not affect the other results (II). As the information on marital history was incomplete, non-differential misclassification is possible, which may have affected the results of this study.

Studies on the effect of age at onset of epilepsy on marriage and fertility have not yielded consistent results. Young age at diagnosis has been associated with reduced fertility in married men with epilepsy (Schupf and Ottman 1994). Also, age at onset of epilepsy has not been associated with marital status in earlier studies (Jalava and Sillanpää 1997). Regarding birthrate in women with epilepsy (I), the results of this study were consistent with those of Dansky et al. (1980), who found that birthrate was

lower among female epilepsy patients with onset at age 20 years or more. In contrast to certain studies (Dansky et al. 1980, Schupf and Ottman 1994, 1996), birthrate was not lower among those with epilepsy diagnosis before 10 years of age in this study.

In both men and women with epilepsy, birthrate for first liveborn child was lower than in the reference cohort also before the start of reimbursement for antiepileptic medication, but without a clear trend by time prior to diagnosis (I). The current diagnostic criteria for epilepsy require at least one seizure, and patients in this study may have had seizures prior to diagnosis, which affected the birthrate. However, it would be expected that this effect would attenuate with time prior to diagnosis.

There was a substantial difference in birthrate between the patients with long follow-up period and the reference cohort without epilepsy (I). One possible explanation for this may be that although antiepileptic medication can be discontinued in many women with epilepsy during the course of the disease, the proportion of patients with poor seizure control and polytherapy may increase with long duration of epilepsy, and this may affect fertility and birthrate.

Two possible modifiers of antiepileptic medication that were available were assessed (I). Analyses by year of diagnosis were conducted to assess the effect of possible changes in antiepileptic medication during the follow-up period. Analyses by follow-up period were conducted to assess the effect of duration of AED use on birthrate. Neither of these factors modified the effect of epilepsy on birthrate.

Both in women and in men with epilepsy on antiepileptic medication, birthrate was closer to patients not using AED than to the reference cohort without epilepsy. When compared to the reference cohort without epilepsy, the birthrate was lower in both sexes on any of the three AEDs. However, when compared with the patients without AED treatment, a significant difference was seen only in men on OXC.

6.2 Occurrence of congenital malformations

The proportion of children with major malformations born to women with epilepsy has varied from 37/1,000 to 155/1,000 births according to earlier research (Battino et al. 1992, Samrén et al. 1997, Olafsson et al. 1998b, Canger et al. 1999, Kaneko et al. 1999). In this study (III), the prevalence of newborns with major malformations (54/1,000) was lower than earlier reported.

Regarding different types of malformations, the results of this study (III) were mostly consistent with those of earlier studies. The highest risk has been found for spina bifida, urogenital and cardiovascular malformations and cleft palate in the offspring of women with epilepsy (Canger et al. 1999, Samrén et al. 1999, Matalon et al. 2002).

However, the risk for cleft palate was not clearly elevated according to this study (III). As information on AED use was not included in publication III, no separate analyses on different AED exposures could be conducted.

The results of this study (III) were consistent with earlier population-based studies on the risk for malformations in the offspring of patients with epilepsy. In a study conducted in the United Kingdom, the risk for malformations was 2.2-fold in the offspring of women with epilepsy in relation to general population (Fairgrieve et al. 2000). In another study conducted in Iceland, the risk for malformations was 2.7-fold in the offspring of patients with epilepsy on AEDs and 2.2-fold in the offspring of patients without AEDs in relation to general population (Olafsson et al. 1998b). However, the overall risk of malformation in the offspring of epilepsy patients was not evaluated in the study by Olafsson et al. (1998b).

The mean number of major malformations was higher in the offspring of women with epilepsy than in the offspring of the reference cohort (III). When minor malformations were included, the difference between the groups increased. The offspring of patients with epilepsy may have more multiple malformations including minor malformations, than the offspring of reference cohort.

The risk for congenital malformations in the offspring of patients treated with CBZ, OXC, PHT, or VPA during pregnancy was evaluated in this study (IV). The offspring of mothers on VPA had a four-fold increased risk for malformations compared to the offspring of women not using AED. No excess risk was related to other AEDs than VPA. As in earlier studies, a clear dose-effect in use of VPA and the risk of malformation in the offspring was found in this study (IV). The offspring of patients taking more than 1,500 mg/day had a more than ten-fold risk for malformations. However, minor and major malformations could not be separated in this study (IV).

More than half of the patients on AED were taking CBZ or VPA in this study (IV). Other AEDs were used less commonly. Therefore, the risk associated with these AEDs could not be evaluated in this study. However, the 99 children of patients on OXC monotherapy in this study (IV) was the largest number of offspring exposed to OXC so far studied. Nevertheless, a larger study population would be needed to evaluate the teratogenic effects of the newer AEDs.

When AEDs used as monotherapy were pooled together, the risk for malformations in the offspring was not elevated. The risk for malformations was elevated in offspring exposed to VPA monotherapy but not for other AEDs used as monotherapy. As in other studies, a clearly elevated risk for malformations in the offspring of patients on polytherapy was found in this study (IV) (Olafsson et al. 1998b, Samrén et al. 1999, Holmes et al. 2001). As the number of patients with more than two

AEDs was small (N = 26), the risk according to the number of AEDs used in polytherapy could not be evaluated in this study (IV).

The information on congenital anomalies was incomplete and minor anomalies could not be excluded (IV). Therefore, results of this study (IV) are not directly comparable with those of studies on major malformations alone. However, the results of this study (IV) for patients without AED treatment (277/10,000 births) were comparable to the prevalence of major malformations in the Finnish general population between 1993 and 2000 (286/10,000 births) (Ritvanen and Sirkiä 2004). One possible explanation for this is that not all malformations are identified at birth, but are reported to the registry later during the first year of life.

As in earlier studies (Lander and Eadie 1990, Canger et al. 1999, Kaneko et al. 1999), adjustment for maternal age at delivery or number of older children did not affect the risk of congenital malformation in our study (III, IV).

Because information on type of epilepsy or antiepileptic medication was not available, duration of epilepsy was used as an effect modifier for use of antiepileptic medication (III). Jalava and Sillanpää (1997) found that more than two thirds of their study patients achieved remission and did not require further pharmaceutical treatment for their epilepsy. The definition of remission was not defined in the study by Jalava and Sillanpää (1997). According to ILAE, epilepsy can be considered as being in remission after freedom from seizures for 5 years with or without antiepileptic medication (Commission on the Epidemiology and Prognosis of the ILAE 1993). If the possibility for discontinuation of antiepileptic medication increases with duration of epilepsy, the risk for congenital malformations in the offspring is expected to decrease. In this study, the risk for malformations was highest for offspring born $\geq$ 10 years after reimbursement (III). One possible explanation for this is that although antiepileptic medication may be discontinued in many women with epilepsy, the proportion of patients with poor seizure control and treatment with polytherapy may increase with long duration of epilepsy. However, it has also been reported that duration of maternal epilepsy is not associated with the incidence of malformations in the offspring (Lander and Eadie 1990).

The use of valproate or carbamazepine during the first trimester of pregnancy elevates the risk for neural tube defects, especially spina bifida (Bjerkedal et al. 1982, Koren et al. 1998, Hernández-Diaz et al. 2000, Matalon et al. 2002). Periconceptional folic acid supplementation is known to reduce the risk for neural tube defects (Berry et al. 1999). As the risk for neural tube defects is elevated in the offspring of women on antiepileptic medication, these women are recommended to take 0.4 mg of supplementary folic acid four weeks prior to conception and during the first 12 weeks of pregnancy (Ministry of Social Affairs and Health, Finland 1995). Information on folic

acid use was not available for this study. This may have caused confounding regarding on the risk for these types of malformations in the offspring of patients with epilepsy in this study, if the pregnancy-related use of folic acid supplementation differed between the patient groups on different AEDs.

Usually severe spina bifida is an indication for selective termination of pregnancy (Botto et al. 1999) and therefore, the prevalence of spina bifida is reduced in stillborn or liveborn children. Kaaja et al. (2003) in their Finnish study found that 0.6% pregnancies were terminated due to fetal congenital malformations in women with epilepsy. In this study, the risk for spina bifida was substantially elevated in the offspring of women with epilepsy (III). However, only 5% of the congenital malformations were neural tube defects (IV).

As information on spontaneous or selective abortions was not available for this study, the contribution of these events to the risk for malformations in the offspring could not be estimated in this study (III, IV). This does not affect the results of this study unless the rate of spontaneous or selective abortions due to major malformations substantially differs between epilepsy patients and subjects without epilepsy, or between epilepsy patients with difference AED exposures. However, the number of terminations due to fetal indications of major malformations is small overall. Furthermore, inclusion or exclusion of stillbirths did not alter the results on the risk for major malformations in the offspring (III). The overall prevalence of major malformations in the offspring of the reference cohort (28.0 per 1,000 births) (III) was very similar to that of the children born in Finland during the period 1993–2000 (29.3 per 1,000 births) (National Research and Development Centre for Welfare and Health 2000).

Maternal use of phenytoin or phenobarbital is known to elevate the risk of cleft lip and palate in the offspring (Oguni and Osawa 2004), and orofacial clefts and spina bifida are major malformations in valproate syndrome (Clayton-Smith and Donnai 1995, Moore et al. 2000). The risk for orofacial clefts was not elevated in the offspring of mothers with epilepsy in this study (III), but a substantially higher risk for spina bifida was found in the offspring of mothers with epilepsy than in the offspring of mothers without epilepsy. These findings may reflect changes in use of AEDs i.e. decrease in use of phenytoin and phenobarbital and increase in use of valproate (Bolton King et al. 1996). A total of five children exposed to valproate monotherapy had spina bifida and cleft lip/palate in this study (IV).

More intensive medical follow-up with more detailed recording, reporting and registration of malformations during and after pregnancy may affect the prevalence of congenital malformations in the offspring of epilepsy patients (Källén 2005). This may have led to overestimation of the prevalence of malformations in the offspring of women with epilepsy in relation to other children in this study (III).

Information on malformations was abstracted from maternal obstetric records (IV). The proportion of children born with malformation was smaller in publication III (3.9%) than in publication IV (5.4%) even when minor malformations were included in publication III. One explanation for this difference may be that all minor malformations recorded in the maternal obstetric records are not included in the Finnish RCM. Furthermore, the number of born children was clearly smaller in publication IV (235 per year) than in publication III (309 per year).

6.3 Register-based approach to reproductive health in epilepsy patients

Large population-based studies on birthrate in patients with epilepsy are rare. Most studies have been based on clinical records (Dansky et al. 1980, Wallace et al. 1998) including some hundreds of epilepsy patients (Dansky et al. 1980, Jalava and Sillanpää 1997, Olafsson et al. 1998b) without a population-based reference cohort (Dansky et al. 1980, Schupf and Ottman 1994, 1996, Jalava and Sillanpää 1997). Furthermore, few studies have addressed the effects of certain AEDs on birthrate (Jalava and Sillanpää 1997).

Only a few population-based studies have been conducted on congenital malformations in the offspring of patients with epilepsy (Bolton King et al. 1996, Olafsson et al. 1998b, Wide et al. 2004). Most been based on small numbers (Källén 1988, Battino 2001) of offspring without a population-based comparison group, or without a reference group of patients not using AED. As most of the studies have been hospital-based, patients with complicated epilepsy and polytherapy may have been over-represented. Furthermore, the comprehensive and nationwide material of the present study enabled evaluation of risks for the most common types of malformations in the offspring of patients with epilepsy.

This study was mostly register-based: all the information used was obtained from Finnish population statistics and health registers (I–III). In addition, maternal obstetric records were used as source of information (IV). This approach enabled us to conduct a large, population-based study with a large reference cohort of general population, comprehensive information on children born, congenital malformations and AED purchases. The coverage of the Finnish health registers is generally high (Gissler and Haukka 2004). The MBR covers all births in Finland (Teperi 1993, Gissler et al. 1995) and the RCM obtains information on malformations from several sources. The information is updated in the first year after birth. Reimbursement for AEDs is based on diagnosis with well defined criteria, and antiepileptic drugs prescribed for other

indications than epilepsy are not included under the epilepsy category in the SII special refund database.

In this study, record linkages were conducted with permission from the STAKES, SII of Finland and the Population Register Centre of Finland. As the information from the registers was merged through record linkages with Personal Identifier (PID) as a key, the study subjects were not contacted, and therefore informed consent to participate was not needed. Use of individual identification numbers as a key in register linkages improved the completeness of information in the study (Gissler and Haukka 2004). Furthermore, a register-based study was relatively cheap and quick to conduct. Recall bias and low participation rates, which are probable, for example when the information is obtained from interviews, could be avoided with the register-based approach used for this study (Rothman and Greenland 1998).

In this study, identification of patients with epilepsy may have been incomplete. Information on institutionalised patients and information on those not seeking reimbursement for antiepileptic medication is not included in the SII special refund database. As the prices for most of the AEDs are high in Finland, people with epilepsy are not likely to refuse reimbursement for AED purchases. Therefore, exclusion of these epilepsy patients does not greatly affect the results of this study. However, no validation studies on the special refund entitlement register or the drug prescription register have been conducted in Finland.

As the national health registers are mostly created and maintained primarily for administrative purposes, not all the needed information for research purposes may always be available. Information on socioeconomic status was not included in this study, but it was a possible confounding factor. Overall, the number of children is lower among those with higher education than among the most of the population. Patients with epilepsy have lower socioeconomic status and less education than the population in general (Jalava et al. 1997). However, In Finland patients in remission off medication have similar education and socioeconomic status to those without epilepsy (Sillanpää et al. 2004). Therefore, the observed decreased birthrate in patients with epilepsy is not likely to be attributable to epilepsy-related socioeconomic factors. However, epilepsy may affect a person's ability to obtain education and work (Jalava et al. 1997, Sillanpää et al. 2004). In Finland, the out of pocket costs of AEDs for epilepsy patients are low. Furthermore, there are no major differences in the quality of epilepsy care or in the AEDs used among patients with epilepsy due to their socioeconomic status. Therefore, confounding by socioeconomic status was not likely to affect comparisons between patients on different AEDs in this study.

As information on actual drug intake was not available, information on prescribed drug purchases was used as a proxy for AED use (II). Some women with epilepsy may

stop taking AEDs because of potential adverse effects (Chang and McAuley 1998, Williams et al. 2002). However, Olesen et al. (2001) in their Danish study did indeed find that compliance in the use of prescribed AEDs due to epilepsy was high (100% for AEDs) as also in other chronic diseases (such as insulin-dependent diabetes mellitus, thyroid diseases, depression, asthma and hypertension). Furthermore, it is not known whether discontinuation of AED treatment poses a greater hazard for both mother and the fetus than the potential side effects due to AED treatment during pregnancy and women with epilepsy on AED are not likely to discontinue their antiepileptic medication during pregnancy. Therefore, missing information on actual drug intake probably did not substantially affect the results of this study.

Patients with epilepsy have different types of epilepsy syndromes. These groups may also differ in relation to other factors affecting reproduction and childbearing. Furthermore, different AEDs are usually used for different types of epilepsies, and therefore people on AEDs and people without AEDs are not similar in terms of type of epilepsy (including etiology, seizure characteristics and age at onset). As information on type of epilepsy was not included in this study, the effect of epilepsy and AEDs on fertility, birthrate and prevalence of congenital malformations in the offspring of patients with different types of epilepsy could not be distinguished in this study. Also, it is unclear if and which of these factors affect social life and role performance and thereby fertility in different epilepsy types. Therefore, confounding by indication is possible, and the results of this study should be interpreted with caution. It would be important to include psychosocial aspects in future studies on the reproductive health of patients with epilepsy.

Information on the semen quality of men with epilepsy, or female fecundity was not included in this study. Also, information on 'intention to conceive', contraceptive use, or lifestyle-related factors (such as alcohol consumption or smoking) affecting time to pregnancy was not available for this study. Nor was information on fertility treatments included in this study. In future studies on birthrate in patients with epilepsy, it would be important to include these factors.

The study population of this study was large enough to evaluate the prevalence of major malformations in the offspring of patients with epilepsy by type of malformation (III) and by most common AEDs used in Finland (IV). A future study on prevalence of different types of major malformations in offspring exposed to various AEDs during pregnancy would be important in assessing a large population-based cohort of epilepsy patients. In addition, such a study on the effects on reproductive health of using newer AEDs would also yield important information for the clinical treatment of epilepsy patients of reproductive age.

7 Summary and conclusions

The birthrate among epilepsy patients and the prevalence of congenital malformations in their offspring were evaluated in this population-based cohort study. This study was largely based on information obtained from five Finnish registers on population statistics and health: the Population Register, the Special Refund Entitlement Register, the Drug Prescription Register, the MBR and the RCM. In addition, information on maternal drug use during pregnancy and diagnoses of the children born was abstracted from medical records reviewed in 45 hospitals (IV).

The birthrate was lower both in men (HR = 0.58, 95% CI = 0.54–0.62) and in women (HR = 0.88, 95% CI = 0.83–0.93) with epilepsy than in the reference cohort without epilepsy. In men with epilepsy, a negative trend for birthrate was found for increasing age on observation. When marital status was considered as a time-dependent covariate, the effect of epilepsy decreased both in men (HR = 0.69, 95% CI = 0.65–0.74) and in women (HR = 0.94, 95% CI = 0.89–1.00). In women with epilepsy, the birthrate decreased slightly for the first and for the second live birth. In men with epilepsy, the birthrate decreased regardless of previous births. In relation to the reference cohort without epilepsy, birthrate was lower both in men and in women on any of the three AEDs (CBZ, OXC, VPA), but when the birthrate was compared between patients on AED and patients without AED prior to pregnancy, lower birthrate was observed only in men on OXC.

Birthrate was used as a measure of fertility in this study (I, II). As information on intention to conceive or the use of contraceptives was not included in this study, it is unclear whether the lower birthrate was due to a diminished capacity to conceive or voluntary. Furthermore, information on epilepsy type was not available. It is therefore unclear which factors affect social relationship, role performance, and birthrate in different types of epilepsies.

The overall risk for major congenital malformations was two-fold in the offspring of epilepsy patients compared to the offspring of the reference cohort without epilepsy. The risk increased over time since the start of reimbursement for AEDs. A substantially elevated risk was found for spina bifida and congenital anomalies of the genital organs. In addition, the risk for other congenital anomalies of the circulatory system and other congenital anomalies of the limbs was significantly higher in the offspring of the epilepsy patient cohort than in the offspring of the reference cohort. However, these malformations cover only a small proportion of all major malformations.

The overall occurrence of congenital malformations was higher in the offspring of mothers with epilepsy on AED during the first trimester of pregnancy (65/1,411; 4.6%) than in the offspring of mothers with epilepsy not using AED during the first trimester of pregnancy (26/939; 2.8%). The risk for malformations in the offspring was slightly higher for the patients on any AEDs (OR = 1.70, 95% CI = 1.05–2.81) and it was clearly higher for patients on polytherapy (OR = 2.73, 95% CI = 1.26–5.64) than the patients not using any AED. When AED monotherapies were pooled together, no significantly increased risk for malformations in the offspring was found, but the risk was significantly elevated for offspring exposed to VPA used as monotherapy (OR = 4.18, 95% CI = 2.31–7.57). Half of the children with malformation of mothers on AED were born to mothers taking VPA during the first trimester of pregnancy. A clear dose-dependent relationship was found between using VPA and the risk for malformations in the offspring. However, the risk for malformations related to certain AEDs should be considered in relation to the various treatment alternatives in terms of their efficacy and teratogenicity.

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Birth Rate among Patients with Epilepsy: A Nationwide Population-based Cohort Study in Finland

M. Artama[1], J. I. T. Isojärvi[2], J. Raitanen[1], and A. Auvinen[1]

[1] Tampere School of Public Health, University of Tampere, Tampere, Finland.
[2] Department of Neurology, University of Oulu, Oulu, Finland.

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Few reports on population-based studies of birth rate among epilepsy patients have been published. In most previous studies, fertility has been lower among epilepsy patients than in the rest of the population. However, conflicting results have also been reported. Because of small samples and selective material, the generalizability of these results is also limited. The authors conducted a population-based cohort study of birth rate (1985–2001) in a nationwide Finnish cohort of patients with newly diagnosed epilepsy and a population-based reference cohort. All patients (n = 14,077) approved as eligible for reimbursement for antiepileptic medication from the Social Insurance Institution of Finland (KELA) for the first time between 1985 and 1994 were identified from the KELA database. A reference cohort (n = 29,828) was identified from the Finnish Population Register Center, with frequency-matching on age. Information on follow-up status and livebirths were also obtained from the Finnish Population Register Center. The birth rate was lower in patients with epilepsy than in the reference cohort among both men (hazard ratio = 0.58, 95% confidence interval: 0.54, 0.62) and women (hazard ratio = 0.88, 95% confidence interval: 0.83, 0.93). There were a clear decreasing trend by age at observation in men with epilepsy and a moderate decreasing trend by age at start of follow-up in women with epilepsy.

birth rate; cohort studies; epilepsy; Finland

Abbreviations: CI, confidence interval; HR, hazard ratio; KELA, Social Insurance Institution of Finland.

Many studies have found fertility to be lower in epilepsy patients than in the rest of the population. Most previous studies have shown that fertility is reduced among both men and women with epilepsy (1, 2). However, in a population-based study conducted in Iceland, no difference in birth rate was found between epilepsy patients and the reference cohort (3).

Epilepsy (4, 5) and use of antiepileptic medication (6, 7) may affect reproductive endocrine function, and reproductive endocrine disorders are more common in patients with epilepsy than in the general population (4–6). Hence, both male (5, 7) and female (4, 6) epilepsy patients may be more susceptible to a reduced birth rate than the rest of the population.

Epilepsy may also have negative social and psychological implications. The frequency of marriage is decreased among patients with epilepsy (1, 2, 8), but the birth rate is also decreased among married epilepsy patients (1, 2, 8, 9). Sexual dysfunction due to social and cognitive factors and lowered self-confidence appear to be more common in patients with epilepsy than in the rest of the population (10, 11).

During pregnancy and delivery, women who have epilepsy or use antiepileptic medication are predisposed to complications (12), and they may have an elevated risk of seizures (13). Some studies have reported that women with treated epilepsy have more miscarriages (14) and malformations (15) than women without treatment or without epilepsy. Increased risks of pregnancy complications may affect the decision to have children in some patients with epilepsy.

Most previous studies of birth rate in patients with epilepsy have been based on small samples and selective clinical materials. Therefore, we conducted this population-based study to obtain valid and accurate estimates of birth rate in patients with epilepsy based on a large and representative patient cohort.

Correspondence to M. Artama, Tampere School of Public Health, 33014 University of Tampere, Tampere, Finland (e-mail: miia.artama@uta.fi).

MATERIALS AND METHODS

All Finnish citizens are entitled to Finland's national health insurance, which is maintained by the state and financed through tax revenues. The national health insurance program also includes a pharmaceutical reimbursement system covering the costs of prescribed medicines. There are three reimbursement categories: basic, special (75 percent), and complete (100 percent). The pharmaceutical reimbursement system covers a total of 35 diseases in the complete reimbursement category, including epilepsy (16). Because classification is based on diagnosis, antiepileptic medication prescribed for indications other than epilepsy is not registered in this category. The prerequisite for reimbursement is a medical certificate showing that the diagnosis of epilepsy was based on clinical examination, that it fulfills international criteria, and that it was made by a board-certified neurologist. The diagnostic criteria for epilepsy include recurrent seizures or a single seizure with underlying pathology suggesting a high risk of recurrent seizures (such as trauma, disease, or abnormal electrophysiologic and/or neuroimaging findings).

The epilepsy patients included in this study were identified through the Social Insurance Institution of Finland (KELA). The patient cohort (n = 14,077) consisted of all patients with epilepsy who were approved as eligible for reimbursement for the purchase of antiepileptic medication from KELA for the first time between January 1, 1985, and December 31, 1994, who were alive on January 1, 1990, and in the fertile age group (15–49 years) during the study period. The information obtained from KELA included full name, personal identification number, and date of eligibility approval. Persons who had died before January 1, 1990, were excluded from the KELA database; information on them was not available. Information on type of epilepsy or antiepileptic medication was not available either.

The reference cohort (n = 29,828) was formed as a stratified random sample of all persons who were alive and resident in Finland on January 1, 1990. These persons were identified through the Finnish Population Register Center, with frequency-matching to the patient cohort by 5-year age group.

Rates of livebirth were estimated using information obtained from the population registry. The information covered number and dates of birth of liveborn children, date of first marriage, marital status, vital status, date of emigration, and date of death. Information was obtained through computerized record linkage with the unique personal identification number assigned to all residents of Finland. Information on stillbirths or miscarriages was not available.

Only persons aged 15–49 years during follow-up contributed person-years to the analysis. For the epilepsy patients, follow-up started at the start of reimbursement or the 15th birthday, whichever was later. For the reference cohort, the beginning of follow-up was the 15th birthday or the mean starting date of reimbursement among patients with epilepsy in that 5-year age group. The closing date was livebirth, the 50th birthday, emigration, death, or the common closing date (March 28, 2001), whichever was earliest. Follow-up was complete.

In the analyses carried out by start of reimbursement, the start of follow-up was divided into two periods for the epilepsy patients: 1985–1989 and 1990–1994. Follow-up for the reference cohort was subdivided into two groups regarding the start of reimbursement for the patients in every 5-year age group. The starting date of follow-up was July 1, 1987, or July 1, 1992.

Primary analyses were performed for the first liveborn child born after the start of follow-up (including all subjects). Separate analyses were performed for the first liveborn child (including only subjects without previous children), for the second liveborn child (including only subjects with one previous child at the start of follow-up), for the third liveborn child (including only subjects with two previous children at the start of follow-up), and for the fourth or subsequent liveborn child (including only subjects with three or more previous children at the start of follow-up).

Similar analyses were performed for the 5 years preceding the index date, which was defined in the patient cohort as the starting date of reimbursement for antiepileptic medication and in the reference cohort as the mean starting date of reimbursement among patients with epilepsy in that 5-year age group. The analyses were performed separately for each of the 5 years preceding the index date, with the start of follow-up at the date 1–5 years before the index date (or the 15th birthday if it was later). As in other analyses, only person-years accrued between the ages of 15 and 49 years were included in the analyses. The closing date was the birth of a liveborn child, the 50th birthday, emigration or death within each year, or the end of the year, whichever was earlier.

Since information was available on date of first marriage but not on dates of divorces and bereavements, marital status was classified as never married versus ever married. Information on date of marriage was missing for 44 persons (0.1 percent of subjects). Of those persons, the year of marriage was known for 17, and their marriage date was imputed as July 1 of that year. Persons with an unknown year of marriage (n = 18) or an unknown marital status (n = 9) were treated as having missing values.

The study protocol was approved by the ethical review committee of the Pirkanmaa Hospital District. Record linkage with the population registry was conducted with permission from the National Center for Research and Development in Health and Welfare. Because the study subjects were not contacted, informed consent to participate was not required.

In the statistical analysis, factors considered potential confounders and modifiers were sex, age, marital status, and previous livebirths. Analyses were conducted separately for men and women and were stratified according to age at start of follow-up, age at observation, year of start of follow-up, follow-up period, marital status, and number of previous children at start of follow-up. The analyses were performed using the Cox proportional hazards model, and the outcome was the birth of a liveborn child.

RESULTS

The epilepsy cohort comprised 7,542 men and 6,535 women (table 1). The reference cohort comprised 15,124

TABLE 1. Demographic and follow-up data on patients with epilepsy and a nonepileptic reference cohort and number of livebirths in both groups, Finland, 1985–2001

	No. of subjects		Person-years of follow-up		No. of livebirths	
	Patients	Referents	Patients	Referents	Patients	Referents
Sex						
Male	7,542	15,124	66,447	147,588	1,869	6,974
Female	6,535	14,704	61,759	142,810	3,018	7,723
Year of birth						
1940–1949	2,679	6,219	14,606	32,828	50	145
1950–1959	3,178	6,491	31,695	71,859	665	2,313
1960–1969	3,506	7,406	39,199	87,299	2,698	8,354
1970–1979	4,435	9,703	42,266	98,412	1,474	3,885
Age (years) at start of follow-up						72
0–9	731	957	5,730	6,393	98	4,406
10–19	3,872	9,378	41,182	99,506	1,749	7,830
20–29	3,341	6,879	36,632	80,997	2,461	2,245
30–39	3,019	6,418	29,920	70,992	536	144
40–49	3,114	6,196	14,741	32,510	43	
Age (years) at observation						
15–19	4,603	10,335	17,646	40,564	162	318
20–29	7,913	17,164	38,032	83,253	2,827	7,898
30–39	6,876	14,915	28,158	56,461	1,752	5,857
40–49	6,262	13,403	31,372	71,112	146	624
Follow-up period (years)						
0–4	14,077	29,828	65,101	141,318	2,040	5,973
≥5	12,052	26,770	62,984	125,458	2,858	8,792
Marital status at start of follow-up						
Never married	9,519	18,708	94,220	196,769	3,844	11,048
Ever married	4,553	11,081	33,964	93,301	1,043	3,644
No. of previous children at start of follow-up						
0	9,413	18,460	92,733	193,371	3,870	11,315
1	1,621	3,505	13,563	32,715	593	1,786
2	1,967	5,145	14,882	43,330	282	1,017
≥3	1,076	2,718	7,027	20,983	142	579

men and 14,704 women. The mean follow-up time was 9.1 years in the patient cohort and 9.7 years in the reference cohort. The mean age at the start of follow-up was 27.9 years in the patients and 27.5 years in the referents. During follow-up, the number of liveborn children was 4,887 among the patients and 14,697 among the referents.

Birth rate varied by age at the start of follow-up and by age at observation (table 2). Epilepsy patients aged 20–39 years at the start of follow-up had a substantially lower birth rate than the referents. Overall, the birth rate was lower in patients with epilepsy than in the reference cohort among both men (hazard ratio (HR) = 0.58, 95 percent confidence interval (CI): 0.54, 0.62) and women (HR = 0.88, 95 percent CI: 0.83, 0.93) (table 3). Year of diagnosis or follow-up period did not modify the birth rate in patients with epilepsy.

Among men with epilepsy, there was a negative trend with increasing age at observation for birth rate (table 3). Among women, no clear differences were observed between different ages at observation, but the birth rate showed a moderate decreasing trend with increasing age at the start of follow-up. Marital status did not modify the effect of epilepsy in stratified analyses, but the effect of epilepsy decreased when marital status was considered as a time-dependent covariate in both men (HR = 0.69, 95 percent CI: 0.65, 0.74) and women (HR = 0.94, 95 percent CI: 0.89, 1.00).

Among men with epilepsy, the birth rate was decreased regardless of previous livebirths. In female patients, the birth rate was slightly reduced for the first livebirth (HR = 0.84, 95 percent CI: 0.79, 0.90) and for the second livebirth (HR =

TABLE 2. Cumulative incidence of livebirth and rate of livebirth among patients with epilepsy and a nonepileptic reference cohort according to various demographic factors and factors related to follow-up, Finland, 1985–2001

	No. of livebirths/1,000 persons				No. of livebirths/1,000 person-years of follow-up			
	Men		Women		Men		Women	
	Patients	Referents	Patients	Referents	Patients	Referents	Patients	Referents
Year of birth								
1940–1949	26	39	8	7	5	7	1	2
1950–1959	192	430	230	279	20	39	22	25
1960–1969	602	1,057	924	1,202	55	90	81	102
1970–1979	183	289	475	514	19	28	50	51
Age (years) at start of follow-up								
0–9	75	28	201	120	10	4	26	18
10–19	256	347	631	595	24	33	59	56
20–29	580	1,073	880	1,207	54	91	80	102
30–39	195	428	156	267	20	39	15	24
40–49	19	39	5	8	4	7	1	2
Age (years) at observation								
15–19	10	12	60	50	2	3	16	12
20–29	227	375	482	548	41	64	83	94
30–39	234	414	275	370	47	82	57	73
40–49	29	71	16	22	6	13	3	4
Follow-up period (years)								
0–4	104	190	192	211	23	40	41	45
≥5	173	305	304	354	34	55	57	64
Marital status at start of follow-up								
Never married	271	518	558	674	28	49	55	64
Ever married	193	352	268	309	28	43	34	36
No. of previous children at start of follow-up								
0	272	536	574	703	28	51	57	67
1	303	550	432	475	39	60	48	50
2	137	196	148	199	19	24	18	23
≥3	111	254	153	178	18	33	22	23

0.89, 95 percent CI: 0.76, 1.04) but not for the third or subsequent livebirths.

Before epilepsy diagnosis, birth rates for the first liveborn child were also reduced in both men with epilepsy (HR = 0.76, 95 percent CI: 0.72, 0.80) and women with epilepsy (HR = 0.79, 95 percent CI: 0.76, 0.83) for the entire 5-year period preceding diagnosis. No clear trend by time to diagnosis was observed (table 4).

DISCUSSION

In this study, the birth rate was clearly lower among men with epilepsy and older patients than among referents. The effect of epilepsy was less pronounced in women than in men.

Few large population-based studies of birth rate in patients with epilepsy have been conducted. Most previous studies have been based on a few hundred patients (2, 3, 8), with data collected from clinical records (2, 17) and without a population-based reference group (1, 2, 8, 9).

Our study population was unselected, since coverage of newly diagnosed patients was high and the reference cohort was population-based. In addition, the large study population and the register-based approach enabled us to obtain comprehensive information on livebirths. The age-specific birth rate for women in the reference cohort was similar to that of the general Finnish female population (18).

The results of previous studies on birth rate in patients with epilepsy have been partly conflicting. In most of the previous studies, the birth rate has been lower among epilepsy patients than in the general population. However, in a population-based study conducted in Iceland, no difference in birth rate was found between patients with epilepsy and the reference cohort (3). Several studies have suggested that the birth rate is reduced in both sexes, especially among men after diagnosis (1, 19). In addition, the birth rate has been

TABLE 3. Hazard ratio for a subsequent child among patients with epilepsy in relation to members of a nonepileptic reference cohort, according to various demographic factors and factors related to follow-up, Finland, 1985–2001

	Men		Women	
	HR*	95% CI*	HR	95% CI
Age (years) at start of follow-up				
0–9	1.20	0.55, 2.63	1.13	0.75, 1.72
10–19	0.69	0.61, 0.79	1.02	0.94, 1.12
20–29	0.55	0.50, 0.61	0.73	0.67, 0.79
30–39	0.49	0.42, 0.56	0.64	0.54, 0.76
40–49	0.61	0.40, 0.91	0.62	0.26, 1.52
Age (years) at observation				
15–19	0.77	0.46, 1.28	1.26	1.01, 1.57
20–29	0.66	0.60, 0.72	0.88	0.82, 0.94
30–39	0.52	0.48, 0.57	0.74	0.68, 0.81
40–49	0.45	0.35, 0.56	0.78	0.55, 1.11
Year of start of follow-up				
1985–1989	0.67	0.61, 0.73	1.03	0.96, 1.12
1990–1994	0.57	0.51, 0.63	0.82	0.75, 0.90
Marital status				
Never married	0.56	0.52, 0.61	0.85	0.79, 0.90
Ever married	0.63	0.56, 0.72	0.87	0.77, 0.98
No. of previous children at start of follow-up				
0	0.54	0.50, 0.59	0.84	0.79, 0.90
1	0.59	0.50, 0.70	0.89	0.76, 1.04
2	0.77	0.62, 0.96	0.75	0.61, 0.94
≥3	0.59	0.42, 0.83	0.80	0.57, 1.12
Total	0.58	0.54, 0.62	0.88	0.83, 0.93

* HR, hazard ratio; CI, confidence interval.

reported to be lower among female epilepsy patients than among male patients (1, 9). In our study, the birth rate was decreased in both sexes, especially in men.

Our results regarding age at the start of follow-up were partly consistent with the previous studies. As in our study, lower fertility rates have been reported among female patients with onset at age 20 years or higher (2). In contrast to previous findings (1, 2, 9), we found no effect of epilepsy among persons diagnosed before age 10 years. Most patients with onset before age 10 years have generalized epilepsy. The prognosis for generalized epilepsy is favorable, and antiepileptic medication is often discontinued. In our study, differences in birth rates between the patients and the referents increased with age. However, the number of children was small in both groups.

Marital status strongly affects birth rate, and it can be regarded as both a potential confounder and an effect modifier in studies of epilepsy and birth rate. We did not have complete information on marital status, only information on the date of first marriage. Adjustment for marital status decreased the differences between patients with epilepsy and the reference cohort, especially when marital status was used as a time-dependent covariate. It has been reported that epilepsy patients frequently have children after marrying, but the birth rate is still lower than in the general population (1, 2, 8, 9). In our study, the effect of epilepsy did not differ between never-married persons and ever-married persons.

TABLE 4. Hazard ratio for a first liveborn child among patients with epilepsy in relation to members of a nonepileptic reference cohort, by number of years before the start of follow-up, Finland, 1985–2001

Years before start of follow-up	Men		Women	
	HR*	95% CI*	HR	95% CI
1	0.70	0.58, 0.83	0.85	0.72, 1.00
2	0.53	0.44, 0.65	0.69	0.58, 0.82
3	0.75	0.63, 0.89	0.75	0.63, 0.89
4	0.66	0.55, 0.78	0.76	0.64, 0.91
5	0.68	0.58, 0.81	0.86	0.73, 1.02

* HR, hazard ratio; CI, confidence interval.

This may be partly due to nondifferential misclassification induced by incomplete information on marital history.

Number of previous children modified the birth rate in women with epilepsy but not in men with epilepsy. Regardless of number of children, men with epilepsy had a decreased rate of livebirth. Correspondingly, female epilepsy patients without children or with one previous child had a lower birth rate than women without epilepsy.

The birth rate for a first liveborn child was reduced before the start of follow-up in both men and women with epilepsy. Three possible explanations could account for this finding. First, because the diagnosis of epilepsy requires recurrent seizures, patients may have convulsions preceding diagnosis, which could affect sexual relationships, behavior, function, and birth rate. This seems unlikely, however, since there was no trend by time to diagnosis. Second, this could be attributable to shared risk factors, that is, an external factor's affecting both fertility and epilepsy, such as socioeconomic status. This is possible, but we did not have information with which to investigate this possibility. Third, this finding could be due to misclassification, that is, missing dates of the first epilepsy diagnosis. This is unlikely, since the coverage of reimbursement files in Finland is very high and we have checked the reimbursement decisions back to the 1960s.

There were some limitations in our study. Identification of patients with epilepsy may have been incomplete. Information on epilepsy patients who did not want reimbursement for the purchase of antiepileptic medication was not available. If a diagnosis of epilepsy is made for an institutionalized patient, information on reimbursement is not necessarily included in the KELA database. Those patients were probably underrepresented in our study. However, the cost of antiepileptic medication is high in Finland, and therefore few people with epilepsy refuse reimbursement for antiepileptic medication. Furthermore, the proportion of institutionalized epilepsy patients is small overall. Therefore, the exclusion of these persons is not likely to have substantially affected our results.

Information on type of epilepsy or medication was not available in this study. However, we were able to assess two modifiers of antiepileptic medication. We conducted analyses by year of diagnosis to assess the effect of possible changes in antiepileptic medication during the follow-up period. We conducted analyses by follow-up period to evaluate the effect of duration of use of antiepileptic medication on birth rate. Neither year of start of reimbursement nor follow-up period was a modifier of birth rate in patients with epilepsy. However, the most common types of antiepileptic medication in Finland are carboxamide derivates such as carbamazepine and oxcarbazepine, which are used mainly in partial epilepsies, and valproate, which is used mainly in generalized epilepsies (20).

Many patients probably discontinued use of antiepileptic medication during follow-up. Jalava and Sillanpää (8) reported that more than two thirds of their study patients achieved remission and did not require further medication. Those with active epilepsy who were taking two or more antiepileptic drugs had a fourfold increased risk of childlessness (95 percent CI: 1.3, 12.5) relative to the control group. Patients in remission were at similar risk as the control group. Patients with a long follow-up period are less likely to use antiepileptic medication, and they should have a birth rate similar to that of the reference cohort. However, in this study, there was a substantial difference between the patients with a long follow-up period and the reference cohort in terms of birth rate.

There are several possible explanations for the persisting differences. Decreased fertility may not be attributable to antiepileptic medication. Our follow-up time was twice as long as in most previous studies. Therefore, our follow-up time was probably sufficient to evaluate the effect of changes in or duration of use of antiepileptic medication. In addition, there may be maternal epilepsy-related factors that affect fertility, including comorbidity such as mental disability or sequelae of trauma. Increased risk of congenital malformations in epilepsy may lead to induced abortions and a decreased rate of livebirth.

Socioeconomic factors may also influence birth rate. Epilepsy may affect people's ability to obtain education and to work, although Schupf and Ottman (9) did not find any difference in educational background between female patients and their unaffected siblings. Generally, the number of children is lower among persons with higher education than among others; therefore, it is unlikely that epilepsy-related socioeconomic factors would have influenced the observed low birth rate in persons with epilepsy. We did not have information on socioeconomic factors.

Several studies have shown that stillbirths and spontaneous abortions are more common among patients with epilepsy than in the general population. Information on stillbirths or abortions was not available in this study. Therefore, we could not estimate the contribution of these events to the decreased birth rate. Furthermore, we were not able to assess whether the reduced birth rate among patients with epilepsy was voluntary or due to a reduced capability to conceive.

In conclusion, our results suggest that birth rate is decreased in patients with epilepsy, especially among men and persons aged 20 years or more.

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Antiepileptic drug use and birth rate in patients with epilepsy—a population-based cohort study in Finland

Miia Artama[1,4], J.I.T.Isojärvi[2,5] and A.Auvinen[1,3]

[1]School of Public Health, University of Tampere, Tampere, [2]Department of Neurology, University of Oulu, Oulu and [3]Pediatric Research Centre, Tampere University Hospital, Tampere, Finland

[4]To whom correspondence should be addressed at: Tampere School of Public Health, University of Tampere, Tampere 33014, Finland. E-mail: miia.artama@uta.fi

[5]Address during the study: GlaxoSmithKline, Neurosciences MDC, Research Triangle Park, NC 27709, USA

BACKGROUND: Antiepileptic medication use affects reproductive endocrine function, but its impact on fertility is not well known. METHODS: All epilepsy patients, who were approved as being eligible for reimbursement for antiepileptic drug (AED) costs from the Social Insurance Institution (SII) of Finland for the first time 1985–94, were identified from the SII database. A reference cohort without epilepsy was identified from the Finnish Population Register Centre. Information on AED purchases 1996–2000 was obtained from the SII database through computerized record linkage with the unique personal identification number assigned to all residents of Finland. The three AEDs included were carbamazepine, oxcarbazepine (OXC) and valproate. RESULTS: Birth rate was lower in both men and women with epilepsy on AEDs than in the reference cohort without epilepsy. However, compared with patients not using AED during the study period, the birth rate was lowered only among men on OXC [rate ratio (RR) = 0.52, 95% confidence interval (CI) = 0.32, 0.84]. CONCLUSIONS: The birth rate was lower in both women and men on any of the three AEDs compared with the reference cohort without epilepsy. However, a statistically significant difference between treated and untreated patients was only seen in men on OXC. It is unclear to what extent the differences found in this study are due to social or biological factors.

Key words: antiepileptic drug/birth rate/cohort study/epilepsy

Background

Birth rate is lowered in both female and male patients with epilepsy (Artama *et al*., 2004). This is partly explained by the decreased rate of marriages (Schupf and Ottman, 1994, 1996; Jalava and Sillanpää, 1997), but birth rate is also lower in married persons with epilepsy than in the general population (Dansky *et al*., 1980; Schupf and Ottman, 1994, 1996; Jalava and Sillanpää, 1997).

Epilepsy itself, but also antiepileptic drug (AED) use, may affect reproductive endocrine function (Herzog *et al*., 1986a,b; Isojärvi *et al*., 1990, 1993; Mikkonen *et al*., 2004), and these alterations may be associated with reduced fertility. Among women with epilepsy, menstrual disorders reflecting ovulatory dysfunction related to, for example, polycystic ovaries, hyperandrogenism and anovulatory cycles are more common than in general population (Herzog *et al*., 1986a; Isojärvi *et al*., 1993). These conditions may reduce fertility in women with epilepsy (Isojärvi *et al*., 2005).

In men with epilepsy, long-term use of liver enzyme inducing AEDs is associated with increased serum concentrations of sex hormone-binding globulin and reduced bioactive serum testosterone, which may affect reproductive functions (Isojärvi *et al*., 2005). In addition, the use of certain AEDs may reduce sperm motility, induce sperm abnormalities and decrease testicular volume (Røste *et al*., 2003; Isojärvi *et al*., 2004). Changes in sperm quality can obviously have direct effects on fertility in men.

Previous population-based studies on birth rate among patients with epilepsy are few (Webber *et al*., 1986; Jalava and Sillanpää, 1997; Olafsson *et al*., 1998; Wallace *et al*., 1998; Artama *et al*., 2004), and those addressing the effects of specific AEDs on birth rate have been based on small samples (Jalava and Sillanpää, 1997). We conducted this population-based study to evaluate the role of commonly used AEDs on birth rate among patients with epilepsy in a large and representative patient cohort using comprehensive information on AED purchases and live-born children.

Materials and methods

In Finland, all permanent residents are entitled to national health insurance, which is maintained by the state and financed by tax revenues. The national health insurance includes a drug reimbursement system, which covers fully or partially the costs of prescribed medications. This reimbursement system consists of three categories: basic, special (75% of cost) and complete (100% of cost). Epilepsy is one of

the approximately 50 diseases in the complete reimbursement category. The requirement for the reimbursement of costs for AEDs is a medical certificate showing that the epilepsy diagnosis is based on clinical examination; it fulfils the international diagnostic criteria (Fisher *et al*., 2005) and is made by a board-certified neurologist. The medical certificate needs to include sufficient information to confirm the diagnosis of epilepsy. This information consists of medical history with description of the seizure symptomatology, the possible aetiology of epilepsy, if known, the duration of epilepsy symptoms and other relevant medical history. Data on the results of imaging studies of the brain and EEG are included, when available. AEDs that are prescribed for indications other than epilepsy are recorded under other disease categories.

The study cohort consisted of all epilepsy patients who were approved for complete reimbursement for antiepileptic medication purchases from the Social Insurance Institution (SII) of Finland for the first time in life between 1 January 1985 and 31 December 1994 and were alive on 1 January 1990. Because persons who had died before 1 January 1990 were eliminated from the SII database, we did not have information on them. Information obtained from SII included personal identification number and the date of eligibility approval.

The reference cohort without epilepsy was identified through the Finnish Population Register Centre with frequency matching to the patient cohort on year of birth (5-year age groups). The cohort comprised of a stratified random sample of all persons who were alive and residing in Finland on 1 January 1990.

Information on AED purchases for epilepsy from 1 January 1996 to 31 December 2000 was obtained from SII. Information covered personal identification number, anatomic therapeutic chemical (ATC) code of the drug (from N03AA to N03AX) and the date of purchase. Information was obtained on all AED purchases under AED category (ATC:N03).

Information on live-born children and vital status was obtained from the Population Registry for both epilepsy patients and reference persons without epilepsy. The information covered personal identification number, possible birth dates of children, date of first marriage, current marital status, vital status, date of emigration and date of death. Information was available up until 28 March 2001.

Study subjects contributed person-years to the analyses only during fertile ages (15–49 years). In patients with AED use, the start of follow-up was the first purchase of the AED, because all the patients were >15 years at the start of follow-up. As the follow-up time varied by type of AED and type of AED use, we defined the start of follow-up for untreated patients and reference cohort without epilepsy separately for each AED. The start of follow-up for untreated patients and reference persons was assigned as the mean starting date of the AED use among the patients with that medication in the corresponding 5-year age group.

In Finland, the prescription of reimbursed drugs is regulated in 3-month batches. Therefore, the end of medication exposure was defined as 3 months after the last purchasing date. In patients on AEDs, the closing date was the end of medication exposure, 50th birthday, emigration, death, the common closing date (28 March 2001) or the first pregnancy, whichever was earliest. Because we did not have information on the start of the first pregnancy, it was estimated by subtracting 9 months from the birth date of the first live-born child. In patients without AED use and in the reference cohort without epilepsy, the closing date was the 50th birthday, emigration, death, the common closing date (28 March 2001) or the first pregnancy, whichever was earliest.

Persons who used more than one AED during the follow-up (at subsequent periods as monotherapy or simultaneously as polytherapy) contributed person-years to each of the type of AED treatment (monotherapy/polytherapy). Persons who did not use any AEDs during the entire follow-up were used as the untreated epilepsy patient group (no medication at any time during the study period).

Separate comparisons for the first live-born child were performed between patients with AED use and reference persons without epilepsy and between epilepsy patients with AED use and epilepsy patients without any AED use during the study period. Only childless persons were included in the analyses. Analyses by type of medication were conducted pertaining to use of carbamazepine (CBZ), oxcarbazepine (OXC) and valproate (VPA). For other AEDs, the number of subjects was too small to conduct meaningful analysis. Analyses were conducted separately for monotherapies (use of CBZ, OXC or VPA with no other AEDs in use simultaneously). There were 422 patients on polytherapy including VPA + CBZ, 236 patients on polytherapy including VPA + OXC and 98 patients on CBZ + OXC polytherapy.

Data analyses were performed using Poisson regression modelling with the first live-born child as the outcome. Persons with any children before the start of the follow-up (1 January 1996) were excluded from the analyses. Statistical analyses were performed using STATA 8.2 (Stata 8.0). In the analyses, the factors considered potential confounders were age and marital status at the start of the follow-up.

The study protocol was approved by the ethical review committee of the Pirkanmaa Hospital District. Record linkages were conducted with permission from the National Centre for Research and Development in Health and Welfare and the SII of Finland.

Results

The number of patients on antiepileptic medication varied by type of medication (CBZ overall, n = 2689, monotherapy, n = 2365; OXC overall, n = 832, monotherapy, n = 631; VPA overall, n = 1546, monotherapy, n = 1116). Because the follow-up time for patients in each AED treatment group varied by AED and type of the therapy, the beginning of the follow-up was defined for untreated patients and the reference persons without epilepsy separately in each analysis by specific AED. Therefore, the number of untreated epilepsy patients ranged between 2714 and 2785, and the number of reference persons without epilepsy was between 13 378 and 13 689, depending on the type of AED and mode of therapy (all users/monotherapy).

The mean follow-up times varied slightly between patients with AED use, untreated patients and the reference cohort, depending on AED (CBZ: 3.39–3.86 years, monotherapy: 3.09–3.80 years; OXC: 3.05–3.60 years, monotherapy: 2.44–3.59 years; VPA: 3.20–3.68 years, monotherapy: 2.79–3.63 years) (Table I).

Overall, birth rate was lower among both men and women with epilepsy than in persons without epilepsy (Table II). Birth rate was decreased both among epilepsy patients on AEDs and untreated epilepsy patients in relation to the reference cohort without epilepsy in both sexes. The birth rates were lower among men than among women on CBZ and OXC (interaction CBZ overall, P = 0.02; CBZ monotherapy, P = 0.02; OXC overall, P = 0.05; OXC monotherapy, P = 0.03) in relation to reference persons without epilepsy. No interaction was found for VPA. CBZ and OXC were associated with lower birth rates than VPA in both sexes. The findings were similar in patients on monotherapy and in all users with the three most commonly used AEDs.

Table I. Number, total follow-up time[a] (person-years, pyrs), the mean and median length of follow-up in patients with epilepsy on antiepileptic medication before pregnancy, patients without antiepileptic medication and reference cohort without epilepsy according to antiepileptic drugs (AEDs), Finland 1996–2000

	Patients on therapy			Untreated patients			Referents		
	n	Total (pyrs)	Mean/median length of follow-up[a]	*n*	Total (pyrs)	Mean/median length of follow-up[a]	*n*	Total (pyrs)	Mean/median length of follow-up[a]
Carbamazepine									
All users									
Female	1058	3591	3.39/4.28	1211	4504	3.72/4.19	6151	22 755	3.70/4.19
Male	1631	5834	3.58/4.33	1574	6081	3.86/4.19	7538	28 977	3.84/4.30
Monotherapy									
Female	921	2847	3.10/3.94	1205	4413	3.66/4.10	6125	22 274	3.64/4.10
Male	1444	4743	3.28/4.24	1570	5960	3.80/4.10	7521	28 417	3.78/4.22
Oxcarbazepine									
All users									
Female	399	1215	3.05/3.57	1169	4121	3.52/3.85	5987	20 674	3.45/3.85
Male	433	1412	3.26/4.18	1545	5562	3.60/3.93	7528	26 285	3.56/3.85
Monotherapy									
Female	319	778	2.44/2.50	1168	4108	3.52/3.90	5992	20 638	3.44/3.85
Male	312	941	3.02/3.79	1546	5557	3.59/3.90	7385	26 308	3.56/3.90
Valproate									
All users									
Female	758	2431	3.21/4.13	1182	4250	3.60/4.10	6054	21 388	3.53/4.09
Male	788	2715	3.45/4.32	1552	5712	3.68/4.10	7441	27 135	3.65/4.09
Monotherapy									
Female	579	1616	2.79/3.15	1177	4168	3.54/4.01	6020	20 949	3.48/4.00
Male	537	1586	2.95/3.69	1546	5610	3.63/4.01	7414	26 607	3.59/3.98

[a]In the patients without antiepileptic medication and in the reference cohort without epilepsy, the start of the follow-up was the mean date of the first purchase of AED in patients with the AED in that 5-year age group.

Table II. Live births and birth rate (per 1000 person-years) with 95% confidence intervals (CI) in patients with epilepsy on antiepileptic medication before pregnancy, patients without antiepileptic medication and reference cohort without epilepsy according to AEDs, Finland 1996–2000

	Patients on therapy		Untreated patients		Referents	
	Births	Rate[a] (95% CI)	Births	Rate[a] (95% CI)	Births	Rate[a] (95% CI)
Carbamazepine						
All users						
Female	130	36.2 (30.3, 42.8)	201	44.6 (38.8, 51.1)	1302	57.2 (54.2, 60.3)
Male	101	17.3 (14.1, 21.0)	151	24.8 (21.1, 29.1)	1147	39.6 (37.4, 41.9)
Monotherapy						
Female	98	34.4 (28.0, 41.8)	195	44.2 (38.3, 50.7)	1279	57.4 (54.4, 60.6)
Male	77	16.2 (12.8, 20.2)	151	25.3 (21.5, 29.6)	1131	39.8 (37.6, 42.1)
Oxcarbazepine						
All users						
Female	41	33.7 (24.3, 45.5)	172	41.7 (35.8, 48.3)	1165	56.3 (53.2, 59.6)
Male	18	12.7 (7.57, 20.1)	144	25.8 (21.9, 30.4)	1030	39.2 (36.9, 41.6)
Monotherapy						
Female	28	36.0 (24.0, 51.6)	172	41.9 (36.0, 48.5)	1172	56.8 (53.7, 60.0)
Male	10	10.6 (5.10, 19.5)	145	26.1 (22.1, 30.6)	1034	39.3 (37.0, 41.7)
Valproate						
All users						
Female	99	40.7 (33.2, 49.4)	186	43.8 (37.8, 50.4)	1222	57.1 (54.1, 60.3)
Male	58	21.4 (16.3, 27.5)	150	26.3 (22.3, 30.7)	1077	39.7 (37.4, 42.1)
Monotherapy						
Female	62	38.4 (29.5, 48.9)	180	43.2 (37.2, 49.8)	1196	57.1 (54.0, 60.3)
Male	36	22.7 (15.9, 31.3)	147	26.2 (22.2, 30.7)	1060	39.8 (37.5, 42.3)

[a]Live birth rate per 1000 person-years.

In the regression analyses, both women and men on AED had significantly lower birth rates than the reference group without epilepsy (Table III). In comparison with the untreated patients, women on any of the three AEDs had non-significantly lower birth rates. Analyses of patients on monotherapy gave similar results. Among men, birth rate was decreased in those on OXC but was not clearly lower among those on CBZ or VPA when compared with untreated patients. In men on OXC, birth rate was lower among men on monotherapy than among all males on OXC.

Adjustment for marital status and age at the start of the follow-up was used, because it decreased the effect of CBZ in

Table III. Adjusted[a] rate ratios with 95% confidence intervals (CI) for the first live-born child among patients with epilepsy on antiepileptic medication before pregnancy in relation to reference cohort without epilepsy and patients without antiepileptic medication, Finland 1996–2000

	Women				Men			
	All users		Monotherapy		All users		Monotherapy	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Reference cohort without epilepsy	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Epilepsy patients on AED								
Carbamazepine	0.69	0.58, 0.83	0.66	0.54, 0.81	0.47	0.38, 0.58	0.44	0.35, 0.55
Oxcarbazepine	0.60	0.44, 0.82	0.64	0.44, 0.94	0.34	0.21, 0.54	0.28	0.15, 0.52
Valproate	0.65	0.51, 0.83	0.68	0.53, 0.88	0.52	0.38, 0.72	0.55	0.40, 0.77
Epilepsy patients without AED	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Epilepsy patients on AED								
Carbamazepine	1.01	0.80, 1.27	0.97	0.75, 1.25	0.86	0.66, 1.13	0.79	0.59, 1.06
Oxcarbazepine	0.83	0.59, 1.17	0.90	0.61, 1.36	0.52	0.32, 0.84	0.42	0.22, 0.80
Valproate	0.87	0.66, 1.15	0.91	0.68, 1.21	0.78	0.55, 1.11	0.84	0.58, 1.20

AED, antiepileptic drug; RR, rate ratio.
[a]Adjusted for marital status and age at start of follow-up.

relation to the untreated patients in both men [unadjusted rate ratio (RR) 0.70, 95% confidence interval (CI) = 0.54, 0.90; adjusted RR 0.86, 95% CI = 0.66, 1.13] and women (unadjusted RR 0.81, 95% CI = 0.65, 1.01; adjusted RR 1.01, 95% CI = 0.80, 1.27), even though it did not affect other results than CBZ.

Discussion

In our study, birth rate was lower in both women and men with epilepsy than in persons without epilepsy. The birth rate in both women and men treated for epilepsy was closer to the untreated patients than to the reference cohort without epilepsy. The birth rates were lower in both women and men on any of the three AEDs when compared with the reference cohort without epilepsy. However, a statistically significant difference between treated and untreated patients was seen only in men on OXC.

Few previous population-based studies on birth rate in patients with epilepsy have been published. Most of the studies have been based on small samples and lacked comparison between treated and untreated patients, as well as reference group without epilepsy (Dansky *et al*., 1980; Jalava and Sillanpää, 1997; Olafsson *et al*., 1998). Furthermore, few studies have estimated birth rate by type of AED (Webber *et al*., 1986; Schupf and Ottman, 1994, 1996; Olafsson *et al*., 1998; Wallace *et al*., 1998). In our register-based study, large study population and comprehensive information on live births and AED purchases enabled us to evaluate the effect of specific AEDs (CBZ, OXC and VPA) on birth rate in a representative patient cohort with epilepsy.

Some of the previous studies have suggested that birth rate is lower in men than in women with epilepsy (Webber *et al*., 1986; Schupf and Ottman, 1996; Artama *et al*., 2004). Consistent with this, birth rate was clearly decreased among men with epilepsy but less affected among female epilepsy patients in this study. The birth rates were lower in both women and men on any of the three AEDs when compared with the reference cohort. Nevertheless, a statistically significant difference between treated and untreated patients was only seen in men on OXC.

In this study, the birth rate was decreased in both treated and untreated women with epilepsy. This suggests that in women, epilepsy itself substantially contributes to the reproductive dysfunction, which is consistent with previous reports of high prevalence of reproductive endocrine disorders in women with epilepsy (Herzog *et al*., 1986a). On the contrary, there were no significant differences in the birth rates of women on different AEDs. This is surprising, because many studies have shown that VPA is more commonly associated with reproductive endocrine disorders characterized by anovulatory dysfunction than some other AEDs (Morrell *et al*., 2002; Betts *et al*., 2003). There are no data on the effects of OXC on reproduction in women with epilepsy, but one animal study found decreased birth rate in female monkeys treated with OXC (Lockard *et al*., 2000).

Previous studies have suggested that endocrine dysfunction is more common in men with epilepsy treated with AEDs than in the general population (Herzog *et al*., 1986b; Isojärvi *et al*., 1990, 1995; Rättyä *et al*., 2001). Sperm abnormalities have also been common among men on CBZ, OXC or VPA (Isojärvi *et al*., 2004). Consistent with this, birth rate was lower in men on any of these drugs than in the reference cohort in our study. However, compared with untreated men with epilepsy, birth rate was significantly reduced only among men on OXC.

The outcome in our study was the birth rate, which is a crude measure of fertility. We did not have information on semen quality or female fecundity. Similarly, information on intention to conceive and contraceptive use was not available because of register-based approach. Our findings need therefore supporting evidence from more detailed studies addressing these factors. Our patient cohort consists of patients who were eligible for reimbursement for the cost of AEDs. Information on institutionalized patients with epilepsy is not included in the SII database. These patients are probably underrepresented in our study. Also, patients who did not want the reimbursement are not included in our cohort. Few patients decline reimbursement for AEDs, because the costs of AEDs are high in Finland.

Therefore, our material is likely to be highly representative of all non-institutionalized epilepsy patients in Finland.

We were able to evaluate the effect of AED usage based on the information on AED purchases. Therefore, actual drug compliance could not be evaluated in our study. Pregnant women with epilepsy may discontinue AEDs because of potential side effects (Chang and McAuley, 1998; Williams *et al*., 2002). We evaluated the effect of AED exposure before conception. Thus, potential non-compliance may have biased our results only if it differs between the AED groups.

In Finland, the prescription of reimbursed drugs is regulated in 3-month batches. Therefore, the end of medication exposure was defined as 3 months after the last purchasing date during the follow-up. In most of the patients on CBZ + OXC polytherapy, the overlapping period of different AED usage was very short (from few days to few weeks). Probably these patients were not in polytherapy, but their antiepileptic medication was changed from CBZ to OXC or vice versa. Similar overlapping was also found between other AEDs. This possible misclassification of AED exposure has not affected our results. We did not conduct separate analyses on polytherapy combinations, because we did not know the actual drug intake. We analysed monotherapy periods separately, because it allowed the identification of the effects of a single pharmaceutical agent.

We obtained information on all live births and used it as a measure of fertility. Yet, we were not able to assess the time of conception, because the 'intention to conceive' was not available. Women with epilepsy may have an increased risk for spontaneous abortions (Nakane *et al*., 1980; Yerby and Cawthon, 1996; Schupf and Ottman, 1997). The use of certain AEDs increases the risk for spina bifida in the offspring (Koren *et al*., 1998; Hernandez-Diaz *et al*., 2000; Matalon *et al*., 2002), and severe spina bifida is an indication for induced abortion (Botto *et al*., 1999). In a Finnish study (Kaaja *et al*., 2003), 0.6% of pregnancies in patients with epilepsy were terminated because of fetal congenital structural anomalies. The corresponding proportion was 0.2% in the general Finnish female population in 1999 (Gissler *et al*., 2000). We did not have information on spontaneous or induced abortions. Hence, we could not estimate the impact of these factors on decreased birth rate in patients with epilepsy. However, this is not likely to affect our results, because the number of terminations due to fetal congenital structural anomalies is overall small.

Maternal use of AEDs can seldom be discontinued before pregnancy because of increased risk for seizures (Sabers *et al*., 1998). The use of certain AEDs during pregnancy increases the risk for specific congenital malformations in the offspring (Arpino *et al*., 2000; Barrett and Richens, 2003; Artama *et al*., 2005). Furthermore, pregnancy complications are more common among women with epilepsy than in other female population (Fonager *et al*., 2000). In some epilepsy patients, these risks may affect the decision to have children. We could not estimate the effect of psychosocial aspects on reproduction in our patient cohort.

When antiepileptic medication is started after epilepsy diagnosis, ~60% of patients become seizure-free (Kwan and Brodie, 2000). For among 50–60% of these patients, antiepileptic medication can be discontinued successfully at some point. If there are no specific risks and the patient is compliant, antiepileptic medication is usually discontinued from 4 to 5 years after the latest seizure. Untreated epilepsy patients are a heterogeneous group including also patients who are not compliant with AED treatment.

Most patients on CBZ or OXC have partial epilepsy, whereas VPA is used mainly for generalized epilepsy. That is, patients on different AEDs or patients without AEDs may also differ in terms of epilepsy type (including aetiology, seizure characteristics and age at onset), treatment response (disease duration and seizure frequency) and comorbidity. It is unclear, if and which of these factors affect social relationships and role performance and thereby fertility in different types of epilepsy. As we did not have information on epilepsy type, we could not distinguish the effect of epilepsy and antiepileptic medication on fertility, that is, confounding by indication is possible. Therefore, our findings should be interpreted with caution.

Conclusions

Our results suggest that birth rate is decreased among patients with epilepsy on AEDs, more so in men. Among male patients with epilepsy, CBZ, OXC and VPA all were associated with low birth rate in relation to men without epilepsy. However, only OXC was related to reduced birth rate compared with untreated patients. Among women on any of the three AEDs (CBZ, OXC and VPA) for epilepsy, birth rate is decreased in relation to reference persons without epilepsy but not compared to untreated patients.

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Congenital structural anomalies in offspring of women with epilepsy—a population-based cohort study in Finland

Miia Artama,[1]* Annukka Ritvanen,[2] Mika Gissler,[3] Jouko Isojärvi[4] and Anssi Auvinen[1,5]

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Background Offspring of women with epilepsy may have an increased risk for congenital malformations, probably attributable to maternal antiepileptic medication. We conducted this population-based study to obtain valid and accurate estimates on major congenital malformations in the offspring of women with epilepsy, based on a large and representative patient cohort.

Methods We identified all women ($n = 6535$) entitled to full reimbursement for antiepileptic medication indicated for epilepsy for the first time between 1985 and 1994 from the Social Insurance Institution of Finland database. A reference cohort ($n = 14\,704$) was identified from the Finnish Population Register Centre. Information on children born between 1993 and 2000 (patient cohort, $n = 2162$; reference cohort, $n = 5413$) was obtained from the Medical Birth Register. Information on children born with malformation (patient cohort, $n = 116$; reference cohort, $n = 151$) was obtained from the Finnish Register of Congenital Malformations.

Results The prevalence of major malformation was 54/1000 births among patients with epilepsy and 28/1000 births among mothers without epilepsy, corresponding to a 2-fold overall risk for malformation in the offspring of women with epilepsy. The risk for spina bifida [odds ratio (OR) = 11.3, 95% confidence interval (CI) 2.34–108] and congenital anomalies of genital organs (OR = 8.38, 95% CI 2.15–47.4) was substantially elevated in the offspring of mothers with epilepsy.

Conclusions The absolute excess in the prevalence of major malformations was 26/1000 births in the offspring of mothers with epilepsy in relation to the offspring of reference mothers. The highest relative risk was observed in spina bifida and congenital anomalies of genital organs. However, these malformations cover only a small proportion of all major malformations.

Keywords Children, cohort studies, congenital anomalies, epilepsy, prevalence

Maternal use of antiepileptic medication during pregnancy increases the risk for congenital malformations in offspring. Teratogenicity of older antiepileptic drugs (AEDs) has been well established.[1–3] In the 1960s, Hanson and Smith[2] recognized the fetal hydantoin syndrome, which comprises facial abnormalities, spina bifida, cardiac defects, and limb anomalies among children exposed to phenytoin *in utero*. DiLiberti *et al.*[3] described the valproate syndrome, consisting of cranial–facial defects, cleft palate, radial ray defects, cardiac anomalies, and opthalmological, learning, and behavioural problems. Carbamazepine and valproate increase, especially, the risk of spina bifida.[4,5]

In most previous studies, risk of malformations has not been elevated in the offspring of mothers without medication.[6–8] Some studies suggest that genetic factors underlying epilepsy may increase the risk for congenital malformations in offspring,[9–11] but the evidence for this hypothesis is not strong.[12]

Most previous studies on major congenital malformations in the offspring of women with epilepsy have been based on small

[1] Tampere School of Public Health, University of Tampere, Tampere, Finland.
[2] The Finnish Register of Congenital Malformations, National Research and Development Centre for Welfare and Health, Helsinki, Finland.
[3] Social Welfare and Health Care Statistics, National Research and Development Centre for Welfare and Health, Helsinki, Finland.
[4] Department of Neurology, University of Oulu, Oulu, Finland.
[5] Pediatric Research Center, Tampere University Hospital, Tampere, Finland.
* Corresponding author. School of Public Health, FIN-33014 University of Tampere, Finland. E-mail: miia.artama@uta.fi

numbers and, therefore, they lack statistical power.[13,14] Moreover, the majority have been hospital-based including patients with complicated epilepsy unlikely to be representative of all patients.[15,16] We conducted this population-based study to obtain more valid and accurate estimates of major congenital malformations in the offspring of women with epilepsy, based on a large and representative patient cohort with comprehensive assessment of major congenital anomalies. Furthermore, we were able to use comprehensive assessment of congenital anomalies and analyse the risks by type of malformation.

Methods

All the Finnish citizens are entitled to reimbursement of medications for certain conditions. The reimbursement system of the Social Insurance Institution (SII) of Finland is organized through the National Health Insurance, which is maintained by the state, and financed through tax revenues. The costs of prescribed medicines are reimbursable partly or completely.[17] The patient pays a fixed deductible per purchase, and of the balance remaining, reimbursement is percentage-based and divided into three categories: basic (50%), lower special (75%), and higher special (100%). The pharmaceutical reimbursement system currently covers ~50 chronic diseases in higher special refund category at the moment, including epilepsy. Reimbursement requires a medical certificate demonstrating that the epilepsy diagnosis is based on clinical examinations, fulfils international criteria, and is made by a board-certified neurologist. Medical certificate is submitted to the SII when the medical treatment for epilepsy is started.

Women entitled to fully reimbursable antiepileptic medication for epilepsy were identified from the SII of Finland (Figure 1). The information covered personal identification number and date of eligibility approval. The female epilepsy patient cohort (n = 6535) consisted of all women who were approved as eligible for reimbursement for antiepileptic medication from the SII for the first time between January 1, 1985 and December 31, 1994, were in fertile ages (15–49 years), and were alive on January 1, 1990. Persons, who had died before January 1, 1990, had been removed from the SII database and information on them was not available. We did not have any information on maternal use of antiepileptic or any other medication.

The reference cohort (n = 14 704) was formed as a stratified random sample of all women alive and resident in Finland on January 1, 1990. The subjects were identified from the Finnish Population Register Centre with frequency-matching by 5 year age group to the epilepsy patient cohort. For assessment of maternal age at reimbursement and time since reimbursement, the mean starting date of reimbursement in the patients with

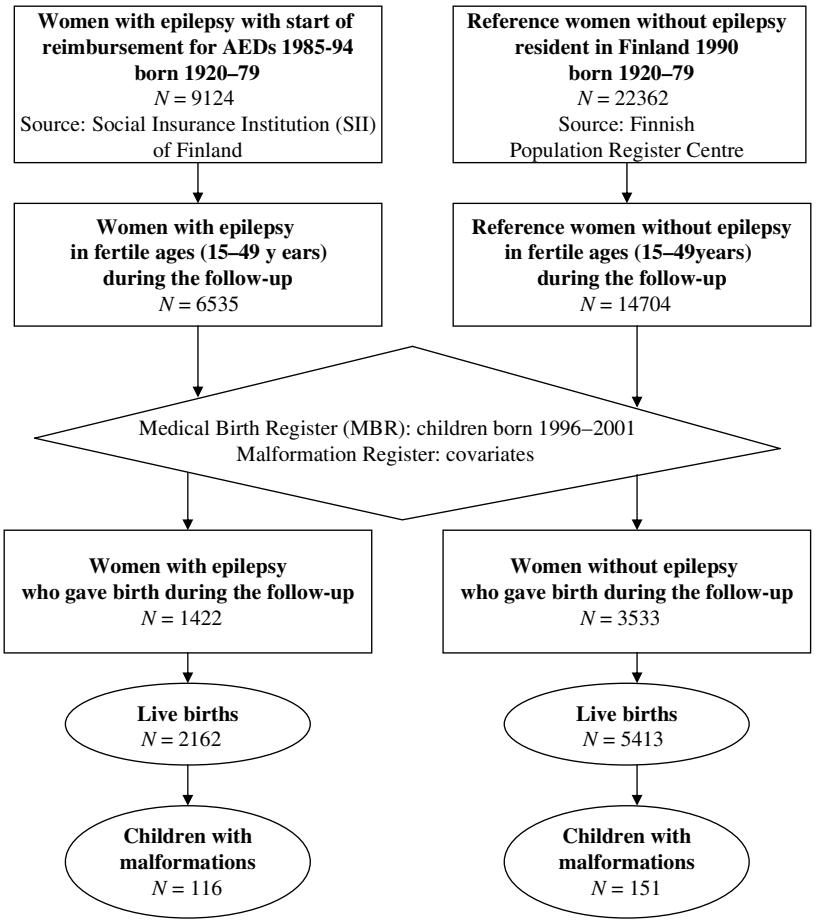

Figure 1 Flowchart summarizing the procedures and material of the study

epilepsy in that 5 year age group was used as a surrogate for index date (date of reimbursement) in the reference cohort.

Children were identified from the Medical Birth Register maintained by STAKES—the National Research and Development Centre for Welfare and Health. Information included personal identification numbers of mothers, and of their live or stillborn children, as well as the numbers of babies born in case of multiple births. Information on previous pregnancies, deliveries, and previous stillbirths (with fetal weight of at least 500 g or gestational age of at least 22 weeks) was also available. Information on previous stillbirths was missing for 106 births. In women with epilepsy, only children born after reimbursement were included in the analyses. In women without epilepsy, only children born after the index date were included in the analyses.

Information on congenital anomalies was obtained from the Finnish Register of Congenital Malformations maintained by STAKES. Information on malformations in the register is completed over the first year of life. The method of compiling the Finnish Register of Congenital Malformations was revised in 1993[18] and case ascertainment of the register improved substantially. Therefore, information on malformations before and after 1993 is not directly comparable. Only births between January 1, 1993 and December 31, 2000 were included in the analyses in this study.

Information covered the personal identification number of the mother and the live or stillborn children, as well as diagnosis according to ICD-9 (International Classification of Diseases, ninth revision). Only major congenital malformations were included in the analyses. Minor anomalies were excluded according to the exclusion list of European Registration of Congenital Anomalies (EUROCAT).[19] If a child had more than one major congenital malformation of one organ system, those malformations were treated as one outcome in the analyses by organ system.

Information from the registers was merged through computerized record linkage based on the unique personal identification number assigned to all residents of Finland.

The study protocol was approved by the ethical committee of the Pirkanmaa Hospital District. Register-based studies were conducted with permission from STAKES, SII of Finland, and the Finnish Population Register Centre. Because the study subjects were not contacted, informed consent to participate was not required according to the Finnish data protection legislation.

In the statistical analyses, factors considered potential confounders were maternal age at delivery and number of previous parities. Factors considered potential effect modifiers were maternal age at reimbursement for antiepileptic medication and maternal age at delivery. The analyses were performed using exact logistic regression in LogXact 4.1[20] with major congenital anomaly as the outcome. Confidence intervals (CIs) for differences in prevalence proportions were calculated with Stata 7.0.[21]

Results

The number of births during the study period was 2162 among the women with epilepsy (n = 1422) and 5413 among the reference women without epilepsy (n = 3533). The gender ratio of newborns in the female patients with epilepsy was similar to the women without epilepsy: 48.2% of the offspring were girls among women with epilepsy and 48.9% among women without epilepsy. The mean maternal age at delivery was lower among the mothers with epilepsy ($\bar{x}$ 28.1) than among the mothers without epilepsy ($\bar{x}$ 28.7) ($P < 0.01$). The mean number of previous live births in the mothers with epilepsy ($\bar{x}$ 0.92) was comparable with the mothers without epilepsy ($\bar{x}$ 0.96) ($P = 0.16$), as was the mean number of previous stillbirths (patients: $\bar{x}$ 0.01; referents: $\bar{x}$ 0.01) ($P = 0.92$).

The prevalence of births with major malformation was 54/1000 births (n = 116) among the mothers with epilepsy and 28/1000 births (n = 151) among the mothers without epilepsy (Table 1). In terms of absolute difference between the offspring of mothers with and without epilepsy ranging from 3.5/1000 to 7.0/1000 births, the greatest excess was observed in the prevalence of bulbus cordis anomalies and cardiac septal closure, congenital anomalies of the urinary system, other congenital anomalies of limbs, other congenital anomalies, congenital anomalies of genital organs, spina bifida, and other congenital anomalies of the circulatory system in the offspring of mothers with epilepsy. No obvious differences between the cohorts were observed in congenital anomalies of the skin, hair and nails, other anomalies of upper alimentary tract, other congenital anomalies of the heart, other congenital anomalies of the digestive system, and chromosomal anomalies.

The overall risk for major congenital malformation was clearly elevated in the offspring of mothers with epilepsy (OR = 1.98, 95% CI 1.53–2.55) (Table 1). The risk for spina bifida (OR = 11.3, 95% CI 2.34–108) and congenital anomalies of genital organs (OR = 8.38, 95% CI 2.15–47.4) was substantially higher in the offspring of mothers with epilepsy than the mothers without epilepsy. In addition, the offspring of women with epilepsy had a statistically significantly higher risk for other congenital anomalies of the circulatory system (OR = 4.19, 95% CI 1.38–14.0), other congenital anomalies (OR = 3.20, 95% CI 1.35–7.80), and other congenital anomalies of limbs (OR = 2.66, 95% CI 1.29–5.51). Adjustment for maternal age at delivery did not materially affect the results. Adjustment for previous parities had no substantial effect on the risk estimates with the exception of other congenital anomalies of the nervous system.

No clear trend was observed in the risk for major congenital anomalies by maternal age at delivery (P = 0.07 for trend) (Table 2). Regardless of the number of previous parities, the offspring of women with epilepsy had a 2-fold risk for malformations in relation to the offspring of women without epilepsy. The risk increased with time since reimbursement for antiepileptic medication (P = 0.02 for trend). Six confirmed and two suspected valproate syndromes were observed in the offspring of women with epilepsy.

Discussion

Few large population-based studies on malformations in offspring of women with epilepsy have been conducted[16,22] (Table 3). Most of the previous studies have been based on small numbers of live births without a population-based reference group.[7,8,23–26] In this study, comprehensive and nationwide material consisting of 2162 children of whom 116 were malformed, enabled evaluation of risks for most common types of malformations in offspring of mothers with epilepsy.

Table 1 The prevalence and number (*n*) of major congenital malformations in the offspring of women with and without epilepsy, and the ORs with 95% CIs for major congenital malformation in the offspring of mothers with and without epilepsy, by type of malformation, Finland 1993–2000

	Prevalence/1000 births		OR (95% CI)		
	Patients	Referents	Crude	Adjusted for maternal age at delivery	Adjusted for previous parities
Type of anomaly (ICD-9 code)[a]					
Anencephaly (740)	– (0)	– (0)	– (–)	– (–)	– (–)
Spina bifida (741)	4.16 (9)	0.37 (2)	11.3 (2.34–108)	11.1 (2.38–51.4)	11.2 (2.41–51.7)
Other congenital anomalies of nervous system (742)	3.24 (7)	1.11 (6)	2.93 (0.84–10.6)	2.81 (0.94–8.41)	3.48 (1.10–11.0)
Congenital anomalies of eye (743)	2.78 (6)	1.29 (7)	2.15 (0.60–7.48)	2.01 (0.67–6.00)	2.49 (0.80–7.72)
Congenital anomalies of ear, face and neck (744)	3.7 (8)	1.1 (6)	3.35 (1.02–11.7)	3.42 (1.18–9.88)	3.35 (1.16–9.67)
Bulbus cordis anomalies and anomalies of cardiac septal closure (745)	15.7 (34)	8.68 (47)	1.82 (1.13–2.91)	1.78 (1.14–2.77)	1.84 (1.18–2.88)
Other congenital anomalies of heart (746)	3.2 (7)	3.0 (16)	1.10 (0.38–1.00)	1.08 (0.44–2.64)	1.08 (0.44–2.63)
Other congenital anomalies of circulatory system (747)	4.6 (10)	1.1 (6)	4.19 (1.38–14.0)	4.38 (1.59–12.1)	4.17 (1.52–11.5)
Congenital anomalies of respiratory system (748)	5.1 (11)	3.0 (16)	1.72 (0.72–3.96)	1.69 (0.78–3.66)	1.84 (0.85–4.02)
Cleft palate and cleft lip (749)	5.1 (11)	3.1 (17)	1.62 (0.69–3.68)	1.54 (0.72–3.31)	1.71 (0.79–3.69)
Other anomalies of upper alimentary tract (750)	1.4 (3)	0.9 (5)	1.50 (0.23–7.73)	1.38 (0.33–5.79)	1.49 (0.36–6.24)
Other congenital anomalies of digestive system (751)	1.9 (4)	2.2 (12)	0.83 (0.23–2.76)	0.85 (0.27–2.64)	0.84 (0.27–2.61)
Congenital anomalies of genital organs (752)	4.6 (10)	0.6 (3)	8.38 (2.15–47.4)	8.25 (2.26–30.1)	8.30 (2.28–30.2)
Congenital anomalies of urinary system (753)	8.8 (19)	3.3 (18)	2.66 (1.32–5.38)	2.70 (1.41–5.15)	2.64 (1.38–5.04)
Certain congenital musculoskeletal deformities (754)	5.1 (11)	2.2 (12)	2.30 (0.92–5.71)	2.29 (1.01–5.22)	2.26 (1.00–5.14)
Other congenital anomalies of limbs (755)	8.3 (18)	3.1 (17)	2.66 (1.29–5.51)	2.65 (1.36–5.16)	2.78 (1.41–5.46)
Other congenital musculoskeletal anomalies (756)	5.1 (11)	2.2 (12)	2.30 (0.92–5.71)	2.29 (1.01–5.20)	2.27 (1.00–5.15)
Congenital anomalies of skin, hair, and nails (757)	2.3 (5)	0.4 (2)	6.27 (1.03–65.9)	6.66 (1.29–34.4)	6.34 (1.23–32.7)
Chromosomal anomalies (758)	1.9 (4)	2.4 (13)	0.77 (0.18–2.50)	0.73 (0.24–2.25)	0.83 (0.27–2.56)
Other congenital anomalies (759)	6.5 (14)	2.0 (11)	3.20 (1.35–7.80)	3.35 (1.52–7.41)	3.18 (1.44–7.01)
Overall	54.0 (116)	28.0 (151)	1.98 (1.53–2.55)	1.96 (1.53–2.51)	1.97 (1.54–2.52)

OR, odds ratio; CI, confidence interval; ICD-9, International Classification of Diseases, ninth revision.
[a] More than one major congenital malformation of one organ system in a child was treated as one outcome of the organ system.

The comprehensive register-based approach offers extensive information on births and malformations in a nationwide study population. Coverage of the Birth Register is >99% and its information is supplemented by the Population Register Centre information on live births and by Statistics Finland information on stillbirths and infant deaths to attempt to ensure completeness.[18]

Certain major congenital malformations are not always identified at birth (e.g. major congenital malformations of the cardiovascular or genitourinary system).[24] Therefore, the prevalence of these major congenital malformations is underestimated in studies where only malformations diagnosed at birth are included. In Finland, coverage of the Register of Congenital Malformations is 100% of the births[27] and information on malformations in the register is completed over the first year of life.

In previous studies, the overall proportion of children born with malformations to mothers with epilepsy has varied from 37/1000 to 155/1000 births.[6,8,15,16,23,28–30] In this study, the prevalence of births with malformation (54/1000 births) in patients with epilepsy was lower than in most previous studies. The definition of major congenital anomaly differs between the studies.[31] Also, most of the previous studies are hospital-based and, therefore, women with complicated epilepsy and polytherapy may be overrepresented in these studies.

Table 2 Total number of children, number of children with malformation in the epilepsy cohort and the reference cohort, and the odds ratio (OR) with 95% confidence interval (CI) for major congenital malformation in the offspring of women with epilepsy in relation to reference cohort, by maternal age, duration of follow-up, and reproductive factors, Finland 1993–2000

	Patients		Referents			
	Children	Children with malformation	Children	Children with malformation	OR	95% CI
Maternal age at start of reimbursement/index date[a] (full years)						
13–19	1089	61	2426	75	1.86	1.29–2.67
20–24	639	35	1824	48	2.14	1.33–3.42
25–29	324	15	917	22	1.97	0.94–4.04
30–34	82	4	226	5	2.26	0.44–10.8
35–42	28	1	20	1	0.71	0.01–58.1
Maternal age at delivery (full years)						
15–19	84	5	141	6	1.42	0.33–5.79
20–24	547	27	1,169	42	1.39	0.82–2.34
25–29	804	45	2026	55	2.12	1.39–3.24
30–34	517	26	1448	30	2.50	1.41–4.42
35–39	176	12	541	15	2.56	1.07–6.00
40–47	34	1	88	3	0.86	0.02–11.1
Time since reimbursement/index date (full years)						
0–4	565	28	946	33	1.44	0.83–2.49
5–9	1151	56	3635	103	1.75	1.23–2.47
⩾10	446	32	832	15	4.20	2.18–8.46
Number of previous parities						
0	955	55	2316	75	1.83	1.25–2.64
1	712	37	1737	45	2.06	1.28–3.29
⩾2	478	24	1271	30	2.19	1.21–3.91
Unknown	17	0	89	1	–	–
Total	2162	116	5413	151		

OR, odds ratio; CI, confidence interval.

[a] Index date = surrogate for date of reimbursement in the reference cohort (the mean starting date of reimbursement in the patients in that 5 year age group).

Regarding the risk for different types of malformations, the offspring of women with epilepsy have the highest risk for cardiovascular and urogenital malformations, spina bifida, and cleft lip/palate.[8,24,29,31,32] Our results were mainly consistent with the previous studies, though, we did not find a clearly increased risk for cleft lip/palate in the offspring of women with epilepsy. However, we could not analyse the offspring of mothers on different antiepileptic medication separately.

Our results regarding risk for malformation in the offspring of women with epilepsy were consistent with the previous population-based studies. In a British study, the risk for malformations in the offspring of women with epilepsy was 2.2-fold relative to the general population.[33] In a study conducted in Iceland, the risk for malformations was 2.7-fold (95% CI 1.4–4.5) in the offspring of patients on AEDs and 2.2-fold (95% CI 0.3–8.0) in the offspring of patients without AEDs in relation to the general population.[16] Overall risk, regardless of maternal AED use, was not reported in this study. In accordance with these findings, our results indicate that approximately half of the malformed children born to mothers with epilepsy were attributable to maternal epilepsy and/or AED use. We did not find an association between the occurrence of malformations in newborn and maternal age at delivery in women with epilepsy. This result was consistent with the previous studies.[6,8,34]

Information on epilepsy types or medication was not available in this study, but we were able to assess one modifier of antiepileptic medication. Discontinuation of medication increases with duration of epilepsy, and therefore, the risk for malformations is expected to decrease. However, in the analysis by time since reimbursement for antiepileptic medication, the highest risk was observed for ⩾10 years after start of reimbursement. In contrast to this finding, Lander and Eadie[34] did not find an association between the incidence of malformations in the offspring and duration of maternal epilepsy. One possible explanation for our results is that despite the discontinuation of medication in many women, the proportion of patients with refractory epilepsy and polytherapy increases with long duration of epilepsy, which elevates the risk for malformations.

Because of epilepsy, medical follow-up during and after pregnancy may be more intensive in epilepsy patients than in other women. Therefore, malformations may be detected more comprehensively in the offspring of mothers with epilepsy than in other children. Also, reporting of major malformations for

Table 3 A summary of the results from selected previous studies on congenital anomalies in the offspring of mothers with epilepsy

Study	Number of births by group	Overall result	Ascertainment of study subjects[a]	Inclusion of terminations/stillbirths	Information on AED use
				Yes/No	Yes/No
Kaneko *et al.*[6] (Japan)	885/98[b]	OR[b] = 3.1 (95% CI Unknown)	Hospital patients (with consent)	No/No	Yes
Holmes *et al.*[7] (United States)	316/98/508[c]	OR[d] = 3.3 (95% CI 0.9–8.3)	Hospital patients (with consent)	No/No	Yes
Canger *et al.*[8] (Italy)	427/25[b]	–	Hospital records	Yes/No	Yes
Olafsson *et al.*[16] (Iceland)	221/42/82 217[c]	SMR[e] = 2.7 (95% CI 1.4–4.5) SMR[f] = 2.2 (95% CI 0.3–8.0)	Hospital records	No/No	Yes
Wide *et al.*[22] (Sweden)	1398/581 258[e]	OR[e] = 1.86 (95% CI 1.42–2.44)	National Birth Registry	No/No	Yes
Samrén *et al.*[23] (The Netherlands)	192/158[d]	RR[d] = 2.3 (95% CI 1.2–4.7)	Hospital patients (information on consent not reported)	No/Yes (2 centres)	Yes
Samrén *et al.*[24] (The Netherlands)	1411/696/2000[c]	–	Hospital records	Yes/Yes	Yes
Fairgrieve *et al.*[33] (United Kingdom)	400/65 478[e]	OR(a = 2.15 (95% CI 1.30–3.37)	Maternity clinic visitors (with consent)	Yes/Yes	Yes

[a] Mothers with epilepsy.
[b] Offspring of patients on AED/patients without AED.
[c] Offspring of patients on AED/patients without AED/control women.
[d] Offspring of patients on AED/control women.
[e] Offspring of patient on AED/other female population.
[f] Offspring of patients without AED/other female population.

registration may be more complete and more detailed in the offspring of mothers with epilepsy than in other children. More extensive surveillance may lead to information bias and overestimation of the risk. As would be expected, the mean number of reported major anomalies/child with anomaly was higher in the patients with epilepsy than the referents (1.8 vs 1.5, $P = 0.07$) in our study. However, the difference was larger (2.2 vs 1.6, $P < 0.01$) when minor anomalies were included. The offspring of patients with epilepsy may have more multiple malformations including minor anomalies than the offspring of mothers without epilepsy.

Periconceptional folic acid supplementation is known to reduce the risk for malformations, especially neural tube defects in the offspring.[35] Because the offspring of women with antiepileptic medication have an elevated risk for neural tube defects, the Finnish Ministry of Social Affairs and Health has recommended, since 1995, that all women on antiepileptic medication take 0.4 mg of extra folic acid supplements daily, 4 weeks prior to conception and during the first 12 weeks of pregnancy.[36] Information on folic acid use was not available in this study.

Women with epilepsy are at a higher risk for early pregnancy losses and spontaneous abortions than women in general.[37] We did not evaluate these aspects, and, therefore, the effect of epilepsy on prevalence of major congenital malformations in offspring of epilepsy patients may have been underestimated. We did, however evaluate stillbirths and their inclusion or exclusion did not alter the results.

In our study, the risk for spina bifida was substantially elevated in the offspring of patients with epilepsy. In 1993–2002, one-third of all spina bifida pregnancies and nearly 90% of anencephaly pregnancies were terminated in Finland.[18] Overall, 226 pregnancies were terminated because of fetal congenital structural anomalies in Finland in 2002.[18] We did not have information on selective pregnancy terminations performed for fetal indications. Pregnant women with epilepsy are considered a high-risk group and are commonly under intensive obstetric surveillance. Therefore, structural anomalies may be more likely to be detected at an early stage, increasing also possibility of induced abortion. This may have underestimated the risk for congenital anomalies in the offspring of patients with epilepsy in our study, if the proportion of terminated pregnancies due to these types of malformations differs between patients with epilepsy and other population.

Identification of patients with epilepsy may have been incomplete. However, costs of antiepileptic medication are high in Finland. Therefore, few people with epilepsy do not seek reimbursement of antiepileptic medication. If an epilepsy diagnosis was made for an institutionalized patient, information on reimbursement is not necessarily in the SII database. Probably those patients are underrepresented in our study. Furthermore, the proportion of institutionalized epilepsy patients is overall small and the effect of exclusion of these persons is not likely to substantially affect our results, because they have a low birth rate. Information on epilepsy patients who have not wanted reimbursement for antiepileptic medication was not available.

Use of some antiepileptic medications during pregnancy may be associated with certain types of malformations. We did not have information on maternal use of AEDs. Although we did not find an association between maternal epilepsy and e.g. cleft palate and/or cleft lip, this does not exclude a possible association within subgroups of patients with specific medication.

Conclusions

Risk for major congenital malformations is 2-fold in the offspring of women with epilepsy in relation to the offspring of women without epilepsy. The highest relative risk was observed in spina bifida and congenital anomalies of genital organs. However, these malformations cover only a small proportion of all major malformations. These results pertain to follow-up on average of 7.3 years since diagnosis of epilepsy, regardless of antiepileptic medication usage.

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KEY MESSAGES

- The offspring of women with epilepsy are known to have an increased risk of congenital anomalies.
- In this study, overall risk for congenital anomalies was 2-fold in the offspring of mothers with epilepsy in relation to the offspring of mothers without epilepsy.
- Highest excess risk was found for spina bifida and anomalies of the genital organs.

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HIGH LIGHT

Antiepileptic drug use of women with epilepsy and congenital malformations in offspring

M. Artama, MSc; A. Auvinen, MD, PhD; T. Raudaskoski, MD, PhD; I. Isojärvi, RN; and J. Isojärvi, MD, PhD

Abstract—*Objective:* To compare the risk for congenital malformations in offspring between women with epilepsy being treated with antiepileptic drugs (AEDs) during pregnancy and those who discontinued their antiepileptic medication before pregnancy in a population-based cohort of female patients with epilepsy. *Methods:* All patients with epilepsy (n = 20,101) eligible for AED reimbursement for the first time during 1985 to 1994 were identified from the Social Insurance Institution of Finland. Information on births during 1991 to 2000 was obtained from the National Medical Birth Registry. Information on AED use during pregnancy and on pregnancy outcomes was abstracted from medical records. *Results*: Congenital malformations were more common among offspring of women on antiepileptic medication (65/1,411; 4.6%) than among offspring of untreated patients (26/939; 2.8%) ($p = 0.02$). The risk of malformations was substantially higher in the offspring of patients using valproate as monotherapy (OR = 4.18; 95% CI: 2.31, 7.57) or valproate as polytherapy (OR = 3.54; 95% CI: 1.42, 8.11) than of untreated patients. Polytherapy without valproate was not associated with increased risk of malformations. *Conclusion*: Excess risk was confined to patients using valproate during pregnancy. The risk for malformations was not elevated in offspring of mothers using carbamazepine, oxcarbazepine, or phenytoin (as monotherapy or polytherapy without valproate).

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Use of certain antiepileptic drugs (AEDs) during pregnancy increases the risk for specific congenital malformations, such as neural tube defects, cleft lip and palate, and cardiovascular malformations.[1-4] The teratogenicity of valproate, in particular, has been well established. The valproate-related risk for congenital malformations appears to be dose dependent,[4-6] and the overall risk of congenital malformations may increase when valproate is combined with other AEDs.[5,7] In contrast, most previous studies show no increased risk for congenital anomalies in newborns of mothers with untreated epilepsy.[5,7,8]

Since 1990, options for epilepsy treatment have substantially increased, but there is still little or no information on the teratogenic effects of the lately licensed AEDs, such as oxcarbazepine, gabapentin, tiagabine, topiramate, and levetiracetam.[1,9] However, rather substantial information on lamotrigine use is available in the International Lamotrigine Pregnancy Registry.[10]

In the evaluation of the teratogenicity of AEDs, untreated patients with epilepsy provide the optimal reference group. Few large studies on the teratogenic effects of specific AEDs, however, have used a reference group of untreated patients with epilepsy.[2] Emerging prospective pregnancy registries provide new information for safety assessments of AED use in pregnancy. However, not all of these registries monitor patients with untreated epilepsy. We conducted this population-based study to obtain valid and precise estimates of congenital malformations in the offspring of mothers with epilepsy who were taking specific antiepileptic medications, in comparison with outcomes in the offspring of patients who were untreated during the first trimester of pregnancy.

Additional material related to this article can be found on the *Neurology* Web site. Go to www.neurology.org and scroll down the Table of Contents for the June 14 issue to find the title link for this article.

Methods. All Finnish citizens are entitled to reimbursement for prescribed medications. The pharmaceutical reimbursement system is organized through the Social Insurance Institution (SII) of Finland, which is funded through tax revenues. The costs of prescribed medicines are reimbursable partly or completely. Reimbursement is percentage based and divided into three categories: basic (50%), special (75%), and complete (100%).

The complete reimbursement category covers 38 diseases, including epilepsy. Reimbursement for epilepsy requires a medical certificate demonstrating that the diagnosis is based on clinical examinations, fulfills international criteria, and is made by a board-certified neurologist. The medical certificate is issued when the antiepileptic medication for epilepsy is started.

From Tampere School of Public Health (M. Artama and Dr. Auvinen), University of Tampere; Pediatric Research Center (Dr. Auvinen), Tampere University Hospital; and Department of Neurology (Dr. Raudaskoski, I. Isojärvi, and Dr. Isojärvi), University of Oulu, Finland.

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Address correspondence and reprint requests to Miia Artama, Tampere School of Public Health, University of Tampere, FIN-33014, Finland; e-mail: miia.artama@uta.fi

The patient population in this study was obtained from the SII database. We identified all women (n = 6,535) who became eligible for full reimbursement for AEDs with epilepsy as indication for the first time between January 1, 1985, and December 31, 1994, and who were alive on January 1, 1990. The SII information covers full name, personal identification number (assigned to all residents of Finland), and the date of eligibility approval. Persons who had died before January 1, 1990, had been removed from the SII database and thus information on them was not available.

Children (n = 2,350) born to the women in the cohort from 1991 to 2000 were identified from the Medical Birth Register maintained by the National Research and Development Centre for Welfare and Health. Information included the personal identification numbers of the mothers and their children, as well as the numbers of babies. Information on previous pregnancies, deliveries, and stillbirths (with fetal weight of at least 500 g or a gestational age of at least 22 weeks) was also available. Only children born after diagnosis of maternal epilepsy and born during the study period (from January 1, 1991, to December 31, 2000) were included in the analyses. Information was obtained from the registers through computerized record linkage with the unique personal identification number as the key.

We conducted detailed analyses pertaining to the use of carbamazepine, oxcarbazepine, phenytoin, and valproate. Other AEDs were used in only a few pregnancies: lamotrigine, in 25 pregnancies (of which four involved monotherapy), and clonazepam, in 76 pregnancies (of which 16 involved monotherapy); other AEDs were used in fewer than 10 pregnancies each. In the data analyses, all of these drugs were combined into an "other medication" group. Carbamazepine, oxcarbazepine, phenytoin, and valproate were included in the polytherapy combinations of "other medication." The one third of mothers who were untreated during the first trimester of pregnancy were used as the reference group in the analyses.

Information on the AEDs received during pregnancy and on pregnancy outcomes was abstracted from medical records of the mothers with epilepsy from 45 hospitals. Information included use, type, and dose of antiepileptic medication during the first trimester of pregnancy and the type of congenital malformation as documented at discharge from the maternity unit. Anomalies were classified according to the International Classification of Diseases, ninth revision (ICD-9). Information on congenital malformations was missing for 36 births (1.5% of the total). Of these mothers, 25 were not on medication, 9 were on monotherapy, and 2 were on polytherapy. These 36 births were excluded from the analyses.

Because detailed information on congenital malformations was not always available in the medical records, we could not distinguish between minor and major malformations. Therefore, we included only main categories of malformations, as defined by ICD-9, in the analyses. In accordance with ICD-9, bulbus cordis anomalies and anomalies of septal closure, other congenital anomalies of the heart, and other congenital anomalies of the circulatory system were classified as congenital anomalies of the cardiovascular system. If a child had more than one congenital anomaly of one organ system, those anomalies were considered as a single outcome of the organ system.

In the statistical analyses, factors considered potential confounders were maternal age at delivery and number of previous births. The analyses were performed using exact logistic regression in LogXact 4.1,[11] with congenital malformation as the outcome. Significance for differences in prevalence proportions was calculated with Stata 7.0.[12]

The study protocol was approved by the ethics committees of the Pirkanmaa and the Pohjois-Pohjanmaa Hospital Districts. Medical records were obtained with permission from the Ministry of Social Affairs and Health. Because the study subjects were not contacted, informed consent was not required, according to the Finnish regulations.

Results. Overall, 939 births occurred among the 561 untreated patients and 1,411 occurred among the 857 patients using AEDs in the first trimester between January 1, 1991, and December 31, 2000. The mean time interval from epilepsy reimbursement to delivery was 8.2 years (SD, 3.6 years) among the untreated patients and 6.5 years (SD, 3.4 years) among the patients on AEDs. The mean maternal age at delivery was 27.5 years (SD, 5.2 years) among the untreated patients and 28.2 years (SD, 4.9 years) among the patients on AEDs. Most patients on AEDs were on monotherapy (n = 1,231). The most frequently used AEDs were carbamazepine (n = 919) and valproate (n = 361). They were used both as monotherapy (carbamazepine n = 805; valproate n = 263) and polytherapy (carbamazepine n = 114, valproate n = 98, including 56 patients on carbamazepine and valproate).

Table 1 *Number of congenital malformations by type of malformation in the offspring of female patients with epilepsy not treated with AEDs (n = 561) and with different AEDs (n = 857) as monotherapy or polytherapy during the first trimester of pregnancy, Finland 1991 to 2000*

Type of malformation	Untreated women	Women treated with AED, monotherapy/ polytherapy
Spina bifida	0	5/1
Ear, face, and neck	2	0/1
Cardiovascular	7	7/2
Cleft lip/cleft palate	2	5/2
Eye	1	0/0
Upper alimentary tract	3	0/1
Genital organs	5	10/3
Urinary system	1	3/0
Certain musculoskeletal deformities*	4	7/0
Other anomalies of limbs†	3	11/3
Other musculoskeletal anomalies	0	3/1
Chromosomal anomalies	0	4/2
Other congenital anomalies	1	2/0
Total no. of malformations	29	73
Total no. of children with malformation	26/939	65/1,411

Values are no. of children with malformation. One child may have had more than one malformation from two different organ systems (untreated women, n = 3; women with monotherapy, n = 5; women with polytherapy, n = 3).

* Including subluxation of the hip (n = 2) and luxation of the hip (n = 6).

† Including polydactylia (n = 9) and syndactylia (n = 2).

AED = antiepileptic drug.

The most frequently occurring types of congenital malformations in children of both the untreated patients and patients on AEDs were anomalies of the cardiovascular system (n = 16), cleft lip and palate (n = 9), anomalies of the genital organs (n = 18), certain musculoskeletal deformities (n = 11), and other anomalies of the limbs (n = 17) (table 1 and table E-1 on the *Neurology* Web site at www.neurology.org) Furthermore, six children were born with spina bifida.

Eleven children had two malformations each: four were born after maternal valproate monotherapy, one carbamazepine monotherapy, two polytherapy with carbamazepine plus valproate, one polytherapy with oxcarbazepine plus valproate, and three after an untreated pregnancy.

The overall proportion of children with congenital mal-

Table 2 *Number and prevalence of congenital malformations in the offspring of mothers with antiepileptic medication during the first trimester of pregnancy, and OR with 95% CI for congenital malformation in relation to the offspring of epileptic mothers without antiepileptic medication during the first trimester of pregnancy by type of antiepileptic medication, Finland 1991 to 2000*

	No. of births with malformation	Prevalence per 1,000 births	OR*	95% CI*
No AED	26	28	1.00	Reference
Carbamazepine	32	35	1.27	0.72, 2.23
Polytherapy	10	88	3.43	1.44, 7.61
Excluding VPA	4	69	2.60	0.64, 7.88
Oxcarbazepine	3	23	0.83	0.16, 2.77
Polytherapy	2	65	2.42	0.27, 10.5
Excluding VPA	1	59	2.19	0.05, 15.2
Valproate	37	102	4.01	2.32, 7.01
Monotherapy	28	107	4.18	2.31, 7.57
Polytherapy	9	92	3.54	1.42, 8.11
Other medication*	5	38	1.37	0.40, 3.72
Polytherapy	5	47	1.75	0.51, 4.77
Excluding VPA	3	41	1.48	0.28, 5.02
Total therapy	65	46	1.70	1.05, 2.81
Excluding VPA	38	36	0.96	0.54, 1.72
Total monotherapy	52	42	1.55	0.94, 2.60
Excluding VPA	24	25	0.89	0.49, 1.63
Total polytherapy	13	72	2.73	1.26, 5.64
Excluding VPA	4	49	1.80	0.45, 5.38

* Other medication: acetazolamide, clobazam, clonazepam, ethosuximide, gabapentin, lamotrigine, phenobarbital, primidone, tiagabine, topiramate, or vigabatrin.

AED = antiepileptic drug; VPA = valproate.

formations was higher for the mothers using AEDs (65/1,411; 4.6%) than for the mothers not receiving AEDs during pregnancy (26/939; 2.8%). Congenital malformations occurred in 52/1,231 births (4.2%) following pregnancies with AED monotherapy and in 13/180 births (7.2%) following pregnancies involving polytherapy. Out of all children with malformations born to mothers on AEDs, more than half were born to mothers taking valproate (37/65; 57%).

Comparison with the untreated patients showed that the risk of congenital malformations in offspring was slightly higher overall for the patients on any antiepileptic therapy (OR = 1.70; 95% CI: 1.05, 2.81) (table 2 and table E-2). In comparison with the reference group, we found no significantly increased risk associated with the use of AED monotherapy (OR = 1.55; 95% CI: 0.94, 2.60) but a clearly elevated risk related to the use of any AED polytherapy (OR = 2.73; 95% CI: 1.26, 5.64).

Use of valproate during pregnancy substantially increased the risk of congenital malformations in offspring compared with untreated mothers, whether the valproate was used as monotherapy or in combination with any other AED (see table 2). Mothers using AEDs other than valproate (carbamazepine, oxcarbazepine, phenytoin, or other AEDs combined) did not have a higher overall risk of congenital malformations among offspring than the untreated patients (see table 2).

For mothers on any carbamazepine therapy, the overall risk of congenital malformations in offspring was not significantly higher than that of untreated patients. No excess risk was related to carbamazepine monotherapy. However, the risk of congenital malformations in offspring was substantially elevated for patients on carbamazepine polytherapy. Yet, when carbamazepine polytherapy combinations with valproate were excluded, the risk for congenital malformations in offspring was not significantly higher than in untreated patients (see table 2).

For mothers on valproate monotherapy during pregnancy, the risk of congenital malformations in offspring increased with the daily valproate dose (p for trend < 0.0001) (table 3 and table E-3). We did not observe a significant dose-dependent relationship for carbamazepine monotherapy. Adjustment for maternal age at delivery or number of previous births did not affect the risk of congenital malformations in offspring related to different antiepileptic medications (results not shown).

Discussion. Few large population-based studies have evaluated congenital malformations in the offspring of patients with epilepsy using AEDs during pregnancy. Most of the previous studies have not included a reference group of untreated patients with epilepsy.[2] For our study, we had access to extensive data containing detailed information on AED use, which enabled us to evaluate the risk of congenital malformations in the offspring of patients using the most common types of AEDs (carbamazepine, oxcarbazepine, phenytoin, and valproate) during pregnancy.

Patients with epilepsy differ from the general population not only because of the epilepsy itself but also with regard to other characteristics, such as co-

Table 3 *Risk for congenital malformation in offspring of female patients with epilepsy treated with valproate monotherapy by daily dose in relation to offspring of untreated female patients with epilepsy during the first trimester of pregnancy, Finland 1991 to 2000*

AED dose, mg/day	No. of birth with malformation	Prevalence per 1,000 births	OR	95% CI
No AED	26	27.7	1	Reference
Valproate				
≤1,500	23	95.0	3.68	1.97, 6.86
>1,500	5	238	10.89	2.90, 34.3

AED = antiepileptic drug.

morbidity (including hereditary diseases), use of other medications besides AEDs, and socioeconomic status. Inasmuch as our reference cohort consisted of patients with epilepsy not receiving treatment during pregnancy, differences in these characteristics were smaller in relation to the patients who were taking AEDs than they would be to a reference group consisting of the general population.

Nevertheless, patients on AED therapy may differ generally from untreated patients according to the type or etiology of the epilepsy or in terms of seizure characteristics or occurrence of psychogenic seizures. Therefore, the effect of epilepsy and antiepileptic medication cannot be distinguished, i.e., there is confounding by indication.

Use of older AEDs during pregnancy, such as carbamazepine, phenytoin, and valproate, has been reported to increase the risk of congenital malformations two- to threefold.[5,7,13] However, recent studies suggest differences in teratogenicity between various AEDs.[14,15] In our study, the offspring of mothers on valproate had a fourfold increased risk for congenital malformations as compared with an untreated group, but we found no excess risk related to AEDs other than valproate. In previous studies higher daily doses of valproate during pregnancy, e.g., more than 1,000 mg/day, significantly increased the risk for congenital malformations.[5,16,17] In our study, the risk for congenital malformations was tenfold in the offspring of patients taking valproate at doses of more than 1,500 mg/day.

More than half of the patients in our study were using carbamazepine or valproate. Other AEDs were not used as commonly, and therefore we could not assess the risk associated with these medications equally accurately. Oxcarbazepine was first licensed in Finland in 1991. Few studies have evaluated the teratogenic effects of oxcarbazepine in humans,[18-20] and these involve only a small number of pregnancies and malformations. One study[19] found no malformations in the offspring of 35 patients treated with oxcarbazepine monotherapy and found only one malformation out of 20 children born to mothers treated with oxcarbazepine polytherapy. Another study[20] reported one case of malformation associated with oxcarbazepine monotherapy and one with oxcarbazepine polytherapy, among 37 pregnancies. Our cohort of patients on oxcarbazepine is, to our knowledge, the largest studied so far. Among the 99 patients receiving oxcarbazepine monotherapy, we identified one urogenital malformation. The nine pregnancies reported in a previous Finnish study[18] may overlap with our cohort. Newer AEDs introduced after oxcarbazepine are frequently used in polytherapy regimens in combination with older AEDs. Collaborative multicenter studies or ongoing prospective pregnancy registries involving large numbers of patients will facilitate the evaluation of the teratogenic effects of these newer AEDs.

Previous studies suggest that the risk for congenital anomalies increases with the number of AEDs used in polytherapy.[7,13,21] We also found a clearly increased overall risk for congenital malformations in the offspring of patients with epilepsy on polytherapy, but not for the offspring of patients with epilepsy on monotherapy. However, we could not evaluate the risk for congenital malformations according to the number of AEDs used in polytherapy because the number of patients taking more than two AEDs was small (n = 26). As the data in prospective pregnancy registries accumulate, blinded teratologic review will provide us with more detailed information on the congenital malformations occurring with various polytherapy regimens.

Our study had limitations. Because the information on congenital anomalies was incomplete, we could not exclude minor congenital anomalies. Therefore, our results are not directly comparable with those from previous studies focusing only on major malformations in the offspring of patients with epilepsy. In our study, even with the inclusion of minor malformations, the prevalence of malformations in the offspring of patients not taking AEDs (277/10,000 births) was comparable with the prevalence of malformations in the Finnish general population as recorded between 1993 and 2000 (on average 286/10,000 births).[22] One possible contributor to this difference is that all malformations are not identified at birth (e.g., major congenital malformations of the cardiovascular or the genitourinary system)[23] but are reported to the registry at a later stage. We could not identify such cases.

We did not have information on folic acid use, which may have caused confounding, if the pregnancy-related use of folic acid supplementation differed between the therapy groups. However, only 5% of the congenital malformations identified in our study were neural tube defects.

Women with epilepsy are at higher risk for spontaneous abortions than other women. Increased risk may be associated with AED use.[24,25] This may have biased our results if the risk for spontaneous abortions differs between women using AEDs and women without AED. We did not have information on spontaneous abortions.

Severe spina bifida frequently leads to either spontaneous or induced abortion.[26] This reduces the prevalence of spina bifida in live and stillborn children. Use of valproate or carbamazepine as monotherapy or polytherapy during pregnancy is known to increase the risk of spina bifida in the offspring.[2,27,28] We did not have information on selective pregnancy terminations. This does not affect our results, unless induced abortions due to spina bifida are more frequent among carbamazepine or valproate users than in other women with epilepsy.

Socioeconomic status is a potential confounder in our study, but no information was available. In Finland, the out of pocket costs of epilepsy treatment for the patient are low, and there are no major differences in the quality of epilepsy care or in the AEDs used in the patients with epilepsy depending on their

socioeconomic status. Therefore, confounding by socioeconomic status is not likely to affect our results.

Substantially increased risk of congenital malformations was found in the offspring of mothers with valproate therapy during pregnancy. The offspring of mothers using CBZ, OXC, or PHT had no excess risk of congenital malformations. The risk of malformations was elevated in the offspring of mothers on polytherapy including valproate, but not in AED combinations without valproate. However, the risk of congenital malformations should be considered in relation to different treatment alternatives in terms of their treatment efficacy and teratogenicity.

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