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Eeva Löfgren

EFFECTS OF EPILEPSY AND ANTIEPILEPTIC MEDICATION ON REPRODUCTIVE FUNCTION

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DEPARTMENT OF NEUROLOGY,
DEPARTMENT OF PUBLIC HEALTH SCIENCE AND GENERAL PRACTICE,
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Abstract

Epilepsy is associated with reproductive disorders and decreased fertility. The role of antiepileptic medication and type of epilepsy in development of these disorders has been widely debated. The effects of oxcarbazepine on reproductive function in women and the effects of antiepileptic medication on male fertility have not been previously studied, and only a few studies have evaluated fertility in subjects with epilepsy in a population based setting.

This study aimed to analyze predictors of reproductive disorders and the effects of oxcarbazepine on reproductive function in women. Moreover, the effects of antiepileptic medication on male reproductive health were also evaluated, and finally, the reproductive health of patients with epilepsy and the normal population was compared in a population based setting.

The study was conducted in the Departments of Neurology, Gynecology and Obstetrics and Public Health Science and General Practice in the University of Oulu. Studies I–III were cross-sectional studies consisting of 249 subjects with epilepsy and 247 control subjects. Study IV was a retrospective study; the data was based on Northern Finland Birth Cohort 1966(NFBC1966), consisting of 12,058 subjects, of which 222 had epilepsy. In studies I–III all subjects were interviewed, clinical examinations were done, blood samples were analyzed and ovarian ultrasound examination or testicular ultrasound examination and sperm samples were studied. In study IV all subjects with epilepsy were identified from NFBC1966 and patient files were reviewed. Fertility analyses were based on information obtained from the Finnish Population Center and Finnish Birth Register.

Reproductive disorders were more common in women with idiopathic generalized epilepsy and in women taking valproate. Also young age increased the risk of these disorders. Oxcarbazepine was associated with reproductive disorders in women with epilepsy. In men all antiepileptic drugs studied were associated with sperm abnormalities, and sperm abnormalities in men taking valproate were associated with decreased testicular volume. In a population based setting active epilepsy and antiepileptic medication during adulthood decreased fertility.

The reproductive endocrine effects of AEDs should be taken into consideration when prescribed to fertile aged men and women, especially, if the anticipated duration of treatment is long.

Keywords: epilepsy, fertility, oxcarbazepine, reproduction, valproic acid

The real voyage of discovery consists not in seeking new landscapes but in having new eyes.
Marcel Proust

To my family

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Kokkola, November 2007 Eeva Löfgren

Abbreviations used in the text

A	androstenedione
ACTH	adrenocorticotropin
AED	antiepileptic drug
CBZ	carbamazepine
CZP	clonazepam
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone sulphate
E_2	estradiol
EEG	electroencephalography
ESM	etosuximide
FSH	follicle-stimulating hormone
GABA	gamma-amino-butyric acid
GH	growth hormone
GnRH	gonadotropin releasing hormone
HA	hyperandrogenism
IGE	idiopathic generalized epilepsy
IGF-I	insulin-like growth factor I
IGFBP-I	insulin-like growth factor binding protein I
ILAE	International League Against Epilepsy
LH	luteinizing hormone
LRE	localization related epilepsy
LTG	lamotrigine
MRI	magnetic resonance imaging
MWE	men with epilepsy
NFBC	Northern Finland Birth Cohort
OXC	oxcarbazepine
PCO	polycystic ovaries
PCOS	polycystic ovary syndrome
PHT	phenytoin
PROG	progesterone
PWE	patients with epilepsy
RIA	radioimmunoassay
SHBG	sex hormone binding globulin
SII	Social Insurance Institution
SUD	sudden unexplained death

SUDEP	sudden unexplained death in epilepsy
T	testosterone
VPA	valproate
WWE	women with epilepsy

List of original articles

This thesis is based on the following articles, which are referred to in the text by Roman numerals:

I Löfgren E, Mikkonen K, Tolonen U, Pakarinen AJ, Koivunen R, Myllylä VV, Tapanainen JS & Isojärvi JIT (2007) Reproductive endocrine function in women with epilepsy - The role of epilepsy type and medication. Epilepsy Behav10: 77-83.

II Löfgren E, Koivunen R, Pakarinen A, Tapanainen JS &Isojärvi JIT (2006) Effects of carbamazepine and oxcarbazepine on reproductive function in women with epilepsy. Epilepsia 47: 1441-6.

III Isojärvi JI, Löfgren E, Juntunen KS, Pakarinen AJ, Päivänsalo M, Rautakorpi I & Tuomivaara L (2004) Effect of epilepsy and antiepileptic drugs on male reproductive health. Neurology 62: 247-253.

IV Löfgren E, Pouta A, von Wendt L, Tapanainen JS, Isojärvi JIT & Järvelin M-R (2007) Epilepsy and fertility in Northern Finland Birth Cohort 1966. Submitted.

Contents

1 Introduction

Epilepsy is a common neurological disorder that consists of a wide variety of symptoms arising from abnormal, excessive or synchronous neuronal activity in the brain (Browne & Feldman 1983, Engel & Pedley 1997). It can manifest at any age, however, in most cases, it begins before adulthood or after 50 years of age (Hauser 1997). The first descriptions of epileptic seizures are from over 4000 years ago and for centuries patients with epileptic seizures have been assumed to be possessed by demons, which has associated a strong stigma with epilepsy. Moreover, even in Finland the laws restricting marriages and pregnancies in patients with epilepsy (PWE) remained in force until 1969-1970 (Lindberg 1995).

The current classification of epilepsy is based on the etiology and the type of seizures (Commission on Classification and Terminology of the International League Against Epilepsy 1989). As a chronic disease, epilepsy can continue for years or even a lifetime and therefore long-term medication is needed. During the last decades scientific research has provided new diagnostic tools and treatment options which have improved the prognosis of epilepsy. Surgical treatment has become a treatment option and the spectrum of antiepileptic drugs (AEDs) that are available has widened which allows the selection of an optimal AED for a specific epilepsy syndrome. Furthermore, awareness and knowledge of various side-effects of AEDs has also increased which makes it possible to tailor the medication to the needs of individual patients and thus improve compliance. (Shorvon 2000, 2004)

The association between epilepsy and reproductive disorders was first described in the 1950s (Gastaut & Colomb 1954). Today the roles of epilepsy and antiepileptic medication in contributing to reproductive endocrine disorders in people with epilepsy are still widely debated. Epilepsy itself may disturb the regulation of secretion of reproductive hormones (Dana-Haeri & Trimble 1984). On the other hand, AEDs are also known to induce reproductive endocrine disorders. It is well known that valproate (VPA) is associated with reproductive disorders and obesity in women with epilepsy (WWE). (Isojärvi *et al.* 1993, 1996, 1998, 2001, Betts *et al.* 2003)

It has been suggested that especially active epilepsy during fertile age may predispose to reproductive dysfunction and possible infertility (Mikkonen et al. 2004b). Some studies have indeed reported decreased fertility in PWE in a population based setting (Wallace *et al.* 1998, Artama *et al.* 2004).

This study aimed to evaluate the role of epilepsy and antiepileptic medication in the development of reproductive disorders in PWE and to assess fertility in PWE in a population based setting.

2 Review of literature

2.1 General aspects of epilepsy

2.1.1 Definition

Epilepsy is a relatively common neurological disorder resulting from abnormal and excessive discharges of electrical activity of cerebral neurons. Epileptic seizures can manifest as such symptoms as altered consciousness, involuntary movements, abnormal sensory phenomena, increased autonomic activity or transient disturbances of behavior depending on the localization of the epileptic disorder. In addition to symptoms of the seizures, the pathologic electrical discharges detectable in the electroencephalography (EEG) during the seizures and in the interictal period can also reveal the site of origin of the dysfunction. Although epileptic seizures can be symptoms of a causative brain disease, in the majority of cases of epilepsy the cause is unknown and the diagnosis is solely based on description of seizures and findings in EEG. (Waltimo 1983, Browne & Feldman 1983, Engel & Pedley 1997)

2.1.2 Epidemiology

The prevalence of active epilepsy is 3.6-7.8 per 1000 inhabitants in Western countries, and it is suggested to be higher in the developing countries (Forsgren 2004). However, the comparison between the observed prevalence rates in different studies is difficult due to the variation of definitions of seizure disorders used in the different studies. The risk for epilepsy is highest during the first year of life and it decreases during childhood and adolescence, but in the age range of 50-60 years the risk for epilepsy starts to increase again. According to the Rochester study approximately 50% of cases of epilepsy begin in childhood or adolescence (Hauser *et al.* 1993, 1997), but in other epidemiological studies 75-90% of cases of epilepsy have started before adulthood (Sillanpää M 1994). The lifetime cumulative incidence of epilepsy has varied between 1-3% in different studies, and epilepsy is more often found in men (Hauser 1997). In Finland in 2005 54 000 patients received antiepileptic medication according to the Finnish Social Insurance Institution (SII).

2.1.3 Etiology

All factors that cause pathologic structural or functional changes in the brain may predispose to epilepsy (Vinters *et al.* 1993). In adults trauma, brain tumors and vascular diseases of the brain are the most common causes of epilepsy, while in children metabolic defects, congenital malformations, infections, genetic diseases and perinatal injuries are among the common etiologies. However, the etiology of epilepsy remains unresolved in a large number of patients (Beghi 2004).

Genetic factors can also predispose to epilepsy. In a majority of the cases epilepsy is caused by interactions of many genes and environment, and in a minority of cases of epilepsy can be attributed to a single gene disorder (Gutierrez-Delicado & Serratosa 2004).

2.1.4 Classification

Epilepsy is classified according to the etiology of the symptoms. Localization-related epilepsy (LRE) is called is symptomatic if there is known etiology, and if the presumed origin of seizures is not detected with the methods used, it is called cryptogenic. Idiopathic generalized epilepsies (IGE) with unknown etiology are much more common in children with epileptic syndromes than in adults with epilepsy. Furthermore, seizures are categorized as partial or generalized. The seizure classification is based on clinical symptoms of the seizures and EEG findings (Commission on Classification and Terminology of the International League against Epilepsy 1981, Commission on Classification and Terminology of the International League Against Epilepsy 1989). A summary of the International Classification of Epilepsies and Epileptic syndromes is presented in Table 1.

Table 1. International classification of epilepsy and epileptic syndromes (Commission on Classificication and Terminology (ILAE) 1989).

Class	Classification
1.	Localization-related (focal, local, partial)
1.1	Idiopathic (with age-related onset)
	Benign childhood epilepsy with controtempolar spikes
	Childhood epilepsy with occipital paroxysms
	Primary reading epilepsy
1.2	Symptomatic
	Chronic progressive epilepsia partialis continua of childhood
1.3	Cryptogenic epilepsies (etiology unknown, propably symptomatic)
	The symptomatic and cryptogenic categories comprise syndromes that are based on:
	Seizure types (according to the International Classification of Epileptic Seizures)
	Anatomic localization: Temporal, frontal, parietal, and occipital lobe epilepsies
	Bi- and multilobar epilepsies
	Etiology (in symptomatic epilepsies)
	Spesific models of precipitation
2.	Generalized
2.1	Idiopathic (with age-related onset, in order of age)
	Benign neonatal familial convulsions
	Benign neonatal convulsions
	Benign myoclonic epilepsy in infancy
	Childhood absence epilepsy (pyknolepsy)
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy (impulsive petit mal)
	Epilepsy with grand mal (GTC) seizures on awaking
	Other idiopathic generalized epilepsies not defined above
	Epilepsies with seizures precipitated by specific modes of activation
2.2.	Cryptogenic or symptomatic (in order of age)
	West syndrome (infantile spasms, Blitz-Nick-Salaam-Krämpfe)
	Lennox-Gastaut syndrome
	Epilepsy with myoclonic-astatic seizures
	Epilepsy with myoclonic absences
2.3	Symptomatic
2.3.1	Nonspecific etiology
	Early myoclonic encephalopathy
	Early infantile epileptic encephalopathy with suppression-burst
	Other symptomatic generalized epilepsies not defined above
2.3.2.	Specific syndromes (see original reference)
3.	Epilepsies and syndromes undetermined whether focal or generalized
3.1.	With both generalized and focal seizures
	Neonatal seizures
	Severe myoclonic epilepsy of infancy
	Epilepsy with continuous spike-waves during sleep
	Acquired epileptic aphasia (Landau-Kleffner syndrome)
	Other undeterminent epilepsies not defined above
3.2.	Without unequivocal generalized or focal features
	(e.g., many cases of sleep-grand mal)
4.	Special syndromes
4.1	Situation-related seizures
	Febrile convulsions
	Isolated seizures or isolated status epilepticus
	Seizures due to acute metabolic or toxic factors such as alcohol, drugs, eclampsia

2.1.5 Diagnosis

Epileptic seizures can manifest under stressful conditions (i.e. sleep deprivation, alcohol or drug abuse, infections, hypoglycemia and metabolic changes) even in persons without epilepsy. Diagnosis of epilepsy is usually made after two or more unprovoked seizures. Medical history with information of possible predisposing factors to seizures and a detailed description of the clinical features of the seizures as well as clinical examination with special respect paid to cardiovascular and neurological findings are essential diagnostic tools when assessing possible epilepsy. An EEG recording is important in providing confirmatory information for the diagnosis and to help define the possible focal or generalized epilepsy syndrome. Magnetic resonance imaging (MRI) is important in helping to detect the underlying structural pathologic conditions of the brain. However, in some cases diagnosis can also be made based on medical history and history of unprovoked seizures even though EEG and MRI are normal. (Moshe & Pedley 1997)

2.1.6 Prognosis

The etiology and the type of the epileptic syndrome are the main factors contributing to the prognosis (Sillanpää *et al.* 1999). More than two-thirds of newly diagnosed PWE achieved at least three year remission in a nine years follow-up study (Cockerell *et al.* 1995, 1997). The terminal remission rate is suggested to be higher in patients with idiopathic or cryptogenic epilepsy (Thurston *et al.* 1982, Oka *et al.* 1989). In patients with newly diagnosed LRE, 62% achieved a seizure-free period lasting at least 12 months. The follow-up period varied from two to 20 years (Mohanraj & Brodie 2005). The risk for seizure recurrence after initiation of AED treatment increases if more than three seizures have occurred before the initiation of the treatment. An underlying neurological disorder or EEG with epileptiform abnormality also increases the risk for seizure recurrence (Kim *et al.* 2006). About 20-30% of PWE will suffer from seizures despite AED treatment (Keränen *et al.* 1997).

In childhood epilepsies the prognosis depends on epilepsy type. Fortunately the terminal remission rate is high, and remission is in most cases achieved before adulthood (Thurston *et al.* 1982, Sillanpää *et al.* 1998). Remission is usually always achieved in benign childhood epilepsy with centrotemporal spikes (Rolandic epilepsy) (Sillanpää *et al.* 1999, Berg *et al.* 2001). On the contrary,

some other epilepsies require long term treatment. Even though the prognosis of IGEs is usually good, juvenile absence and juvenile myoclonic epilepsies need long term drug therapy, sometimes life-long treatment, to keep the patients in remission. Furthermore, generalized syndromes, West syndrome and Lennox-Gastaut syndrome have a poor prognosis; the remission is achieved only in 22% of patients and the mortality is 38% during more than 30 years follow-up (Sillanpää *et al.* 1999).

2.1.7 Mortality

The overall mortality in PWE is two to three times higher than in the general population (O'Donoghue & Sander 1997). Comorbidity, especially brain diseases, accidents during seizures, status epilepticus, and suicides increase the overall mortality (Hauser *et al.* 1993). Age and gender as well as the etiology of epilepsy have an influence on the mortality rate. Age is considered to be a factor that affects the mortality rate in PWE, but the findings have not been congruent. However, it has been suggested that mortality rates are higher in younger PWE (Hauser *et al.* 1980, Harvey *et al.* 1993). The epilepsy type is also a factor that affects the mortality risk. In children with idiopathic epilepsy the all-cause mortality rate is lower than in children with LRE (Harvey *et al.* 1993, Camfield *et al.* 2002, Berg *et al.* 2004). In a Finnish study the epilepsy type strongly influenced the probability to survive to the age of 40. In patients with idiopathic epilepsy the probability to survive was 0.87, in patients with cryptogenic epilepsy the probability was 0.93 and in patients with symptomatic epilepsy it was 0.73 (Sillanpää *et al.* 1998).

Sudden unexpected death in epilepsy (SUDEP) is relatively common in PWE, and overall sudden unexpected death (SUD) is more common in epilepsy patients than in the general population. The incidence varies from 1/100 in severe refractory epilepsy to 1/1000 in well controlled epilepsy (O'Donoghue & Sander 1997, Langan *et al.* 2002). The incidence of SUD is over 20 times higher in PWE than in the general population (Ficker *et al.* 1998). SUDEP is defined as sudden, unexpected, witnessed or non-witnessed, non-traumatic and non-drowning death with or without evidence of seizure and excluding status epilepticus, and autopsy not revealing the cause of death (Nashef 1997, 1998, Sperling *et al.* 1999). The risk factors for SUDEP include young age (20-40 years), alcohol abuse, psychiatric comorbidity, related medication, non-compliance and male gender, but

healthy compliant patients may also die suddenly to SUDEP (Nashef 1997, 1998, Nilsson *et al.* 1999, Sperling *et al.* 1999, Walczak *et al.* 2001).

2.1.8 Treatment

The main goal in the treatment of epilepsy is to achieve complete seizure control. Eventhough AED treatment has improved remarkably in terms of efficacy and tolerability during the last decades, still 20-30% of PWE suffer from drug-resistant epilepsy (Keränen & Kälviäinen 1997, Hauser & Hesdorffer 2001).

Surgical treatment should be considered in patients treated with appropriate AEDs for 2-3 years without sufficient response (Kälviäinen & Keränen 2006). Vagal nerve stimulator is a novel method in the treatment of epilepsy. It is a treatment option for drug refractory epilepsy patients who are not suitable candidates for resective epilepsy surgery (Schachter 2004).

If a specific predisposing factor for seizures has been identified, the patients are recommended to avoid factors with predisposition to trigger seizures (Perucca 1996). In children febrile seizures are not usually considered an indication for antiepileptic treatment (Hirtz *et al.* 2003).

Epileptic syndrome and seizure type should be identified before initiation of rational AED treatment in order to obtain the best possible efficacy and also to improve the prognosis. Some AEDs are efficacious in a certain syndrome, while some other AEDs may aggravate the same syndrome (Genton *et al.* 2000). Usually, drug treatment for epilepsy is started after two unprovoked seizures. However in cases of abnormal interictal epileptiform EEG or of persisting predisposing cause for seizures (i.e brain pathology identified with an abnormal MRI-finding) or even when avoiding the unwanted physical or psychosocial consequences for seizures is especially important, medication can be initiated after one seizure (Hirtz *et al.* 2003). It has been shown that early intervention may prevent the epileptic process from becoming chronic (Scheuer & Pedley 1990).

Most PWE achieve seizure freedom with monotherapy, in the majority of cases with the first or second appropriate AED that is tried (Kwan & Brodie 2000, 2001). Fewer interactions and better compliance are some of the advantages of monotherapy. However, about one-third of patients suffer from a more severe epilepsy syndrome and may need polytherapy (Ferrendelli 1987, Kwan & Brodie 2001). Polytherapy may give better seizure control, but it also increases the risk for interactions and side effects. About 25% of all patients do not respond to drug therapy. Drug refractoriness may be caused by false diagnosis or continuous or

intermittent predisposal to factors that provoke seizures, such as sleep deprivation or alcohol abuse. (Keränen & Kälviäinen 1997)

After five years of adequate AED treatment about 70% of patients achieve remission (Cockerell *et al.* 1997). Discontinuation of medication should be considered after 3-5 years of seizure freedom and if considered appropriate should be done slowly in order to minimize the risk of relapse (Keränen *et al.* 1997). However, some epileptic syndromes such as juvenile myoclonic epilepsy may need life-long medication and the risk for relapse may also be high after discontinuation of medication in LREs (Thurston *et al.* 1982). Furthermore, in 37 year-follow up study drug discontinuation after seizure freedom resulted in relapse in one third of patients (Sillanpää & Schmidt 2006). The recommendations of selection of antiepileptic medication are presented in table 2.

2.1.9 Antiepileptic medication

The efficacy of standard AEDs is well established and some differences in efficacy between VPA, phenytoin (PHT), carbamazepine (CBZ) (Treiman 1987, de Silva *et al.* 1996) and novel AEDs have been observed when these AEDs have been used for appropriate seizure types (Mattson 1995, Marson *et al.* 2007a, 2007b). However, there are only a few head-to-head studies that have compared the efficacy of novel AEDs (Schapel & Chadwick 1996, Wong *et al.* 1999, McDonald *et al.* 2005). The general properties of the AEDs that were used by PWE in the present study are discussed briefly in the following chapter. Reproductive endocrine changes related to AEDs are discussed in chapter 2.4.4.

Table 2. The drug recommendation for various types of epilepsy, medication in alphabetical order. (LaRoche & Helmers 2004, Kälviäinen & Keränen 2006).

Type of epilepsy	Recommended medication
Localization-related epilepsies	First-line therapy
	Carbamazepine
	Oxcarbazepine
	Second-line therapy
	Gabapentin
	Lamotrigine
	Levetiracetam
	Pregabalin
	Valproate
	Topiramate
Generalized seizures	First-line therapy
	Valproate
	Second-line therapy
	Lamotrigine
	Topiramate
Non-classified epilepsy	Therapy to the most propable epilepsy type
Tonic-clonic seizures	

Carbamazepine

CBZ is the most commonly prescribed drug for epilepsy in Europe. It is the drug of choice in partial epilepsies with or without secondary generalization (Shorvon 2000). It is chemically related to tricyclic antidepressants (Ferrendelli 1987) and blocks the sodium channels in neural membranes (McLean & Macdonald 1986). CBZ has limited water solubility, and 75% of CBZ is bound to plasma proteins (Shorvon 2000). CBZ is an inducer of the hepatic P450 enzyme system (Perucca *et al.* 2004), and it also induces its own metabolism. Therefore, higher doses are needed to maintain the plasma concentration in long-term therapy (Liu & Delgado 1994). Due to the hepatic induction, CBZ also has effects on the metabolism of endogenous and exogenous hormones (Crawford *et al.* 1990).

CBZ has pharmacokinetic interactions with other drugs. It increases the metabolism of etosuximide (ESM), VPA, LTG and benzodiazepines which results in accelerated elimination of these drugs (Baciewicz 1986). CBZ has also been reported to decrease the bioavailability of ethinyloestradiol and levonorgestrel used in contraceptive treatment (Crawford *et al.* 1990). On the other hand,

erythromycin inhibits the metabolism of CBZ and may increase the levels of CBZ to toxic levels (Dam & Christiansen 1977, Wong *et al.* 1983).

Neurological adverse effects are fairly often associated with the use of CBZ. Nystagmus, drowsiness, headache and ataxia are often seen. Nausea and rash are also common side effects of CBZ (Pellock 1987). More severe adverse effects of CBZ include effects on cardiac function, e.g. atrioventricular conduction delay and bradyarythmias (Steiner *et al.* 1970, Hamilton 1978, Boesen *et al.* 1983) and aplastic anemia, toxic hepatitis and Stevens-Johnson syndrome (Fawcett 1987, Mattson *et al.* 1992, Brodie & Dichter 1996).

Oxcarbazepine

Oxcarbazepine (OXC) is a keto-analogue of CBZ, and its anticonvulsant efficacy is comparable to that of CBZ in partial seizures with or without secondary generalization (Houtkooper *et al.* 1987, Dam *et al.* 1989). However, OXC has a different metabolic pathway and pharmacokinetic profile from those of CBZ. It is metabolized mainly by reduction to its active metabolite, 10,11-dihydro-10hydroxy-carbamazepine, which is responsible for its antiepileptic efficacy (Bang & Goa 2003). The binding to plasma proteins is about 67% for OXC and 38% for 10,11-dihydro-10hydroxy-carbamazepine (Shorvon 2000). The anticonvulsive action of OXC is mediated by blockage of sodium channels. OXC is considered to be better tolerated than CBZ due to its better pharmacokinetic profile and less potential to induce the liver P450 enzyme system (Patsalos *et al.* 1990). Elimination of OXC is increased by drugs that induce hepatic enzymes, e.g CBZ, PHT and PB (Tartara *et al.* 1993). In women OXC has been shown to reduce the efficacy of oral contraceptives by decreasing the serum concentrations of ethinylestradiol and levonorgestrel (Klosterskov *et al.* 1992, Fattore *et al.* 1999).

Adverse effects of OXC are usually mild e.g dizziness, ataxia, headache, diarrhea, nausea and vomiting (Dam *et al.* 1989, Grant & Faulds 1992). Low serum sodium levels and hyponatremia may be associated with OXC treatment, they are reported to be more common in female patients and in elderly subjects (Grant & Faulds 1992).

Valproate

VPA was first used as a solvent for decades until its potential as an AED was discovered in 1963 (Meunier *et al.* 1963). VPA has a wide spectrum of antiepileptic efficacy and it is used in both LRE and IGE and also in childhood epilepsies. It is the drug of choice for generalized myoclonic epilepsy and absence seizures (Shorvon 2000). VPA is also used in the treatment of bipolar mood disorder (McElroy *et al.* 1989). Its exact antiepileptic mode of action is not known. However, it is assumed that it has multiple mechanisms of action to prevent seizures. VPA is known to affect the voltage-dependent sodium channels and neurotransmitters such as gamma-amino-butyric acid (GABA), and it may also have effect on glutamate transporters (McLean & Macdonald 1986, Van den Berg *et al.* 1993, Hassel *et al.* 2001). The protein binding of VPA is 90% in plasma and due to concentration dependent binding there is a curvilinear relationship between dose and plasma concentration (Gram *et al.* 1979).

VPA does not induce the hepatic P450 enzyme system, but it is an enzyme inhibitor and inhibits the oxidative metabolism of PHT and ESM (Levy & Koch 1982, Perucca *et al.* 2004). It is also known that CBZ and other AEDs with liver enzyme inducing properties can decrease serum VPA levels, while salicylates increase VPA blood levels (Levy & Koch 1982).

The adverse effects of VPA are well established. Gastro-intestinal effects such as nausea or diarrhea are common; also weight gain and neurological adverse effects such as tremor, fatigue and dizziness are often reported. These side effects appear early in the therapy and do not necessarily require dosage adjustments. Hepatotoxicity and hematologic changes, such as thrombocytopenia are more severe adverse effects of VPA. (Dreifuss *et al.* 1987, Dreifuss & Langer 1988, Davis *et al.* 1994)

Exposure to VPA during pregnancy predisposes to congenital malformations, and the risk is higher in women on polytherapy (Lindhout & Schmidt 1986, Holmes *et al.* 2001, Wyszynski *et al.* 2005, Artama *et al.* 2005, Morrow *et al.* 2006). Maternal VPA therapy is also associated with impaired cognitive development and reduced verbal intelligence of the children exposed to VPA in utero (Barrett & Richens 2003, Gaily *et al.* 2004).

Other antiepileptic drugs in the present study

PHT is one of the most frequently used AEDs in the world. It is considered effective, but it is currently a less frequently used AED because of its interaction potential and long-term side effects. It is an inducer of the hepatic p450 enzyme system. PHT is effective in the treatment of focal seizures with or without secondary generalization, and its anticonvulsant efficacy is based on blockage of the voltage dependent sodium channels. PHT has saturable kinetics which may lead to an unexpected increase in serum PHT concentration and related central nervous system side effects. Neurological side effects, gingival hypertrophy, nausea, depression, rash, blood dyscrasias and hepatotoxic effects are some of the side effects of PHT (Eadie 2004). PHT may reduce the amount of bioactive sex steroids by inducing the synthesis of sex hormone binding globulin (SHBG). (Perucca *et al.* 2004)

Lamotrigine (LTG) is a novel AED and is indicated for the treatment of partial and generalized epilepsies as adjunctive therapy or monotherapy, and also as adjunctive treatment in Lennox-Gastaut syndrome. It is a triazine compound which affects the sodium channels in addition to calcium channel blockage. 55% of LTG is bound to plasma proteins and it is metabolized in the liver and eliminated renally as a glucuronide. Liver enzyme inducing AEDs increase the metabolism of LTG and reduce its serum concentrations, whereas VPA inhibits the metabolism of LTG and increases its serum concentrations. Rash, nausea and dizziness are some of the most common side effects of LTG (Matsuo 2004). Stevens-Johnson syndrome and toxic epidermal necrolysis are rare but serious side effects of LTG (Schlienger *et al.* 1998). The prevalence of reproductive disorders have been decreased in PWE using LTG when compared to PWE using liver enzyme-inducing antiepileptic drugs or VPA (Morrell *et al.* 2003, Herzog *et al.* 2004).

2.2 Reproductive endocrine system

2.2.1 Hypothalamic-pituitary unit

The pulsatile secretion of hypothalamic hormones is controlled by neurotransmitters and by concentrations of hormones which are secreted in peripheral glands by feedback mechanism. The hypothalamus secretes regulatory hormones into portal vessels, where they are transported to the pituitary. The

secretion of each pituitary hormone is regulated by at least one of the hypothalamic hormones, and the hormones from peripheral endocrine glands also control the secretion of pituitary hormones by the feedback mechanism. Anterior pituitary secretes luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropin (ACTH), thyrotropin, growth hormone (GH) and prolactin, and posterior pituitary releases antidiuretic hormone and oxytocin, which are secreted in the supraoptic and paraventricular nuclei of hypothalamus and transported to the posterior pituitary. (Lechan 1987, Riskind & Martin 1995, Carr 1998) The regulation of the hypothalamic- pituitary-gonadal axis is presented in figure 1.

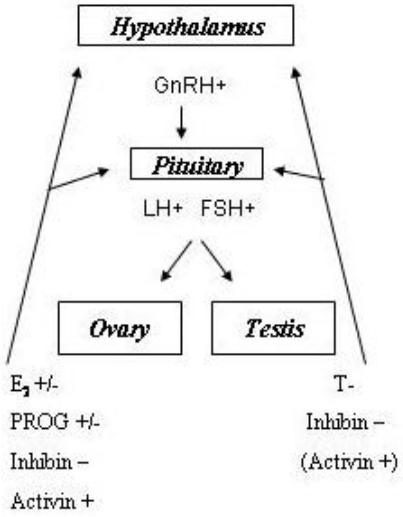

Fig. 1. The regulation of the hypothalamic-pituitary-gonadal axis. + stimulative effect; - inhibiting effect; GnRH, gonadotropin-releasing hormone; LH, luteinising hormone; FSH, follicle stimulating hormone; E_2, estradiol; PROG, progesterone; T, testosterone.

2.2.2 Regulation of testicular function

Testicular function is controlled by pituitary gonadotropins, LH and FSH, which are secreted in response to the gonadotropin releasing hormone (GnRH) secreted from the hypothalamus. LH controls testicular androgen production in Leydig cells (Dufau 1988), while FSH regulates spermatogenesis by acting via Sertoli cells. Furthermore, FSH also has an effect on the Leydig cells by stimulating the

maturation of Leydig cells and also increasing the amount of LH receptors. LH secretion is inhibited by testosterone (T), estradiol (E_2) and dihydrotestosterone through a negative feedback mechanism (Griffin & Wilson 1998). The regulation of FSH secretion is not well understood. However, it is indicated that the peptide hormones inhibin and activin secreted in Sertoli cells have a role in controlling FSH secretion (Crowley, Jr. *et al.* 1991).

Leydig cells are the main source of androgens, while Sertoli cells in seminiferous tubules have an important role in spermatogenesis. T, the most important androgen is produced from cholesterol through five enzymatic steps, in which the rate limiting step is the conversion of cholesterol to pregnenolone. The other androgens and their precursors produced in Leydig cells are androstenedione (A), dehydroepiandrosterone (DHEA), dihydrotestosterone, androsterone and 17-hydroxyprogesterone. The biosynthesis of androgens is presented in Fig 2 (Handelsman 1995). T is also synthesized in peripheral target tissues from weaker androgens. In the blood T is bound to albumin and SHBG (Dunn *et al.* 1981) and only 2 % of T is free and hence biologically active. Adrenal cortex also produces weaker androgens in the biosynthesis, which is stimulated by ACTH. (Huhtaniemi 1977, Waterman & Simpson 1985, Simpson & Waterman 1995)

Sexual maturation during male puberty is controlled by androgens, and in adulthood androgens regulate spermatogenesis, potency and libido. In consequence of the complexity and sensitivity of steroidogenesis and spermatogenesis many conditions, such as chronic diseases, drugs, abuse of alcohol, stress and obesity may disturb these functions. (Griffin & Wilson 1998, Jorgensen *et al.* 2001, Parent *et al.* 2003).

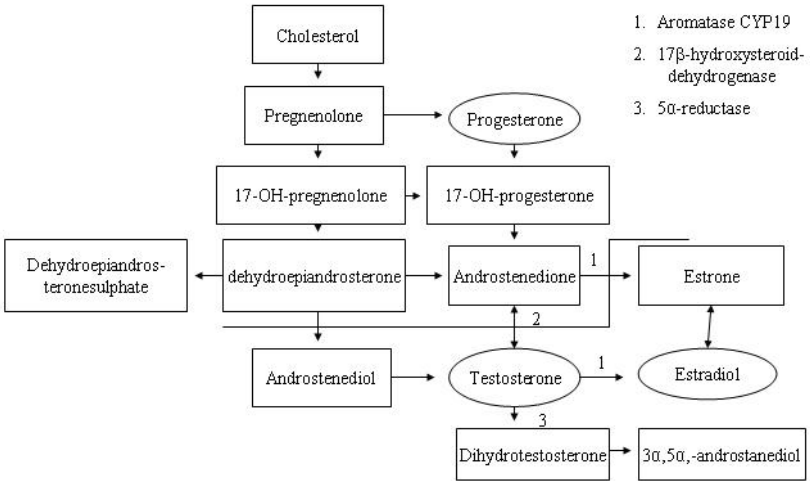

Fig. 2. The general steps of steroidogenesis (Handelsman 1995). The phases above the marked line describe the adrenal steroidogenesis. Testosterone is the major hormone secreted in testis and estradiol and progesterone are major hormones secreted in the ovaries.

2.2.3 Regulation of secretion of reproductive hormones in women

Pituitary FSH and LH regulate the ovarian function. The secretion of gonadotropins varies during the life span of women, i.e. the lowest levels are found in childhood and a circadian pattern of secretion is observed from prepuberty to the beginning of menopause. Gonadotropins regulate the follicle, which is the functional unit of the ovary. LH stimulates the androgen synthesis in the follicular theca cells, while FSH stimulates the maturation of the follicle and the conversion of androgens to estrogens in the granulosa cells. E_2, progesterone (PROG), inhibin and follistatin secreted by follicle have a feedback effect on the release of gonadotropins. (Carr 1998) The ovarian biosynthesis of steroids is also regulated by insulin and insulin-like growth factors (Cataldo 1997).

The menstrual cycle consists of follicular, ovulatory and luteal phases. The median length of the cycle in healthy fertile women is 28 days with a range from 25 to 30 days. During the follicular phase FSH stimulates the maturation of the follicle and the secretion of estrogens and LH regulates the secretion of the androgens. (Goodman & Hodgen 1983, Liu & Hsueh 1986) In the ovulatory phase the increase of serum E_2 levels at the hypothalamic-pituitary level triggers

the ovulatory LH peak through a positive feedback resulting in ovulation. In the luteal phase the endocrine cells of the follicle are transformed into corpus luteum which secretes progesterones and E_2. Progesterones and estrogens prepare the endometrium for the implantation of the fertilized egg. If implantation does not occur, the corpus luteum regresses and PROG secretion drops dramatically causing menstrual bleeding. (Sherman & Korenman 1975, Pauerstein *et al.* 1978, Carr 1998)

E_2 is the most abundant estrogen in women. It is secreted in the ovary from A and T, and it stimulates the development of the uterus and characteristics for feminine appearance. E_2 has a feedback effect on the hypothalamic pituitary unit and it is mainly bound to SHBG. (Carr 1998) A and T are needed as precursors for production of estrone and E_2. They are produced in the ovary and adrenal cortex. DHEA and dehydroepiandrosterone sulphate (DHEAS) are weak androgens and are mainly produced and secreted by the adrenal cortex being indicators of adrenal androgenesis. They are used as precursors when other steroids are synthesized. The synthesis of adrenal androgens is regulated by ACTH. Insulin-like growth factor I (IGF-I) and angiotensin may also contribute to the regulation of adrenal androgen synthesis. (Parker & Odell 1980, Parker *et al.* 1983, Nestler *et al.* 1989, Pham-Huu-Trung *et al.* 1991)

Although T is an important regulator of gonadotropin release in men, in women the serum levels of T are approximately one-tenth of those in men, and hyperandrogenemia does not inhibit the secretion of gonadotropins in women as effectively. Instead, estrogens and PROG regulate the release of gonadotropins. (Marshall & Kelch 1986, Marshall 1995) However, if the serum T concentration in women exceeds the normal male level, the frequency of LH pulses decreases (Conway & Jacobs 1993).

2.2.4 Sex hormone-binding globulin

In the circulation the most important bioactive sex steroids T and E_2 are mainly bound to the plasma proteins SHBG and albumin. SHBG is a glycoprotein synthesized in the liver and has a high affinity and specificity to 17β-hydroxy steroids. It binds dihydrotestosterone and T with high affinity and E_2 less effectively. About 1-2% of T and E_2 is in the biologically active unbound form. In men about 60% of T is bound to SHBG and 40% to albumin, in women the distribution of bound form of T to SHBG/albumin is about 70%/30%. The serum SHBG concentration has an important effect on the bioavailability and peripheral

conversion of T, dihydrotestosterone and E_2. (Hammond *et al.* 1980, 1982, Siiteri *et al.* 1982, Rosner *et al.* 1991, Petra 1991)

Pregnancy, hyperthyroidism, and estrogens increase, and corticosteroids, androgens, progestins, GH, insulin and IGF-I decrease serum SHBG concentration (Preziosi *et al.* 1993). *In vitro* studies have shown that androgens increase the SHBG synthesis in the hepatoma cell line (Lee *et al.* 1987). However, nutritional factors are even more important factors in the regulation of the SHBG production; weight is inversely related to the circulating SHBG level. The assumed mechanism is the effect of insulin and IGF-I, which suppresses the production of SHBG in the liver (Plymate *et al.* 1988, 1990). Some medications may also affect SHBG levels, e.g. the use of hormonal contraceptives is associated with increased levels of SHBG (Siegberg *et al.* 1987).

Altered serum SHBG concentrations have a clinical importance. Women with decreased levels of SHBG may have symptoms of hyperandrogenism (HA), which may be associated with polycystic ovary syndrome (PCOS). A low level of serum SHBG is also a marker for the development of type 2 diabetes (Lindstedt *et al.* 1991) and it can be used as a predictor of insulin resistance in women with PCOS (Cibula *et al.* 2002). Furthermore, decreased serum SHBG is also associated with coronary heart disease in women (Reinecke *et al.* 2002). Respectively, in men with epilepsy (MWE) a high concentration of serum SHBG may be associated with reduced bioactivity of serum androgens, which may manifest as diminished sexual function (Isojärvi *et al.* 1995d).

2.2.5 Polycystic ovary syndrome

PCOS was first described by Stein and Leventhal (Stein & Leventhal 1935) and it is the most common endocrine disorder in women of fertile age. PCOS has an unknown etiology and it is assumed that there are several different pathways that may lead to the development of the syndrome. The prevalence of PCOS in the female population of reproductive age has been reported to be 4-10%. (Knochenhauer *et al.* 1998, Hopkinson *et al.* 1998, Guzick 2004) However, the criteria for diagnosis have not been congruent in different studies. The diagnostic criteria for PCOS have been widely debated during the last decades and the consensus of the new diagnostic criteria was reached in 2003. The criteria for PCOS are (two out of three are needed for diagnosis) 1) oligo- and /or anovulation, 2) clinical (hirsutism, acne, androgenic alopecia) and/or biochemical signs of HA, 3) polycystic ovaries (PCO). PCO are diagnosed when 10 or more

follicles of 2-8mm in diameter and increased and/or hyperechogenic ovarian stroma in ultrasonography or MRI are observed. (Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome 2004) PCO without the other features of PCOS is present in 10-23% of women who are not suffering from menstrual disorders or symptoms of HA (Polson *et al.* 1988, Clayton *et al.* 1992, Farquhar *et al.* 1994, Botsis *et al.* 1995, Borgfeldt & Andolf 1999, Koivunen *et al.* 1999, Michelmore *et al.* 1999). Their prevalence is increased in younger women (Bridges *et al.* 1993, Michelmore *et al.* 1999, Koivunen *et al.* 1999). PCO is not necessarily associated with HA or other signs of PCOS (Polson *et al.* 1988). However, 92% of women with idiopathic hirsutism and 87% of women with oligomenorrhea have PCO discovered in ultrasonography (Adams *et al.* 1986).

The biochemical features of PCOS include increased serum levels of T, A, LH and insulin, and increased LH/FSH ratio (Waldstreicher *et al.* 1988). The serum concentration of SHBG and insulin-like growth factor binding protein 1 (IGFBP-1) are often decreased related to hyperinsulinemia in women with PCOS. The decreased levels of SHBG increase the bioavailability of T, and the androgen production in the ovaries increases due to the increased bioavailability of IGF-I. Anovulatory cycles interfere with the release of FSH, estrogen and progestin and there is no normal cyclic secretion of these hormones in women with PCOS-related anovulation. (Franks 1995) Moreover, the other metabolic alterations that are often associated with PCOS, e.g. obesity, hyperinsulinemia, insulin resistance and dyslipidemia, may all predispose women with PCOS to cardiovascular diseases (Hopkinson *et al.* 1998, Guzick 2004).

2.3 Epilepsy and reproductive function

Reproductive endocrine dysfunction is more common among PWE than in the healthy population (Herzog *et al.* 1986a, 1986b, Bilo *et al.* 1988, Isojärvi *et al.* 1993). Moreover, fertility is decreased in both men and women with epilepsy (Dansky *et al.* 1980, Webber *et al.* 1986, Schupf & Ottman 1994, 1996, Artama *et al.* 2004) which may be a consequence of epilepsy itself or the use of antiepileptic medication which may alter reproductive functions. Social factors may also contribute to reduced fertility in PWE.

2.3.1 Effects of hormones on epilepsy

Hormones can affect seizure activity (Klein & Livingston 1950, Woodbury 1958). In catamenial epilepsy the frequency of seizures depends on the phase of the menstrual cycle as a consequence of altered levels of female sex steroids. It has been shown that estrogen is a proconvulsant, whereas PROG has anticonvulsant properties (Logothetis *et al.* 1959, Bäckström 1976, Bäckström *et al.* 1984). Therefore, in catamenial epilepsy the seizures usually occur in the end of the luteal phase when the levels of PROG rapidly decline. Consistent with this antiestrogenic clomiphene therapy and intermittent PROG therapy have decreased seizure frequency in women with catamenial epilepsy (Herzog 1986, Schachter 1988). Thyroid hormones also have effects on seizure activity. Thyreotoxicocis may predispose to seizures, and status epilepticus may be induced by thyroxine. (Jabbari & Huott 1980, Sundaram *et al.* 1985)

2.3.2 Effects of epilepsy on hormones

The first reports on the association between epilepsy and reproductive function were published in the 1950s suggesting that epilepsy is associated with hyposexuality (Gastaut & Colomb 1954). Thereafter several other reproductive disorders have been associated with epilepsy: irregular menstrual cycles, anovulation, hirsutism in women and decreased potency in men (Isojärvi *et al.* 1993, Isojärvi *et al.* 1995b, 1995d, 1996). Abnormal reproductive function is also more prevalent in untreated PWE than among the general population (Herzog *et al.* 2003). Furthermore, the serum concentrations of several hormones may be altered in PWE, and increased secretion of pituitary hormones has been shown to be associated with seizures (Wyllie *et al.* 1984, Dana-Haeri & Trimble 1984, Sperling *et al.* 1986).

The secretion of gonadal hormones can be affected by increased electrical activity associated with epilepsy. Electrical changes, which occur during the seizures and also during the interictal period, may interfere with the release of pituitary hormones and hence cause reproductive dysfunction (Dana-Haeri & Trimble 1984, Herzog *et al.* 1986a, 1986b). It has been shown that electrical discharges during both generalized and partial complex seizures increase the secretion of pituitary hormones (Dana-Haeri & Trimble 1984). Furthermore, recurrent interictal paroxysmal discharges have also been suggested to interfere with the release of gonadotropins, which may be associated with dysfunction in

the regulation of reproductive function (Herzog *et al.* 1986a, 1986b). An association between the laterality of tempolar lobe epilepsy and occurrence of certain reproductive endocrine disturbances has also been suggested. In Herzog's groups study left lateral discharges were followed by disturbances in LH secretion which affected the serum levels of T and DHEAS and the LH/FSH ratio and was associated with high prevalence of PCOS. On the other hand, right lateral discharges were associated with increased secretion of prolactin associated with hypogonatrophic hypogonadism and disturbed sexual function. (Herzog *et al.* 2003)

2.3.3 Antiepileptic drugs and reproductive function

AEDs affect reproductive endocrine function in both men and women. Changes in reproductive hormone levels, decreased potency, and diminished sexual interest in men and menstrual disorders, PCOS and decreased fertility in women can be manifestations of the reproductive endocrine effects of AEDs. These disorders are frequently seen in association with certain AEDs. However, there is only limited information available on the effects of novel AEDs, e.g. OXC on reproductive endocrine function.

Carbamazepine and other liver enzyme inducing antiepileptic drugs

CBZ and PHT induce the hepatic P450 enzyme system which results in an increased production of hepatic proteins such as SHBG and IGFBP-I (Perucca *et al.* 2004). In men taking CBZ a progressive increase in serum SHBG levels and decrease in FAI ratio results in reduction of bioactive androgens and it has been suggested that these changes may lead to diminished sexual activity (Isojärvi *et al.* 1995d). Also low levels of DHEAS as well as disturbances in sperm motility and morphology have been reported in men taking CBZ (Chen *et al.* 1992, Isojärvi *et al.* 1995d, Rättyä *et al.* 2001a, 2001b). Similarly, increases in serum levels of SHBG and decreases of bioactive androgen levels have been observed in patients taking PHT for epilepsy. PHT increases the serum concentrations of E_2, which has been associated with sexual dysfunction in MWE (Herzog *et al.* 1991).

The effects of CBZ on reproductive function in WWE have been elucidated in several studies. These studies have consistently reported increased levels of SHBG and decreased levels of bioactive E_2 and T in women taking CBZ for epilepsy. (Isojärvi 1990, 1993, 1996, Murialdo *et al.* 1997, 1998, Rättyä *et al.*

2001) CBZ therapy has also been associated with low serum DHEAS levels (Isojärvi 1990, Murialdo *et al.* 1998). However, in previous studies the prevalence of menstrual disorders, PCO or PCOS in subjects on CBZ monotherapy has not been different from that of control subjects (Isojärvi *et al.* 1993, 2001, Murialdo *et al.* 1997, 1998, Bauer *et al.* 2000).

PHT is associated with increased levels of SHBG, and decreased levels of DHEAS in WWE (Dana-Haeri *et al.* 1982, Beastall *et al.* 1985). Both PHT and CBZ reduce the efficacy of oral contraceptives by decreasing the bioavailability of ethinylestradiol and levonorgestrel (Crawford *et al.* 1990).

Oxcarbazepine

Only few studies have been published on the effects of OXC on reproductive functions. OXC is considered a weaker inducer of the liver enzyme system than CBZ (Patsalos *et al.* 1990) and its possible endocrine effects may be dose-related (Rättyä *et al.* 2001b).

A six-month follow-up study in men showed that after replacing CBZ with OXC the CBZ-induced alterations in the serum concentrations of reproductive endocrine hormones normalized during the 6 month follow-up (Isojärvi *et al.* 1995). However, in another study in MWE, high doses of OXC monotherapy were associated with increased serum levels of T, gonadotropins and SHBG (Rättyä *et al.* 2001b). The effects of OXC on reproductive function in WWE have not been studied previously. However, it is known that OXC decreases the bioavailability of ethinylestradiol and levonorgestrel of oral contraceptives and therefore reduces their efficacy (Klosterskov *et al.* 1992, Fattore *et al.* 1999). Furthermore, exposure to OXC has been found to be associated with difficulties in achieving pregnancy in monkeys (Lockard *et al.* 2000).

Valproate

The effects of VPA on reproductive endocrine function have been widely studied and it is well known that the use of VPA is associated with reproductive disorders especially in women (Isojärvi *et al.* 1993, 1996, 2001, Murialdo *et al.* 1998, Isojärvi & Tapanainen 2000, Rättyä *et al.* 2001, Morrell *et al.* 2003). However, also MWE may have reproductive abnormalities related to VPA (Chen *et al.* 1992).

Unlike other older AEDs VPA is not an inducer of the hepatic P450 enzyme system and in the earlier studies it was assumed not to have effects on reproductive endocrine function in men (Macphee *et al.* 1988, Isojärvi *et al.* 1990). Serum concentrations of LH, T, SHBG, and DHEAS have been reported to be normal (Geisler *et al.* 1997), while the concentrations of gonadotropins have been found to be low (Isojärvi *et al.* 1990, Rättyä *et al.* 2001b) and FAI ratio high in men on VPA therapy (Isojärvi *et al.* 1990). Even though VPA has only a minor effect on the serum concentrations of reproductive hormones in men, case reports have associated it with infertility in MWE (Curtis *et al.* 1992, Yerby & McCoy 1999). VPA is also associated with changes in sperm quality in men (Chen *et al.* 1992, Sveberg *et al.* 2001). Furthermore, in rats and dogs VPA has been shown to be associated with testicular atrophy and reduced spermatogenesis (Walker *et al.* 1990, Sveberg Roste *et al.* 2001).

In WWE VPA is often associated with HA, menstrual disorders, PCO (Isojärvi *et al.* 1993, 2001, Vainionpää *et al.* 1999, Morrell *et al.* 2002, 2003, Mikkonen *et al.* 2004), weight gain and hyperinsulinemia (Isojärvi *et al.* 1996, 2001, Morrell *et al.* 2003). It has been suggested that obesity, hyperinsulinemia and low serum IGFBP-1 concentrations contribute to the development of HA associated with the use of VPA (Isojärvi *et al.* 1996). However, HA and PCO are also found in lean women taking VPA for epilepsy. In the follow-up study these types of changes were reversible after discontinuation of VPA therapy (Isojärvi *et al.* 1998). Young age can increase the risk for these disorders. PCO and HA were especially common if VPA medication was started before 20 years of age. In young girls treated with VPA changes in androgen levels are already found before puberty. Increased levels of androgens were detected in all phases of puberty and they were associated with menstrual disorders. (Vainionpää *et al.* 1999) Furthermore, after 5 year follow-up 60% of those girls whose VPA medication was continued had PCOS compared to 5.5% of those whose VPA medication had been discontinued or 8.3% of control subjects (Mikkonen *et al.* 2004b).

The role of VPA as a contributor to the development of reproductive disorders in WWE has also been confirmed in studies evaluating the predictors of ovulatory failure and prevalence of PCOS (Morrell *et al.* 2002a, Betts *et al.* 2003). Interestingly, prolonged menstrual cycles and PCOS are also common in women with bipolar mood disorder on VPA monotherapy (O'Donovan *et al.* 2002). The pathogenesis of the VPA-related reproductive endocrine changes is still unknown. LH is a major inducer of androgen synthesis in the ovary, but its serum concentration is increased in only some patients with VPA related PCO. IGF-I is

known to potentiate the number of the LH-receptors in the ovary, causing stimulation of LH-induced androgen synthesis in the ovary (Adashi *et al.* 1985, Barbieri *et al.* 1986). IGFBP-1 levels are decreased in VPA exposure and in hyperinsulinemia and the amount of bioactive IGF-I increases inducing the ovarian steroid synthesis. Moreover, the bioavailability of androgens increases due to decreased serum levels of SHBG (Isojärvi *et al.* 1993, 1996, 1998). It has also been suggested that VPA has a direct effect on ovarian theca cells inducing the androgen biosynthesis; furthermore, in porcine ovarian follicular cells VPA exposure has inhibited T conversion to estrogen (Tauboll *et al.* 2003, Nelson-DeGrave *et al.* 2004).

3 Purpose of the present study

The aim of the study was to evaluate the effects of epilepsy and antiepileptic medication on reproductive function in PWE. The main objectives of the present study were:

1. To evaluate the prevalence of reproductive endocrine disorders and the associated risk factors in WWE, and the role of AEDs and epilepsy type in the development of these disorders.
2. To evaluate the effects of OXC and CBZ on reproductive endocrine function in WWE.
3. To assess the effects of epilepsy and AEDs on reproductive health in MWE.
4. To compare the reproductive health of PWE and the general population in a population based setting.

4 Subjects and methods

The study was conducted in the Departments of Neurology, Gynecology and Obsterics and Public Health Science and General Practice in University of Oulu. The Departments of Clinical Chemistry and Radiology also participated in the study.

The principles of Declaration of Helsinki were followed when conducting the study. The study was approved by the Ethics Committee of the Medical Faculty of University of Oulu. All subjects gave written informed consent before participating in the study.

4.1 Study design

The reproductive endocrine function in subjects with epilepsy was investigated using cross-sectional and retrospective study designs.

Studies I-III were cross-sectional studies. Study I was a post hoc reanalysis of the data from all studies on reproductive endocrine function in women with epilepsy that were conducted in Oulu University Hospital during the years 1990-1999. New data for studies II-III was collected in 1998-2000.

Studies I-II were to assess the regularity of menstrual cycles with interviews or questionnaire, ovarian structure with ultrasonography and serum levels of reproductive hormones using commercially available assays. Study III was to evaluate semen quality, testicular ultrasonography and serum levels of reproductive hormones in male subjects.

Study IV was a retrospective study to evaluate the prevalence of epilepsy, and effects of epilepsy and antiepileptic medication on reproductive function in a population-based study desing. Data consisted of information obtained from hospital records (patient files), hospital discharge registers, register for reimbursent of antiepileptic medication from SII of Finland, and information on family relations and possible labours were obtained from The Finnish Population Register Center and from The Finnish Birth Register .

4.2 Subjects

4.2.1 Studies I-III

All subjects with epilepsy were studied during the years 1990-2001 in the Outpatient Department of Neurology in Oulu University Hospital, which is the primary referral centre for all adult PWE in the region. Studies I-III consisted of 249 subjects with epilepsy and 247 control subjects. The clinical characteristics of the patients and the control subjects in studies I-III are given in Table 3.

Study I included all 18 to 40- year old WWE who participated in studies on reproductive endocrine function in the Oulu University Hospital during the years 1990-1999. One hundred and thirty women were taking a single drug for epilepsy (67 CBZ, 2 PHT, 48 VPA, 13 OXC) and 18 women were on polytherapy. One hundred and seventy healthy women served as control subjects, they were collected from previous studies and had not been treated for menstrual disturbances, infertility or hirsutism (Koivunen *et al.* 1999, Koivunen *et al.* 2001). In study II the study cohort consisted of 35 18- to 40-year old women WWE on CBZ or OXC monotherapy. Sixteen women were treated with CBZ and 19 women were treated with OXC. 36 healthy women participated in the study as control subjects recruited from the hospital staff. 65 17-45 year old male subjects taking a single AED fo epilepsy participated in study III; 18 were treated with CBZ, 18 with OXC and 29 with VPA. Forty-one healthy men participated in the study as control subjects. They were recruited from the students of the Oulu University and among men seen in Infertility Clinic of the Family Federation of Finland, in couples in which the woman was found to have the cause for infertility.

The main exclusion criteria were regular use of other medication than AEDs, alcohol or drug abuse and symptoms or signs of illnesses other than epilepsy. In addition, in women the use of oral contraceptives during the previous three months or pregnancy or lactation were exclusion criteria.

All subjects were studied once. In study I only the data from the first study that the subject participated in were included in the analysis. The antiepileptic medication had remained unchanged for at least six months before participation in studies I-III.

Table 3. Clinical characteristics of participants in studies I-III.

Study	No. of subjects		AED/ controls	Age		Type of epilepsy			Duration of epilepsy		Duration of the current therapy	
	F	M		Yr (mean)	SD or range	IGE	LRE	Non defined	Yr (mean)	SD or Range	Yr (mean)	SD or range
I	67		CBZ	31.7	5.5	15	51	1	14.1	8.3	9.2	5.9
	2		PHT	27.0	9.9	1	1	0	7.0	2.8	3.0	1.4
	48		VPA	27.0	6.4	36	12	0	12.7	7.1	8.0	5.9
	4		CBZ+PHT	34.0	7.1	1	3	0	25.3	6.4	14.5	8.6
	7		CBZ+VPA	31.7	5.5	3	4	0	14.6	5.9	11.1	6.3
	6		CBZ+CZP	34.5	6.7	0	6	0	26.0	5.3	17.4	8.0
											9.8	4.9
	1		CBZ+PHT	40			1		16.4		16.0	
			+CZP								16.0	
	13		OXC	29.3	7.9	1	12	0	9.3	7.9	2.6	1.3
	170		Controls	33.3								
II	16		CBZ	32	20-39	4	12	0	18.1	3-32	10.5	0.5-29
	19		OXC	29	18-40	1	18	0	13.8	2-26	3.3	1-6
	36		Controls	30	19-40							
III		18	CBZ	27.8	5.5	3	15	0	13.3	8.3	9.5	5.8
		18	OXC	26.2	7.0	0	18	0	8.8	7.4	3.8	2.8
		29	VPA	24.8	6.3	27	2	0	8.1	7.1	4.7	3.2
		41	Controls	26.2	5.7							

IGE, idiopathic generalized epilepsy; LRE, localization-related epilepsy; CBZ,carbamazepine; CZP,clonazepam; OXC,oxcarbazepine; PHT,phenytoin;VPA,valproate

4.2.2 Study IV

Data collected for study IV was based on Northern Finland Birth Cohort (NFBC) 1966, which is an unselected general population sample consisting of 12,058 live births, covering 96.3% of all deliveries in the two northernmost provinces of Finland (Oulu and Lapland) in 1966 (Rantakallio 1969).

Subjects with history of seizures were identified from the NFBC 1966 by using information obtained from several sources. The information from The National Finnish Hospital discharge register was used, in addition the subjects who had received reimbursement for antiepileptic medication from SII of Finland were identified. Data of childhood epilepsies in NFBC had been collected previously (von Wendt *et al.* 1985a, 1985b) and was re-evaluated and analyzed for this study. Also the information from postal inquiry performed at age of 31 years was used. The patient files (hospital records) of subjects with history of

seizures or diagnosed epilepsy were reviewed to identify subjects that met the international diagnostic criteria for epilepsy.

The epilepsy cohort in NFBC included 222 subjects with diagnosed epilepsy; and 24 subjects were predisposed to epilepsy, i.e. they had had at least one seizure, but the diagnostic criteria for epilepsy were not met. The patient files were available for 132 (59.4%) subjects with epilepsy. 11257 subjects from the NFBC without history of epilepsy or seizures served as control subjects. The material is described in table 4 and figure 3.

Table 4. Characteristics of the Northern Finland Birth Cohort 1966(NFBC 1966). Study IV.

Mothers/Pregnancies n=12055	Male	Female	All
Live born	6169	5889	12058
Alive and concented till 2002	5812	5670	11482
Controls[1]	5702	5555	11257
Epilepsy in NFBC 1966			
Epilepsy in patient files[2]	63	69	132
Predisposed to epilepsy	124 (2.0%)	122 (2.1%)	246 (2.1%)
Epilepsy[3] (cumulative prevalence)	111(1.8%)	111 (1.9%)	222 (1.9%)
Answered to 31-year questionnaire (of subjects with epilepsy)	63 (56.8%)	74 (66.7%)	137 (61.7%)
Subjects with epilepsy, alive and consented 2002	98	104	202

[1] Alive and consented in 2002, no predisposition to epilepsy.

[2] Patient files were reviewed for 159 subjects with predisposition to epilepsy, the files were complete for 132 subjects with epilepsy.

[3] Subject was considered to have epilepsy if reimbursement for antiepileptic medication was approved by Social Insurance Institution of Finland or there had been two unprovoked and unferbrile seizure or one unprovoked seizure and epilepsy-related findings in the EEG.

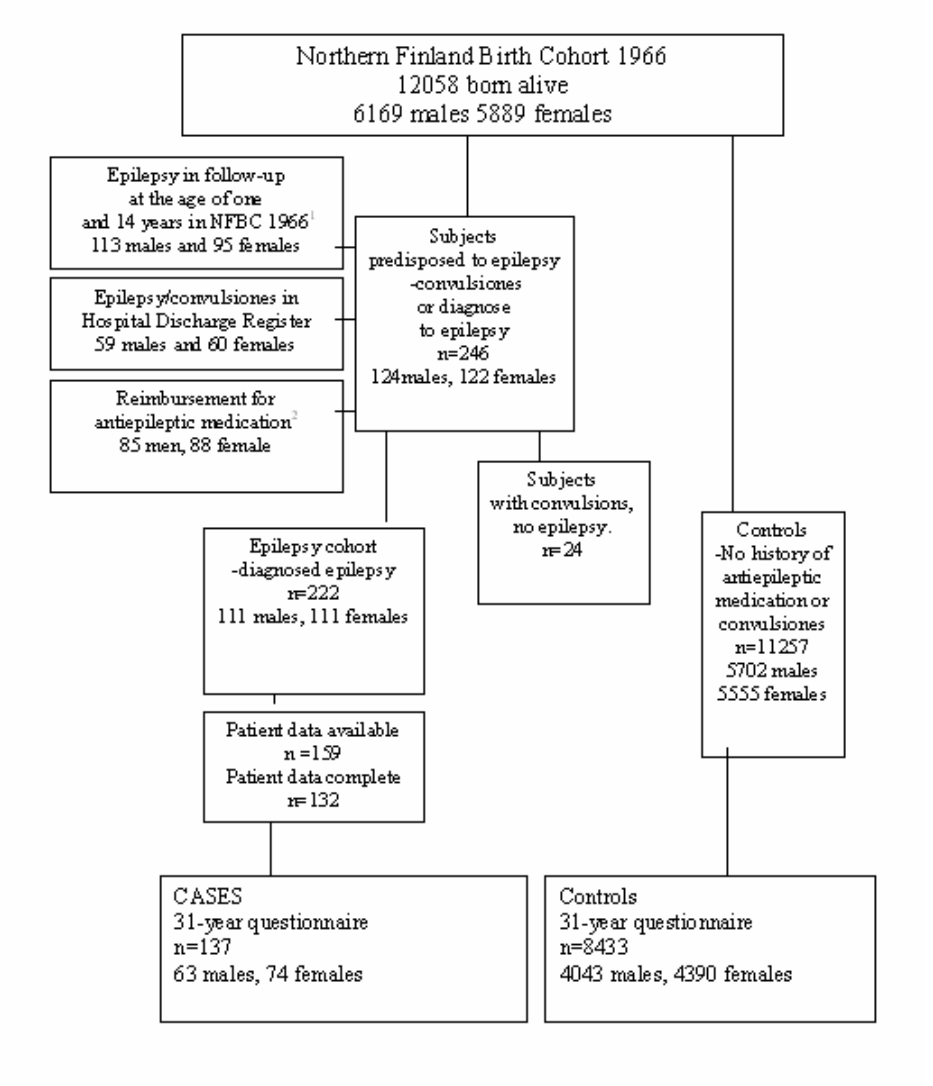

Fig. 3. Flowchart of the cohort study Epilepsy and Fertility in Northern Finland Birth Cohort 1966. [1]von Wendt 1985 a,b [2]The Register of the Social Insurance Institution of Finland.

4.3 Methods

4.3.1 Studies I–III

General medical examination and neurological examination were performed on all patients. The medical history of each subject was obtained by interview from the patients and the male control subjects, and by questionnaire from the female control subjects. The patient files from hospital records were also reviewed.

Epilepsy type was classified according to both the clinical characteristics of the seizures and the EEG findings as localization-related, or generalized or nondefined by following the ILAE recommendations (Commission on Classification and Terminology of the International League Against Epilepsy 1989).

The menstrual history was obtained by interview or using a questionnaire (control subjects). Menstrual cycle was defined as irregular if the following disturbances had been present at least once in 6 months: oligomenstruation (cycle length longer than 35 days), irregular menstrual cycles (the length varying more than 5 days from cycle to cycle) or intermenstrual interval more than 35 days or less than 21 days). Amenorrhea was defined if there had been no menstrual bleeding during the last six months. Transvaginal ultrasonography was performed in the early follicular phase by using a Toshiba SSA-270A or Toshiba SSA-370A ultrasound device. The examination included calculation of the number of follicles (diameter 2-8mm) and the measurement of the size of the ovaries. The ultrasonographic criteria used for the diagnosis of PCO were those described by Adams (Adams *et al.* 1986).

The diagnosis of PCOS was made when two of the three following criteria were present: PCO in ultrasonography, elevated serum T levels (T above mean + 2 SD of the T levels in the control subjects) or irregular menstrual cycles. (Revised 2003 consensus on diagnostic criteria and long term health risks related to polycystic ovary syndrome 2004)

Genital examination was performed in male subjects. It included evaluation of testicular volume with an orchidometer and identification of dilation or distension of epididymis and detection of varicoceles. A sperm sample was collected from all subjects willing to give the sample. Morphological analysis was performed to detect possible changes in the area of the sperm head, midpiece or tail, and the spermatozoa concentration and the motility of the sperm were also analyzed. The procedures and interpretations that were used in analyzing the

semen samples were in accordance with World Health Organization criteria. Testicular ultrasound was performed in male subjects using a Toshiba PowerVision 7000 or 8000 ultrasound system including the measurement of testicular volume.

Blood samples were drawn from all participants after an overnight fast and in female subjects with menstrual cycles during the early follicular phase of the menstrual cycle (cycle days 1-6).

Remission was defined as a seizure freedom after a planned discontinuation of antiepileptic drugs.

Assays

Description of the different assays used in each of the studies I-III are shown in table 6. FAI was calculated from the formula: FAI=100 x serum T (nmol/L)/serum SHBG (nmol/L). The subjects were defined as hyperandrogenic if their serum T level exceeded the mean serum T concentration + 2 SD in the control subjects. Increased serum A and DHEAS levels were defined as serum concentrations exceeding the mean serum concentrations + 2 SD of the control subjects.

Table 5. Characteristics of the assays used in studies I-III.

Assay	Study	Method, Manufacturer	Typical sensitivity values[1]	Typical coefficient of intra-assay variation (%) in the reference interval	Typical coefficient of interassay variation (%) in the reference interval
T	I	RIA, Orion Diagnostica	0.5 nmol/l	7.0	9.7
	I	Chemiluminescence method, ACS-analyzer, Ciba Corning Diagnostics	0.4 nmol/l	6.7	8.6
	II[2]	Immunological chemiluminescence method, Bayer ADVIA centaur analyzer	0.6 nmol/l	5.7	
	III	Automated chemiluminescence method, Chiron Diagnostics	0.1 ngr/ml	6.7	8.6
PROG	II[2]	Immunological chemiluminescence method, Bayer ADVIA centaur analyzer	0.48nmol/l	4.6	
DHEAS	II[2]	RIA, Diagnostic products Co	0.05 µmol/l	4.5	
	III		22 ng/ml	4.5	5.5
A	II[2]	RIA, Diagnostic products Co	0.07 nmol/l	5.0	
	III		0.04 ng/l	4.1	5.3
SHBG	II[2]	Fluoroimmunometric method, Wallac Ltd, 1235 AutoDelfia	0.05 mol/l	4.4	
	III		0.1 µmol/ml	6,7	8.0
E_2	II[2]	RIA, Orion Diagnostica	0.05 nmol/l	4.5	
Prolactin	III	Automated chemiluminescence method, Chiron Diagnostics	6.4 mIU/l	2.8	4.0
FSH	III	Fluoroimmunometric method, Wallac Ltd, 1235 AutoDelfia	0.03 IU/l	1.4	2.6
LH	III	Fluoroimmunometric method, Wallac Ltd, 1235 AutoDelfia	0.03 IU/l	2.3	4.2
Inhibin-B	III	ELISA, Serotec,UK	<15 ng/l	<7	<7
VPA	I-III	Fluorescence polarization immunoassay, AxSym Analyzer, Abbot	0.58mg/l	1.8	2.7
CBZ	I-III	Fluorescence polarization immunoassay, AxSym Analyzer, Abbot	0.2 mg/l	1.2	3.2
OXC	I-III	High-pressure of liquid chromatography	0.2mg/l	<5	<5

[1]Sensitivity= the result differs in 95%propability from zero value. [2]In study III all samples for each test subject were analyzed in the same assay for each analyte. T=testosterone, RIA=radioimmunoassay, PROG=progesterone, DHEAS=dehydroepiandrosterone sulphate, A=androstenedione, SHBG= sex hormone binding globulin, E_2=estradiol, FSH=follicle-stimulating hormone, LH=luteinizing hormone.

4.3.2 Study IV

The information of epilepsy type, the medication used for epilepsy, and duration of epilepsy was based on patient files. However, in some subjects epilepsy was unclassifiable due to incomplete information. The number of children of men were collected from The Finnish Population Register Center. The data of labours and spontaneous and induced abortions in women were obtained from The Finnish Birth Register. Information on marital and socioenonomic status were obtained from the 31-year questionnaire data.

4.3.3 Statistical analysis

The data were analysed with the Statistical Package for the Social Sciences program. In all studies the chi-square test was used to compare frequencies, and the Fisher´s exact test was used when needed. In study I the binary logistic regression analysis was used to detect the predictors of reproductive disorders. HA, PCO and PCOS were dependent variables, and age (as a continuous variable), type of epilepsy, use of VPA-therapy, frequency of seizures and BMI (BMI≤25, 25<BMI≤30, BMI>30) were used as independent variables. For comparing continuous variables between groups a one-way analysis of variance (ANOVA) and Tukey´s post hoc test were used in studies III and IV. In study III nonparametric tests Kruskal-Wallis and Mann-Whitney were used for statistical comparison between groups with skewed distribution of values and in study II the skewed distribution of the values was corrected by using logarithms.

5 Results

5.1 Epilepsy and reproductive health (Study I)

5.1.1 Type of epilepsy and reproductive function

The reproductive endocrine characteristics of women participating in study I are given in Table 6. The prevalence of menstrual disorders was similar in WWE and control women. However, the prevalence of menstrual disorders tended to increase in women with IGE when compared to women with LRE (p=0.063) or to control women (p=0.045). PCO were more frequently found in WWE than in control women (p=0.005). Women with IGE had PCO more often than women with LRE (p=0.027) or the control women (p<0.001). Increased serum T concentrations were more often found in WWE than the control women (p<0.001). Moreover, women with IGE had more often increased T concentrations than women with LRE (p=0.004) or control women (p=0.002). Elevated serum T concentrations were also more common in women with LRE than in control women (p=0.007). The prevalence of PCOS was higher in WWE than in control women (p<0.001). PCOS was also more prevalent in women with IGE than women with LRE (p=0.001) or control women (p=0.0066).

Table 6. Prevalence (%) of menstrual disorders, polycystic ovaries (PCO), hyperandrogenism (HA) and polycystic ovary syndrome (PCOS) in women with epilepsy (WWE) by epilepsy type and medication in Study I.

	WWE				WWE on VPA			WWE on non-VPA therapy				Controls
	All	IGE	LRE	Non defined	All	IGE	LRE	All	IGE	LRE	Non-defined	
n	148	57	90	1	55	39	16	93	18	74	1	170
Menstrual disorders	35	44	29	100	44[1]	49	31	30	33	28	100	29
PCO	34[2]	46[3]	28	0	45[7]	54	56[6]	23	28	22	100	21
HA	21[3]	33[3,4]	13[2,4]	0	34[6]	38	25	13	22	11	100	4
PCOS	28[3]	44[3,4]	19[4]	0	49[7]	54[5]	37[5]	16	22	15	100	11

IGE, idiopathic generalized epilepsy; LRE, localization-related epilepsy; VPA, valproate. [1] p=0.051, [2] p≤0.005, [3] p≤0.001, compared with control subjects, [4] p≤0.005, IGE vs. LRE, [5] p<0.05, [6] p≤0.005, [7] p<0.001, VPA-therapy vs. non-VPA-therapy.

5.1.2 Predictors of reproductive disorders

The predictors of HA, PCO and PCOS in WWE were tested in binary logistic regression analysis. The role of age at the onset of the medication, type of epilepsy, use of VPA- or non-VPA therapy, frequency of seizures and BMI as predictors of reproductive disorders was analyzed. The only predictive factor for PCO was the use of VPA. Furthermore, VPA treatment and young age increased the risk of HA and PCOS; the risk of HA and PCOS decreased with increasing age.

5.2 Antiepileptic drugs and reproductive health in women (Studies I-II)

5.2.1 Carbamazepine

The prevalence of irregular menstrual cycles, PCO or PCOS was similar in women on CBZ monotherapy and the control subjects in Study II. In study I WWE on combination treatment of CBZ plus VPA had HA (p=0.004) and PCO (p=0.022) more often than control women. However, the prevalence of reproductive endocrine disorders in women on CBZ-monotherapy did not differ from that of control subjects.

In study II women on CBZ had lower serum T levels (p=0.02), PROG levels (p=0.001) and FAI values (p=0.006) than control women. Furthermore, SHBG levels were higher in women taking CBZ than in the control women (p=0.02). Serum E2 levels were similar to those observed in the control women (Table 7, Figure 4).

Table 7. Serum concentrations of reproductive hormones in women with epilepsy and in control women, study II.

Medication	n	T Nmol/l	A nmol/l	DHEAS µmol/l	SHBG nmol/l	PROG nmol/l	E_2 nmol/l	FAI	E_2/SHBG
CBZ	16	1.7±0.6[2]	7.4±2.3	4.4±2.2	86.2±34.4[2]	1.3±0.7	0.1±0.06	2.5±1.4[1]	0.18±0.15
OXC	19	1.7±0.7[1]	9.4±4.1[3]	7.4±4.5[3]	70.1±27.1	1.8±1.0	0.1±0.05	2.7±1.3[2]	0.17±0.12
Controls	36	2.2±0.5	9.3±2.3	5.7±2.0	61.7±29.6	4.3±6.2	0.2±0.10	4.4±2.5	0.30±0.37

T,testosterone; A, androstenedione; DHEAS, dehydroepiandrosterone sulphate; SHBG, sex hormone binding globulin; PROG, progesterone; E_2, estradiol; FAI, free androgen index.

[1] p≤0.01, [2] p≤ 0.05, subject with epilepsy versus, controls. [3] p≤ 0.01, OXC versus. CBZ

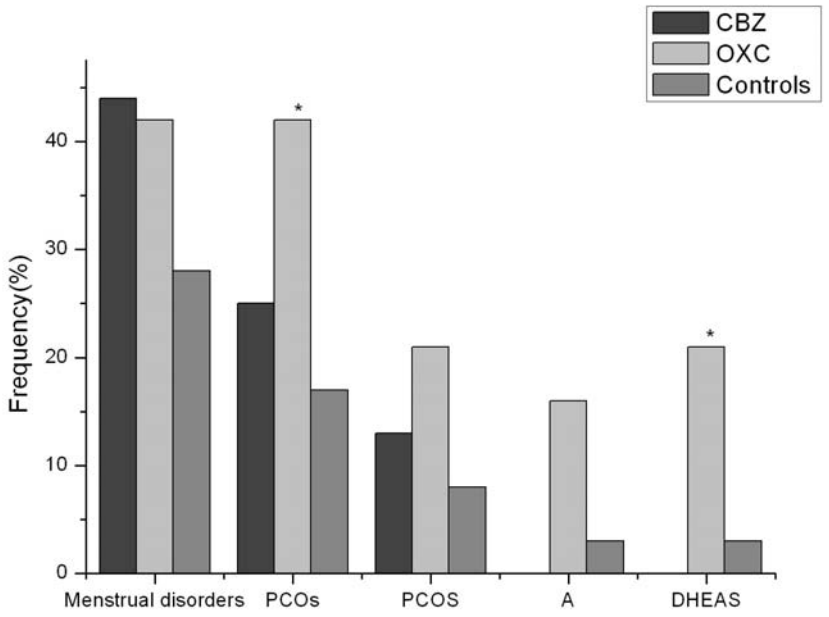

Fig. 4. Frequency of menstrual disorders, polycystic ovaries (PCOs), polycystic ovary syndrome (PCOS) and increased levels (> + SD) of androstenedione (A) and dehydroepiandrosterone (DHEAS) in women with epilepsy and in control women in study II. * p≤0.05

5.2.2 Oxcarbazepine

The prevalence of menstrual disorders or PCOS was similar in women on OXC and control women in Study II. However, the prevalence of PCO was higher in women on OXC ($p \leq 0.05$) than in control women. High serum levels of DHEAS ($p \leq 0.05$) were more common and high serum levels of A ($p \leq 0.1$) tended to be more prevalent in women on OXC than in control women. Moreover, serum T levels ($p = 0.007$), PROG levels ($p \leq 0.01$) and FAI values ($p = 0.017$) were lower in women on OXC than in control women. Serum T levels were similar in women taking low (<900mg/d) or high (≥900 mg/d) doses of OXC. Serum SHBG and E2 levels were similar in women on OXC and control subjects.

Women on OXC had higher levels of A ($p \leq 0.01$) and DHEAS ($p \leq 0.01$) than CBZ treated women (Table 7 and Figure 4).

5.2.3 Valproate

Women taking VPA for epilepsy had high prevalence of elevated concentrations of T, menstrual disorders, PCO and PCOS.

Increased concentrations of T were found in 35% of the women on VPA monotherapy ($p<0.001$) and 29% of women on polytherapy with VPA ($p=0.004$) compared with 4% of the control subjects. The prevalence of menstrual disorders was higher in all women taking VPA as mono- or polytherapy than in the control subjects (44% versus. 29%, $p=0.05$). PCO was present in 54% of women on VPA monotherapy ($p<0.001$) and in 57% of women on polytherapy with VPA ($p=0.022$) compared to 21% in the control subjects. Moreover, the prevalence of PCOS was high in WWE on VPA monotherapy compared to the control women (52% versus. 11%, $p<0.001$).

The prevalence of reproductive endocrine disorders in WWE treated with VPA was also analyzed by the age at which VPA was started (age <25 and age≥25), but there was no difference in the prevalence of PCO, PCOS or HA by the age at which the medication was started.

5.3 Antiepileptic drugs and reproductive health in men (Study III)

5.3.1 Carbamazepine

Serum levels of DHEAS were lower ($p<0.001$) in men on CBZ than in the control men. Serum concentrations of other reproductive hormones and SHBG, and FAI values were similar in CBZ treated MWE and the control subjects. The frequency of abnormally low sperm concentration ($p<0.001$) and poorly motile sperm ($p<0.05$) were increased in CBZ treated men compared to control men. The testicular volumes were similar in men on CBZ and control men (Table 8).

Table 8. Number(%) of men with epilepsy with abnormalities in sperm quality according to established WHO criteria, study III

Abnormality in sperm quality	Carbamazepine n=13	Oxcarbazepine n=17	Valproate n=25	All Patients n=55	Controls n=40
Spermatozoa concentration < 20x 10 ^{6}	5(38)[1]	2(12)	2(8)	9(18)[2]	0(0)
<5% of sperm with normal morphology*	5(38)[2]	4(24)[3]	6(24)[2]	15(27)[1]	1(3)
<50% of sperm motile, grades A+B**	9(69)[3]	7(41)	16(64)[3]	32(58)[3]	14(35)
Any sperm abnormality	10(77)	10(59)	20(80)[2]	40(73)[3]	19(40)

WHO, World Health Organization.* gravely abnormal sperm morphology.

[1] p=<0.001, [2] p=0.01, [3] p=0.05

5.3.2 Oxcarbazepine

Serum concentrations of reproductive endocrine hormones were similar in MWE on OXC and control men. Testicular volumes were also similar in men on OXC and control men. In the semen analysis the frequency of morphologically abnormal sperm was increased in OXC treated men compared with control men ($p<0.01$) (Table 8).

5.3.3 Valproate

Concentrations of serum androstendione ($p<0.001$) were high in men taking VPA for epilepsy, but serum concentrations of other reproductive hormones and SHBG, and FAI values in VPA treated men did not differ from those of the control men. In semen analysis the spermatozoa concentration and frequency of morphologically normal sperm in VPA treated men did not differ from control men, but the frequency of motile sperm was low in men on VPA (44 % versus. 61%, $p<0.05$). In addition the frequency of poorly motile sperm was increased ($p<0.05$) and prevalence of any sperm abnormality was higher ($p<0.01$) in men on VPA compared to control subjects (Table 8). Testicular volume was reduced in men with IGE taking VPA compared to control men ($p<0.01$). Furthermore, men

on VPA and with any sperm abnormality had decreased testicular volume when compared to control men (p=0.003), whereas the testicular volume in men on VPA with normal sperm did not differ from control men.

5.4 Epilepsy and birth rate in Northern Finland Birth Cohort 1966 (Study IV)

5.4.1 Prevalence of epilepsy

The cumulative prevalence of epilepsy was 1.9% in the NFBC. 1.9% of women and 1.8% of men had or had had epilepsy. In addition, 0.2% of subjects had a history of seizures but were not diagnosed to have epilepsy.

The diagnosis of epilepsy was made before the age of 10 in 47% of subjects with epilepsy, and 32% of subjects had their first seizure in the age of 10-20 years. Epilepsy was diagnosed during adulthood in 21% of subjects. Three percent of subjects achieved remission before the second decade of life and 31% of subjects achieved remission before adulthood (<20 years). 55% of subjects were on antiepileptic medication at the time of the study. The mean duration of epilepsy in subjects with epilepsy was 19.4 years (0.1- 40) at the time of analysis. 38% of the subjects had IGE and 43% of the subjects had LRE. The epilepsy type could not be classified in 19% of subjects.

5.4.2 Epilepsy and birth rate

The number of marriages/domestic partners was decreased in MWE when compared to control subjects (p= 0.013). However, the number of children was similar in MWE and control men. This was the case also among men who where married. The type of epilepsy did not have any effect on fertility (the number of children) in MWE. The number of children tended to be higher in MWE if remission was achieved before adulthood than if the subjects had active epilepsy in adulthood (p=0.053). Men who had active epilepsy during adulthood had fewer children than control men (p= 0.022).

The rate of marriages and cohabiting was similar in WWE and control women. Furthermore, WWE did not differ from the control women, when number of deliveries, pregnancies and induced and spontaneous abortions were compared. However, women who had active epilepsy in the adulthood had fewer deliveries

(p=0.032), pregnancies (p= 0.009) and spontaneous and induced abortions (p= 0.045, p= 0.053) than women who had achieved remission before the age of 20 years. WWE who achieved remission before adulthood had more pregnancies (p=0.032) and induced abortions (p=0.001) than control women. The type of epilepsy did not have any effect on the number of deliveries, pregnancies or induced and spontaneous abortions.

Men and women with seizures but without diagnosis of epilepsy did not differ from the control group with regard to marital status or fertility rates.

6 Discussion

6.1 General aspects

The association of reproductive endocrine disorders with epilepsy has been extensively studied during the last decades. However, it is still uncertain whether these disorders are a consequence of epilepsy itself or antiepileptic medication or both. Adequate antiepileptic medication can help subjects with epilepsy to reach complete seizure control, but at the same time AED associated adverse effects may have a negative impact on quality of life of PWE. Epilepsy during adulthood can have a strong influence on reproduction and fertility, and the antiepileptic treatment may also induce reproductive disorders. (Herzog *et al.* 1986a, 1986b, 2003a, 2003b, Isojärvi *et al*. 1990, 1993, 1995d, 1996, 1998, 2001, Chen *et al.* 1992, Vainionpää *et al.* 1999, Bauer *et al.* 2000, Rättyä *et al.* 2001b, Bauer *et al.* 2002, Morrell *et al.* 2002a, Morrell *et al.* 2003, Betts *et al.* 2003, Mikkonen *et al.* 2004a, 2004b) Moreover, AEDs may have teratogenic effects during pregnancy (Schupf & Ottman 1997, Barrett & Richens 2003, Gaily *et al.* 2004, Artama *et al.* 2005), which may change the views of WWE on childbearing and potential pregnancy.

In the present study the effects of AEDs and epilepsy on reproductive endocrine function were evaluated in MWE and WWE. All subjects included in studies I-III were of reproductive age and had no other illnesses than epilepsy, and women taking oral contraceptives were excluded. Moreover, all subjects had been taking the same antiepileptic medication for at least 6 months, a time period long enough to bring out the possible reproductive endocrine effects of the AEDs (Isojärvi *et al.* 1995a, 1995c, Rättyä *et al.* 2001a). In study IV a population based setting was used to estimate the effect of epilepsy on fertility; the study population consisted of 12,600 subjects. More than 93% of subjects born in 1966 in Northern Finland were included in the study cohort, and the information was obtained from several sources to ensure reliability of the findings.

6.1.1 Methodological considerations

Serum gonadotropin concentrations were assayed from two samples taken 30 minutes apart and the mean of these two concentrations was used for the statistical analyses. The serum concentrations of the other hormones were assayed

from only one sample, which is considered appropriate (Connell *et al.* 1984a, 1984b, Macphee *et al.* 1988). In men the testicular ultrasound examinations were performed by the same investigator to maintain consistency. To be consistent and to avoid the effect of menstrual cycle on serum hormone concentrations, women were examined during the early follicular phase (days 3-6 on menstrual cycle), except women with amenorrhea. The ovarian ultrasound examinations were also performed in early follicular phase by the same investigator.

The previously published studies on reproductive disorders in subjects with epilepsy have emphasized different aspects in terms of possible etiological explanations (Herzog *et al.* 1986a, 1986b, 1993, Isojärvi *et al.* 1993, 1998). Overall it has been difficult to differentiate the effects of epilepsy itself and the AEDs on endocrine function and reproduction. In addition, the methodology and definitions used may have varied from study to study. In the present study the definition of PCOS was based on the latest consensus (Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome 2004) and the possible bias was minimized by using a regression model in statistical analysis. Epilepsy was classified to LRE, IGE or unclassified, unfortunately further information of epileptic syndromes was not available for analysis. Furthermore, the population based study evaluated the fertility of subjects with epilepsy using epidemiological methods in a representative cohort consisting over 12600 subjects. Eventhough the data was collected from several sources with objective methods, there were also insufficiencies in data collection, for example, patient records were not available for all subjects with epilepsy. Also the definition of remission was based on discontinuation of antiepileptic drugs, since the information of the seizure-free period during the medication was not reliable.

6.2 Epilepsy and reproductive disorders

6.2.1 Type of epilepsy and reproductive disorders

In the present study women with IGE had more often PCO, HA and PCOS than women with LRE or control women. This is congruent with a previously published study evaluating predictors of ovulatory failure in which women with IGE were at highest risk for anovulatory cycles, polycystic appearing ovaries, elevated body mass index (BMI) and HA (Morrell *et al.* 2002a). However, LRE

has also been observed to increase the risk of certain reproductive disorders, and the laterality of the epileptic focus may be important in this respect so that LRE with left sided focus has been suggested to be associated with PCOS, and LRE with right sided focus to be associated with hypothalamic amenorrhea and hyposexuality (Herzog *et al.* 1986a, 1986b, 2003b).

Epilepsy itself may promote reproductive disorders by disturbing the hypothalamic regulation of secretion of pituitary hormones. Elevated levels of serum pituitary hormones have been measured after both partial and generalized seizure (Dana-Haeri *et al.* 1983). Moreover, interictal electrical discharges can also predispose to increased secretion of pituitary hormones.

The suggested increased prevalence of reproductive disorders in subjects with LRE is explained by the anatomy and physiology of the tempolar lobe. The epileptic focus may disturb the function of the temporolimbic-hypothalamopituitary axis, which regulates the release of reproductive hormones in an asymmetric manner. The electrical discharges during the seizures and in interictal period can spread from the tempolar structures to the hypothalamus through direct connections and cause disturbances in the release of GnRH, which is situated and secreted asymmetrically in the hypothalamus. In Herzog's study in women with tempolar lobe epilepsy the pulsatile secretion of LH and LH/FSH-ratio was increased and concentrations of peripheral gland hormones T and E_2 were also increased in women with left sided focus when compared to WWE with right sided focus (Herzog *et al.* 2003b). Similar results suggesting a different pattern of reproductive endocrine characteristics between patients with right or left sided epileptic focus have also been observed in other studies by the same investigators. However, in all these studies the patient population has been biased towards high seizure frequency and refractory epilepsy, and the patients have been referrals to a highly specialized tertiary care center. (Herzog *et al.* 1986a, 1986b, 1993, 2003a, 2003b) Interestingly, it has also been discussed whether reproductive disorders may promote seizures, since E_2 is known to precipitate interictal epileptic brain wave activity (Bäckström 1976) and PROG is protective against seizures. Moreover, genetic factors in prenatal period can affect both the regulation of reproductive hormones and brain contributing to the development of epilepsy (Herzog *et al.* 1986a, 1986b).

The mechanism of IGE-related reproductive endocrine disorders is unclear, but mechanisms similar to the development of LRE-related reproductive endocrine disorders have been suggested (Morrell *et al.* 2002a). Electrical discharges during generalized seizures disturb the release of pituitary hormones;

increased serum levels of LH and prolactin after generalized tonic clonic seizures have been reported in both men and women with epilepsy (Dana-Haeri *et al.* 1983). The frequency of LH secretion pulses may also be altered in women with IGE. This has been shown in women with IGE and anovulatory cycles (Morrell *et al.* 2002a). Interictal generalized discharges may also disrupt the function of the hypothalamic-pituitary axis.

6.2.2 Predictors of reproductive disorders

In the present study the only factor that predicted the presence of PCO in WWE was the use of VPA. HA and PCOS were also predicted by the use of VPA and young age; these types of disorders were less common with increasing age. These results are consistent with previous reports (Isojärvi *et al.* 1993, 2001, Murialdo *et al.* 1997, Morrell *et al.* 2002a, Betts *et al.* 2003). Morrell et al. analyzed predictors of ovulatory failure in a cohort of WWE, and IGE and the use of VPA during the three previous years were independent factors that predicted ovulatory failure (Morrell *et al.* 2002a). In the present study the role of IGE was not detectable in regression analysis even though the prevalence of reproductive disorders was increased in women with IGE. This may be affected by the small number of patients in the analysis. Young age at the initiation of medication has not been analyzed as a possible factor to predict reproductive disorders in regression models in any of the previous studies. However, results from some studies have suggested that young age may predispose women to VPA-related reproductive endocrine disorders (Isojärvi *et al.* 1993, Vainionpää *et al.* 1999, Betts *et al.* 2003, Mikkonen *et al.* 2004b). Moreover, in a general population of healthy women PCO is more common in women under 36 years of age than in older women (Koivunen *et al.* 1999).

In the present study increased body weight was not found to be a predictor of reproductive disorders, which is surprising since the role of obesity in development of reproductive disorders is well established (Kiddy *et al.* 1990, Pasquali *et al.* 1997, Morin-Papunen *et al.* 1998). In addition, the use of VPA can be associated with weight gain and obesity (Dinesen *et al.* 1984, Biton *et al.* 2001), which has been shown to be associated with reproductive disorders in WWE (Isojärvi et al 1996, 1998, 2001). However, lean women on VPA therapy have also been shown to have high prevalence of reproductive endocrine disorders (Isojärvi *et al.* 1996, 2001).

Despite the fact that the roles of epilepsy and the AED medication in contributing to the development of reproductive disorders in WWE has been widely discussed in the scientific literature during the last couple of decades, only a few previous studies have utilized a regression method in the analysis of factors contributing to the development of reproductive endocrine disorders in PWE (Morrell *et al.* 2002a, Herzog *et al.* 2003a, Mikkonen *et al.* 2004a). The regression method is useful in this type of analysis, because it helps to identify factors that may contribute to the development of these type of disorders and enables the exclusion of the possible confounding effect of correlation between the factors possibly contributing to the development of the disorders. It is possible that in some of the previous studies correlation between the medication and epilepsy type has confounded the analysis and the results.

6.3 Reproductive endocrine effects of antiepileptic drugs

6.3.1 Carbamazepine

Women on CBZ did not differ from control women when prevalences of menstrual disorders, PCO, HA or PCOS were compared. In MWE CBZ was associated with reduced sperm concentration and high frequency of poorly motile sperm. The frequency of sperm with abnormal morphology was also higher in CBZ treated MWE than in the control men. CBZ treated men also had lower serum concentrations of DHEAS than control men.

In WWE the effects of CBZ have been fairly extensively studied (Isojärvi 1990, 1995b, 1996, Murialdo *et al.* 1998, Rättyä *et al.* 2001b). It is well established that CBZ induces the hepatic p450 enzyme system (Perucca *et al.* 2004) and increases the concentration of SHBG and thereby decreases the serum concentrations of bioactive androgens (Isojärvi 1990, 1995c, Rättyä *et al.* 2001b). The increase in serum SHBG concentration has been shown to be progressive (Isojärvi 1990). Low levels of serum DHEAS have also been reported in women taking CBZ for epilepsy (Levesque *et al.* 1986). However, in previous studies the prevalence of reproductive disorders has not been different in women on CBZ from that of control women (Isojärvi *et al.* 1993, Murialdo *et al.* 1997, Murialdo 1998, Bauer *et al.* 2000). The results of the present study were consistent with this. It has been discussed whether increased serum SHBG level may protect against the development of reproductive endocrine disorders in WWE by

decreasing the levels of bioactive androgens (Isojärvi 2002). On the other hand, long-term treatment with CBZ has been associated with menstrual disorders, which may be caused by diminished concentrations of bioactive E_2 as demonstrated by the changes in the E_2/SHBG ratio (Isojärvi *et al.* 1995b). In the present study the frequency of menstrual disorders and ovarian structure of women on CBZ did not differ from those of control women. However, in WWE taking CBZ together with VPA, the prevalence of HA and PCO was high.

CBZ also increases the production of SHBG in men. This results in lower levels of bioactive androgens in target cells and decreased FAI (Isojärvi *et al.* 1988, 1990, 1991, 1995d, Macphee *et al.* 1988, Rättyä *et al.* 2001b). Low serum levels of DHEAS have also been reported in men on CBZ (Levesque *et al.* 1986, Isojärvi *et al.* 1988, 1990, 1991, 1995d, Macphee *et al.* 1988) and this was also observed in the present study. It has previously been shown that CBZ does not change serum concentrations of T, but the level of bioactive free T, as calculated from serum T and SHBG concentrations, diminishes (Isojärvi *et al.* 1988, 1991, 1995d, Macphee *et al.* 1988, Rättyä *et al.* 2001b). This may be associated with sexual dysfunction, e.g. reduced potency and libido in men on long term CBZ treatment (Isojärvi *et al.* 1995d, Rättyä *et al.* 2001b). The decreased levels of bioactive T are also assumed to have a negative impact on sperm quality, and, in addition, in an *in vitro* study CBZ was also shown to directly inhibit the formation of T in Leydig cells (Kuhn-Velten *et al.* 1990), which may affect spermatogenesis. In another *in vitro* study CBZ was associated with decreased sperm motility indicating a direct effect of CBZ on sperm quality (Chen *et al.* 1992). In the present study the serum levels of T in men on CBZ did not differ from those of men on OXC or VPA, or control men.

6.3.2 Oxcarbazepine

In women OXC was associated with higher prevalence of PCO and higher serum concentrations of A and DHEAS than in control women. In men OXC was associated with increased frequency of morphologically abnormal sperm when compared to control men.

In women the effects of OXC on reproductive function have not been previously studied. OXC was not associated with reproductive endocrine abnormalities in girls during pubertal maturation (Rättyä *et al.* 1999), and after a five-year follow-up the reproductive endocrine hormone levels of the same young women were normal. However, the prevalence of PCO was as high as 63% (5 of 8

women) in young women on OXC therapy in the follow-up study (Mikkonen *et al.* 2004b). The prevalence of PCO was increased in women on OXC compared with control women in the present study as well. In addition, the serum levels of A and DHEAS were higher in OXC treated WWE than in WWE on CBZ. This finding supports a hypothesis that OXC associated reproductive disorders may mainly be caused by induction of adrenal steroidogenesis, not the induction of the liver enzyme system. The serum SHBG concentrations of women on OXC did not differ from control women, which supports the hypothesis as well. OXC was also associated with low serum levels of T when compared to those of control women. Interestingly, serum T levels were similar in women taking low (<900 mg /d) or high (≥900 mg /d) doses of OXC. However, it is also possible that the reproductive endocrine disorders in OXC treated WWE are associated with epilepsy, and contrary to CBZ, the normal serum levels of SHBG and lack of effect on the bioactivity of androgens do not protect against the effects of increased serum androgens.

There are only a few published studies on the effects of OXC on reproductive endocrine function in men (Rättyä *et al.* 2001b, Mikkonen *et al.* 2004a, Artama *et al.* 2004). It has been assumed that OXC has less potential to interfere with the endocrine function than CBZ because it induces the liver p450 enzyme system only when taken in high doses (Patsalos *et al.* 1990). Furthermore, when CBZ was replaced with OXC the CBZ-induced alterations in the serum concentrations of reproductive endocrine hormones normalized in MWE (Isojärvi *et al.* 1995c). Normal serum levels of reproductive hormones have also been observed previously in young men on OXC (Mikkonen *et al.* 2004a) and the findings of the present study were consistent with this. The frequency of morphologically abnormal sperm was increased in men on all studied AEDs including OXC even though other parameters in sperm quality were normal in men on OXC. Interestingly, in a population based setting OXC was associated with lower birth rate when compared to untreated patients, while men on VPA or CBZ did not differ from untreated patients (Artama *et al.* 2004). However, it is also possible that in addition to OXC, epilepsy itself may interfere with spermatogenesis and reduce fertility in these patients.

6.3.3 Valproate

In women VPA was associated with elevated serum concentrations of T, and high prevalence of menstrual disorders, PCO and PCOS. In men VPA was associated

with increased concentration of A, abnormalities in sperm quality and reduced testicular volume.

The effects of VPA on women have been extensively studied (Isojärvi *et al.* 1993, 1996, 1998, Rättyä *et al.* 1999, Bauer *et al.* 2000, Morrell *et al.* 2002a, Morrell *et al.* 2003, Betts *et al.* 2003). The role of VPA in the development of reproductive disorders (Isojärvi *et al.* 1993, 1996, Rättyä *et al.* 1999, Isojärvi & Tapanainen 2000, Morrell *et al.* 2002a, Tauboll *et al.* 2003, Mikkonen *et al.* 2004b) has been discussed and the effect of epilepsy has also been emphasized in recent years (Herzog & Schachter 2001, Bauer *et al.* 2002). The methods used in reproductive endocrine studies on WWE have not been consistent throughout the studies. In some studies the information of the medication has not been complete, (Bauer *et al.* 2000) the data on previous medication has been incomplete (Herzog *et al.* 1986a, 1986b, Isojärvi *et al.* 1993, Bauer *et al.* 2000) and the use of imaging methods has varied in different studies (Herzog *et al.* 1986a, 1086b, Isojärvi *et al.* 1993, Bauer *et al.* 2000). Furthermore, the uniform definition for PCOS was not agreed upon until 2003 in Rotterdam, where international consensus of criteria was achieved (Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome 2004).

In previous studies in WWE, VPA has been associated with increased prevalence of menstrual disorders, PCO, HA and PCOS. VPA has also been associated with obesity and hyperinsulinemia (Isojärvi *et al.* 1993, Isojärvi *et al.* 1996, Isojärvi *et al.* 1998, Rättyä *et al.* 1999, Isojärvi & Tapanainen 2000, Isojärvi *et al.* 2001, Morrell *et al.* 2003, Mikkonen *et al.* 2004b). The results of the present study were consistent with an association between VPA and reproductive endocrine disorders. Furthermore, in regression analysis the use of VPA was the most important factor in predicting the presence of HA, PCO and PCOS in WWE. Also in the study by Morrell et al. the use of VPA in the previous three years was one of the predictors of ovulatory failure.(Morrell *et al.* 2002a) Interestingly, VPA has also been shown to be associated with reproductive disorders in women with bipolar mood disorder (O'Donovan *et al.* 2002).

It has been suggested that VPA-related HA, menstrual disorders, PCO and PCOS are associated with obesity and hyperinsulinemia (Isojärvi *et al.* 1996, Isojärvi *et al.* 1998). However, HA and PCO have also been present in lean women without hyperinsulinemia (Isojärvi *et al.* 2001). Therefore, obesity can be included as one of several factors in this complicated syndrome associated with VPA. In fact, VPA may have a direct inhibitory effect on the ovaries and on steroid metabolism. VPA inhibits the conversion of T to estrogen, which may lead

to development of HA in the ovarian microenvironment. This may disturb the follicular maturation and lead to development of polycystic appearance of the ovaries (Tauboll *et al.* 2003).

In men VPA was associated with increased serum levels of A, which is consistent with results of previous studies in men on VPA therapy (Rättyä *et al.* 2001b, Mikkonen *et al.* 2004a). Unlike in the previous studies in which VPA was also associated with increased levels of serum DHEAS and T, and decreased serum levels of gonadotropins (Isojärvi *et al.* 1990, Rättyä *et al.* 2001a), the serum concentrations of these hormones did not differ from those of the control men in the present study.

There are only a few previous studies that have evaluated the possible effects of AEDs on male reproductive function by assessing the impact of the drugs on spermatogenesis (Chen *et al.* 1992, Sveberg *et al.* 2001, Sveberg Roste *et al.* 2003). In the present study VPA was associated with high frequency of poorly motile sperm. Interestingly, VPA was also associated with decreased motility of sperm in an *in vitro* study, which suggests a direct effect of VPA on semen quality. The normal motility of spermatozoa is dependent on adequate mitochondrial function, which may be affected by VPA (Ponchaut & Veitch 1993).

VPA was also associated with increased overall prevalence of sperm abnormalities and reduced testicular volume when compared to those of control men. Furthermore, men on VPA with abnormal sperm had smaller testicular volume than the control men, while men on VPA with normal sperm did not differ from controls when testicular volume was studied. In a previous study in young male subjects on VPA therapy their testicular volumes did not differ from those of control subjects. The sperm was not analyzed due to the young age of the participants. (Mikkonen *et al.* 2004a) Exposure to VPA has also been associated with testicular atrophy and reduced spermatogenesis in animals (Walker *et al.* 1990, Berner *et al.* 1999, Sveberg *et al.* 2001), but the mechanisms for VPA-induced changes in testicular volume are still unclear.

In this study VPA was also associated with abnormal sperm morphology. The effects of VPA on spermatogenesis may be explained by several factors. It has been suggested that VPA modifies the GABAergic neurotransmission (Macphee *et al.* 1988, Isojärvi *et al.* 1990, Arroyo 2004) and thereby affects the secretion of gonadotropins (Macphee *et al.* 1988, Isojärvi *et al.* 1990), which are vital for normal spermatogenesis. The altered serum levels of gonadotropins could also be caused by increased serum levels of T by feedback mechanism in the regulation of the hypothalamic-pituitary-testicular axis. However, the serum levels of

gonadotropins and T in men on VPA did not differ from those of control men in the present study.

6.4 Epilepsy in population based setting

The prevalence rates and incidence rates of epilepsy have been studied in many populations. Methods and the diagnostic criteria have varied and, therefore, comparison of the results of these studies has been difficult (von Wendt L. *et al.* 1985a, 1985b, Hauser *et al.* 1993, Sillanpää M 1994, Zarrelli *et al.* 1999, Hauser & Hesdorffer 2001, Forsgren 2004, Oka *et al.* 2006). In the present study the prevalence of epilepsy was studied in NFBC 1966 which is a unique general population based cohort (Rantakallio 1969). The data have been collected prospectively and thus there is no evident selection bias.

6.4.1 Prevalence of epilepsy

The cumulative prevalence of epilepsy was 1.9% in NFBC 1966 which is relatively high when compared to worldwide prevalence of epilepsy (Sillanpää M 1994, Forsgren 2004). However, the results of the present study are in accordance with lifetime cumulative prevalence, which was 1-3% according to Hauser (Hauser 1997). The difficulties in the comparison of prevalence and incidence rates in different studies are related to variation in definitions of seizure disorders and methods used in the different studies. For example, in the study evaluating the incidence of childhood epilepsies in NFBC 1966 only one seizure was needed for the diagnosis, therefore the cumulative prevalence was as high as 1.4% (von Wendt L. *et al.* 1985a, 1985b). In the present study the diagnostic criteria followed the ILAE recommendations and the diagnosis of childhood epilepsy was re-evaluated and reclassified. The prevalence of childhood epilepsies was congruent with the findings in other epidemiological studies (Sillanpää M 1994). In population based studies conducted in Europe, the age adjusted prevalence rates in adults have been congruent, but these studies were focused on active epilepsy and cumulative prevalence rates have not been reported (Granieri *et al.* 1983, Joensen 1986, Keränen *et al.* 1989, Maremmani *et al.* 1991, Forsgren 1992, Luengo *et al.* 2001, Oun *et al.* 2003). Compared to those studies, the prevalence of active epilepsy in NFBC is relatively high. This may be explained by the characteristics of the study population,e.g. the prevalence of unique hereditary diseases and disabilities has been relatively high in study population, which is

caused by genetic isolation (von Wendt L. *et al.* 1985a, 1985b, Heikura *et al.* 2005).

6.4.2 Epilepsy and fertility

In the present study WWE did not overall differ from control women when fertility rates were compared. However, women affected by epilepsy during the adulthood were less fertile than WWE who had achieved remission before adulthood. Also, in MWE active epilepsy during adulthood was associated with decreased fertility, eventhough in overall comparison of the fertility rates of control men and MWE there were no differences.

It is well established that epilepsy is associated with high prevalence of reproductive disorders, but there are only a few studies that have evaluated fertility in subjects with epilepsy in a population based setting (Webber *et al.* 1986b, Jalava & Sillanpaa 1997, Olafsson *et al.* 1998, Wallace *et al.* 1998, Artama *et al.* 2004, Artama *et al.* 2006). In previous studies subjects with epilepsy have been associated with lower marriage rate and fewer children than control subjects (Webber *et al.* 1986, Jalava & Sillanpaa 1997, Wallace *et al.* 1998, Artama *et al.* 2004, Artama *et al.* 2006), but contradictory findings have also been presented (Olafsson *et al.* 1998).

The reproductive endocrine disorders associated with epilepsy and antiepileptic medication are well established in WWE (Herzog *et al.* 1986a, 1986b, Isojärvi *et al.* 1993, 1996, Rättyä *et al.* 1999, Morrell *et al.* 2002a, Herzog *et al.* 2003). Furthermore, the contributory role of these disorders to infertility is also well known in the general population (Kousta *et al.* 1999). Consistent with these findings, in the present study women who had active epilepsy and who were on antiepileptic medication during adulthood had reduced fertility when compared to women who had achieved remission before adulthood. Similarly, in a long-term follow-up study in young female subjects with epilepsy reproductive disorders were also common in subjects with active epilepsy, whereas the prevalence of reproductive disorders was similar to control subjects if antiepileptic medication was discontinuated at adolescence (Mikkonen *et al.* 2004b). These findings support the view that active epilepsy and antiepileptic medication play an important role in the development of reproductive disorders and infertility in WWE. Interestingly, in the present study WWE who had achieved remission and the antiepileptic medication was discontinued before adulthood had a similar number of children to that of the control subjects. Also in

MWE the number of children tended to be higher in if remission was achieved before adulthood than if the subjects had active epilepsy in the adulthood. It is established that epilepsy itself is associated with reproductive endocrine disorders also in men (Herzog *et al.* 1986b), but also the role of antiepileptic drugs in the development of these abnormalities is established (Macphee *et al.* 1988, Isojärvi *et al.* 1990, Herzog *et al.* 1991). Furthermore, the effects of antiepileptic drugs on testicular structure, spermatogenesis and sperm quality (Kuhn-Velten *et al.* 1990, Chen *et al.* 1992, Yerby & McCoy 1999, Sveberg Roste *et al.* 2003) may also contribute to decreased fertility associated with active epilepsy. However, it has been previously suggested that subjects with childhood epilepsies have fewer children than control subjects, eventhough they have achieved remission (Sillanpää *et al.* 1998, Sillanpää *et al.* 2004). Regardless, it is important to note that the effect of epilepsy on fertility may be different depending on the activity of epilepsy later in life.

In previously published studies MWE were more often single than control men (Wallace *et al.* 1998), which was also found in the present study . Men are more often stigmatized by epilepsy. This may affect social and economical status, which on the other hand may influence marital status (Sillanpää *et al.* 1998, Morrell 2002b, Sillanpää *et al.* 2004). In women the stigmatizing effect of epilepsy may be smaller, and the effect of epilepsy on marriage rate and fertility rates less evident.

Interestingly, despite of lower socioeconomic position and lower marriage rate in MWE, the overall number of children was similar in MWE and control men, which is in discrepancy with previous studies (Webber *et al.* 1986, Wallace *et al.* 1998, Sillanpää *et al.* 1998, 2004, Artama *et al.* 2004). However, consistent with what was seen in WWE, active epilepsy with antiepileptic medication during adulthood also reduced fertility in MWE. On the other hand, if remission was achieved before adulthood, MWE did not differ from control men with regard to fertility. This suggests that both active epilepsy with recurrent seizures and use of AEDs may contribute to reduced fertility in MWE and WWE. On the other hand, the design of the current study and the small number of patients in different subgroups with different epilepsy types or different AED regimens did not allow a reliable analysis of the impact of different epilepsy types or AEDs on reduced fertility.

7 Conclusions

1. Both epilepsy and antiepileptic medication contribute to the development of reproductive disorders in WWE. VPA medication, young age at the start of the medication, and IGE were found to increase the prevalence of reproductive endocrine disorders in WWE.
2. The reproductive endocrine effects of OXC and CBZ are different in WWE. OXC is associated with increased prevalence of PCO and elevated serum levels of A and DHEAS whereas CBZ increases the serum SHBG concentrations and is associated with reduced bioactivity of sex steroids.
3. CBZ, OXC and VPA are associated with high prevalence of sperm abnormalities in MWE. The testicular volume of VPA treated MWE with abnormal sperm quality is reduced. The possible association between VPA therapy and testicular atrophy calls for further studies.
4. Active epilepsy with antiepileptic medication during adulthood reduces fertility in both men and women in a population based setting. If remission is achieved before adulthood, PWE do not differ from control subjects with regard to fertility.

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