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USE AND RISKS OF PRESCRIPTION DRUGS DURING PREGNANCY

WITH SPECIAL EMPHASIS ON SELECTIVE SEROTONIN REUPTAKE INHIBITORS AND VALPROIC ACID

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ACADEMIC DISSERTATION

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To my family

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ABBREVIATIONS

ADEC	Australian Drug Evaluation Committee
ATC	Anatomic Therapeutic Classification of Drugs
DES	Diethylstilbestrol
EMEA	European Medicines Agency
EUROCAT	European Surveillance of Congenital Anomalies
FASS	Swedish System of Approved Drugs
FDA	Food and Drug Administration
ICD	International Statistical Classification of Diseases
IQ	Intelligence quotient
KELA	The Social Insurance Institution of Finland
MDR1	Multidrug resistance 1 gene
MTHFR	Methylenetetrahydrofolate reductase
NSAID	Non-steroidal anti-inflammatory drugs
P-gp	P-glycoprotein
SD	Standard deviation
SSRI	Selective serotonin reuptake inhibitor
STAKES	National Research and Development Centre for Welfare and Health
VSD	Ventricular septal defect
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

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

I Malm H, Martikainen J, Klaukka T, Neuvonen PJ. Prescription drugs during pregnancy and lactation – a Finnish register-based study. Eur J Clin Pharmacol 2003;59:127-133.

II Malm H, Martikainen J, Klaukka T, Neuvonen PJ. Prescription of hazardous drugs during pregnancy. Drug Saf 2004;27:899-908.

III Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol (in press).

IV Malm H, Kajantie E, Kivirikko S, Kääriäinen H, Peippo M, Somer M. Valproate embryopathy in three sets of siblings: Further proof of hereditary susceptibility. Neurology 2002;59:630-633.

ABSTRACT

Firstly, the pattern of prescription drug use has not been investigated extensively in the Finnish pregnant population. Secondly, it is not known to what extent drugs which may cause fetal adverse effects are used during pregnancy. Thirdly, with the increasing use of antidepressants, possible harmful effects of the selective serotonin reuptake ihibitors (SSRIs) on pregnancy outcome warrant investigation to avoid serious public health consequences. Fourthly, valproic acid is a major anti-epileptic drug with an established teratogenic potential. Hereditary susceptibility to valproate teratogenicity may explain why some infants are affected, while the majority are born healthy after exposure to valproate *in utero*.

The overall use of prescription drugs, and the use of prescription drugs suspected or known to be harmful to the fetus were investigated in pregnant women during different pregnancy trimesters, and in matched non-pregnant controls (n=43 470 each). Safety of SSRIs was evaluated by comparing women with SSRI purchases with matched pregnant controls without drug purchases (n=1782 each), and also by comparing women with SSRI purchases in different trimesters. Data for these three studies were derived from nationwide registers. The aetiology of multiple malformations was investigated by clinical evaluation and review of medical records of three sets of siblings, all exposed to valproate *in utero*, and their parents.

Prescription drugs were purchased by 46.2% of pregnant women, compared with 55.2% of non-pregnant controls. Drug treatment for chronic illnesses requiring treatment continued throughout pregnancy. In the second study, *potentially* or *clearly* harmful drugs were used less frequently in the first trimester than in the preconception period. In the third study, first trimester exposure to SSRIs (n = 1398) was not associated with an increased risk of major malformations (adjusted OR 1.0, 95% CI 0.6-1.7). Admission to special or intensive care unit was more common in neonates exposed to SSRIs during the third trimester than in those exposed only during the first trimester (15.7% *vs*. 11.2%; adjusted OR 1.6, 95% CI 1.1-2.2). In the fourth study, all three sets of siblings exposed to valproate *in utero* had developmental delay and a distinctive facial appearance, including a broad nasal root, anteverted nares, and a shallow philtrum, and other malformations characteristic of valproate embryopathy.

The results of prescription drug use are in line with rational drug use during pregnancy. Due to the relatively common occurrence of neonatal problems, SSRI drugs should be used during pregnancy only when clearly indicated. The observed valproate embryopathy in all siblings in the three families strongly suggests hereditary susceptibility to valproate-induced teratogenicity, as, in general, the majority of children are born healthy.

1. INTRODUCTION

Major congenital malformations occur in approximately 2% to 3% of all pregnancies, placing a considerable burden on the affected child, the family and society. In more than half of the cases, the aetiology of the malformation remains unknown (Kalter 2003). For many drugs, including ones recently marketed, data are inadequate to confirm their safe use during pregnancy (Lo and Friedman 2002). Consequently, prescribing drugs during pregnancy presents a challenge in balancing optimal treatment of maternal disease against possible harm to the fetus. On the other hand, when adequate information on drug safety is lacking, essential drug treatment may be avoided, and chronic illnesses requiring drug treatment may be treated suboptimally.

Extensive studies investigating overall use of prescription drugs during pregnancy have not previously been conducted in Finland. One Finnish study, based on prospectively collected interview data for nearly 8000 pregnant women, reported that 1.5% of subjects used psychotropic drugs during pregnancy (Larivaara *et al.*1996). However, no data concerning other drug groups were available (Larivaara *et al.* 1996). Several reports from other countries have suggested extensive use of prescription and over-the-counter (OTC) drugs during pregnancy, indicating marked cultural variation in drug use patterns (Collaborative Group on Drug Use in Pregnancy (CGDUP) 1992; Rubin *et al.* 1993; Olesen *et al*. 1999a; de Vigan *et al*. 1999; Lacroix *et al*. 2000).

Large cultural variations in drug use during pregnancy have also been observed in studies classifying drugs according to fetal safety (CGDUP 1991; Olesen *et al*. 1999b; Lacroix *et al*. 2000). Pregnancies are often unplanned and harmful exposure may occur by accident. First-trimester exposure to a harmful agent may cause structural malformations, but if first-trimester exposure is avoided many drugs may be used relatively safely during the second or third trimester. However, some drugs are known to affect the fetus during the later stages of pregnancy (Barr 1994; Kalter 2003). Surveillance of drug use during pregnancy, and identification of drug prescription practices are therefore important.

The prevalence of major depression in pregnancy is 5-10%, and up to 20% of pregnant women experience some depressive symptoms (Gotlib *et al*. 1989; Pajulo *et al.* 2001; Burt and Stein 2002; Gavin *et al*. 2005). In the last decade, consumption of the newer antidepressants, including selective serotonin reuptake inhibitors (SSRIs), has been steadily increasing in the population (Finnish Statistics on Medicines 2003). No increased risk of major malformations has been confirmed, but most studies have been based on small numbers of exposed. Several case reports and studies have suggested an increased risk of neonatal complications, related to drug withdrawal or serotonergic

overstimulation, after exposure to SSRIs in the third trimester (Chambers *et al*. 1996; Isbister *et al.* 2001; Costei *et al*. 2002). Severe symptoms in the neonate may also contribute to adverse neurodevelopment (Hernandez-Diaz and de Abajo 2003).

The anti-epileptic drug valproic acid is an established teratogen (Yerby 1994, 2000; Polifka and Friedman 2002). However, adequate treatment of epilepsy and seizure control are important also during pregnancy, and the mother should be treated optimally. At present, valproate is also being used in other medical conditions, including bipolar disorders and migraine prophylaxis (Freitag *et al.* 2002; Viguera *et al.* 2002). Existence of a valproate-specific embryopathy with characteristic malformations has been proposed (Clayton-Smith and Donnai 1995). In addition to malformations, several case reports and studies suggest an increased risk of drug-related adverse effects on neurodevelopment (Koch *et al*. 1996; Adab *et al.* 2001; Kozma 2001). One recent, carefully conducted prospective Finnish study has suggested detrimental effects of intrauterine valproate exposure on the intellectual development of preschool and school-age children (Gaily *et al.* 2004). Hereditary factors may predispose to valproate teratogenicity, as in general, the majority of children are born healthy.

2. REVIEW OF THE LITERATURE

2.1. Drugs as teratogens

2.1.1. History

The role of exogenous agents – other than ionizing radiation – in producing abnormal fetal development in humans was not recognized until 1941, when the association between maternal rubella virus infection and embryo-fetal maldevelopment was established (Gregg 1941). Soon thereafter, experimental studies showed that vitamin deficiency could alter normal morphogenesis (Warkany and Schraffenberger 1943). Furthermore, exposure to certain chemicals and drugs was shown to interfere with normal development in experimental animal studies as well as in human trials (Gillman *et al.* 1948; Thiersch 1952). One decade later, the thalidomide tragedy resulted in the births of 6000 – 8000 malformed babies worldwide, however, this number does not include the probably considerable number of abortions and fetal deaths associated with thalidomide exposure (Lenz 1988; Schardein 2000; Kalter 2003). The first report of a suspected association between thalidomide and severe congenital malformations was published in 1961 by McBride (McBride

1961). Typical malformations were bilateral shortened or missing limbs (phocomelia or amelia), but defects in other organ systems (gastrointestinal, cardiovascular, eye and ear anomalies) were also common (Mellin and Katzenstein 1962; Smithells 1973; Lenz 1988; Shepard 1992; Smithells and Newman 1992). The drug had been tested for teratogenicity in rodents without an apparent risk of producing birth defects and was considered and marketed as safe (Mellin and Katzenstein 1962; Lenz 1990). As a practical consequence, amendments were introduced to tighten control over drugs at the investigational level, and requirements for drug safety testing in animals and humans increased (Anonymous 1962; Tuchmann-Duplessis 1972; Schardein 1988; Schardein 2000; Food and Drug Administration FDA 2005). Furthermore, research in the fields of basic, clinical and epidemiologic environmental teratogenesis increased, and malformation registers and teratology information services were established in many parts of the world to prevent the occurrence of a similar disaster (Clementi *et al*. 2002; Reefhuis *et al.* 2002).

In addition to structural malformations, drugs and chemicals were also observed to be able to induce other adverse effects. Impaired growth and neurodevelopment were associated with ethanol exposure (Jones and Smith 1973; Jones *et al*. 1973). Transplacental carcinogenesis was established upon discovery of an association between a cluster of young women with vaginal adenocarcinoma and exposure to diethylstilbestrol (DES) *in utero* (Herbst and Scully 1970; Herbst *et al.* 1971).

2.1.2. Role of placenta

The fertilized ovum attaches to the uterine endometrium six days after fertilization, and by the end of the third week of development anatomical circumstances necessary for physiological exchanges between the mother and the embryo are established (Scialli 1992; Moore and Persaud 2003). In the human placenta, the circulations of the mother and the fetus are separated by the placental membrane, consisting of a single layer of cytotrophoblasts – partially disappearing as pregnancy proceeds –, syncytiotrophoblasts with the underlying basement membrane, and the fetal capillary endothelial cells (van der Aa *et al.* 1998; Audus 1999; Ganapathy *et al.* 2000). A major function of the placenta is to enable the transfer of oxygen and nutrients from the mother to the fetus, and to eliminate metabolic waste products from the fetus (Enders and Blankenship 1999; Ganapathy *et al*. 2000).

Most endogenous and exogenous substances are transferred across the placenta (Pacifici and Nottoli 1995; Hakkola *et al.* 1998; Audus 1999). Drugs cross the placenta mainly by passive diffusion

(Syme *et al*. 2004; Myllynen *et al*. 2005). Lipophilic, unionized and unbound drugs with a low molecular weight (<500-600 D) cross biological membranes more easily than lipophobic, polar compounds bound to plasma proteins (Pacifici and Nottoli 1995). Drugs with a molecular weight >1000 D cross the membrane very poorly. Since most drugs have a molecular weight <500 D, size rarely limits the rate of drug transfer through the placenta (Pacifici and Nottoli 1995). The placenta also expresses several transporter proteins, which are relevant in nutrient transfer to the fetus and may also actively contribute to the functional barrier between maternal and fetal circulations (Knipp *et al.* 1999; Ganapathy *et al*. 2000). While transporters, such as P-glycoprotein (P-gp), may protect the embryo or the fetus from toxic exposures by actively preventing xenobiotics from entering the fetal compartment, inhibition of function of these proteins may increase fetal susceptibility to drug-induced teratogenicity, and some of them may actually facilitate drug transportation from the mother to the fetus (Audus 1999; Ganapathy *et al*. 2000; Young *et al.* 2003; Ganapathy and Prasad 2005; Mölsä *et al.* 2005). The polymorphism observed in the multidrug resistance 1 (MDR1) gene encoding P-gp and resulting in inter-individual variability in P-gp tissue expression may play a role in determining individual drug response (Fromm 2004). The clinical implications in the human placenta are, however, currently unknown (Young *et al.* 2003).

The human fetus and placenta are capable of metabolizing drugs (Hakkola *et al.* 1996, 1998). Enzymatic drug-metabolizing activity has been documented in the fetal liver as early as the seventh or eighth week of pregnancy (Pelkonen 1973; Blake *et al*. 2005). However, due to the small size of the fetus and low placental enzyme activity, the contribution of feto-placental metabolism to the overall drug elimination capacity is probably minor (Hakkola *et al.* 1998; Loebstein and Koren 2002).

2.1.3. Factors determining teratogenicity

2.1.3.1. Dose and timing of exposure

Teratogenic induction is a dose- and time-dependent phenomenon. The dose-response determines whether a true teratogenic effect exists (Brent 2004a). In addition to the nature of the exposure and the dose, the timing of exposure is critical (Kalter 2003, Brent 2004a). The exposure must occur at a sensitive stage of development to cause malformations (Brent *et al.* 1993). Toxic exposures during the first two weeks after fertilization, i.e. during the pre-differentiation period, are considered unlikely to cause congenital malformations in human embryos, as the cells of the conceptus are pluripotent at this stage, and consequently, cells that are killed can be replaced by other cells

(Polifka and Friedman 2002). However, embryonic death and abortion may occur (Brent and Beckman 1994). During the organogenetic period (weeks 3-8 postconception) the embryo is most sensitive to teratogenic exposures and structural malformations are produced (Polifka and Friedman 2002, Brent 2004a). The harmful exposure must have taken place prior to differentiation of the particular malformed organ if causality between an exposure and structural malformation is suspected.

2.1.3.2. Genetic susceptibility

All species are not equally susceptible to the developmental toxic influence of a given chemical. An agent that is teratogenic in one species may have little or no teratogenic effect in another species, or may produce entirely different defects (Warkany 1947; Jelovsec *et al.* 1989; Brent *et al.* 1993; Brent 2004b). The mechanisms involved in embryonic development differ between species, therefore determining drug-specific susceptibility (Schardein 2000). Similarly, there are genetic differences within species that may influence the teratogenic response (Shepard 1982). Polymorphisms in maternal or fetal genes can modify the individual susceptibility to adverse effects of exogenous agents (Cummings and Cavlock 2004). In humans, genetic predisposition for teratogenicity in the mother has been postulated for several agents (Strickler *et al.* 1985; Dean *et al.* 1999). In addition, polymorphism in fetal drug metabolizing enzyme expression or polymorphism in placental transport protein expression may contribute to individual pharmacological and teratogenic responses in the fetus (Lankas *et al.* 1998; Chen *et al*. 2000; Hakkola *et al*. 2001).

2.1.4. Manifestations of developmental toxicity

A teratogen is defined as any exogenous agent capable of causing abnormal fetal development, mainly structural malformations (Schardein 2000). However, there are several recognized manifestations of developmental toxicity. In addition to malformations deviant development may manifest as growth retardation, embryo-fetal death, functional impairment or transplacental carcinogenesis (Shepard and Fantel 1979; Kalter and Warkany 1983b; Abel 1984; Brent and Beckman 1994; Mittendorf 1995; Mantovani and Calamandrei 2001). The known human teratogenic drugs are presented in Table 1.

2.1.4.1. Definition and prevalence of congenital malformations

Major congenital malformations are defined as physical defects causing a significant functional disturbance and requiring medical or surgical intervention (Kalter 2003). They occur at a frequency of 20-40:1000 live-births (Schardein 2000; Kalter 2003). Minor congenital anomalies are relatively mild physical divergences from the normal, with little or no medical or cosmetic consequence (Kalter 2003). The prevalence of minor congenital anomalies has been reported to vary between 14-45%, depending on what is considered a normal phenotypic variant (Marden *et al.* 1964; Holmes *et al.* 1985; Kalter 2003). The presence of several minor malformations is predictive of a major malformation (Leppig *et al*. 1987). The aetiology of most malformations is unknown. However, drug-induced birth defects are estimated to account only for 1% of all birth defects (Kalter and Warkany 1983a; Kalter 2003; Brent 2004a).

2.1.4.2. Relevance of animal studies to humans

Animal teratology studies are helpful in raising concerns about the reproductive effects of drugs and chemicals. However, negative results in animal studies do not guarantee that these agents are safe in humans (Brown and Fabro 1983; Jelovsek *et al.* 1989). All agents that have produced human developmental toxicity have also been developmental toxicants in some animal species at doses that are not toxic to the mother (Brown and Fabro 1983; Koren *et al.* 1998). Nevertheless, all animal species are not similarly susceptible to human teratogens (Jelovsek *et al.* 1989; Scialli 1992). As an example, thalidomide was not teratogenic in standard teratology testing in rodents but induced malformations in rabbits and non-human primates (Scialli 1992). In an analysis comparing positive and negative teratogenicity testing in animals for their ability to identify human teratogens, animal developmental toxicity tests had a positive predictive value of 75-100% and a negative predictive value of 64-91% (Jelovsek *et al.* 1989; Scialli 1992). Thus, while animal studies can provide valuable information pertaining to vulnerability of chemicals and drugs, they should be interpreted with caution when applied to risk assessment in humans (Brent 2004b).

Table 1. Human drug teratogens.

Drug	Susceptible period	Developmental toxicity	Reference
Androgens	Gestational week 8 onwards	Virilization of external genitalia (female fetus)	Reschini *et al*. 1985
Alkylating agents (cyclophosphamide)	1st trimester	Multiple organ malformations, growth restriction	Ebert *et al*. 1997
Antimetabolites (methotrexate, aminopterin)	1st trimester	Central nervous system and skeletal defects	Thiersch 1952; Polifka and Friedman 2002
Carbamazepine	1st trimester	Neural tube defects	Matalon *et al*. 2002
Coumarin anticoagulants	Gestational week 6 onwards	Abnormal calcification of cartilaginous parts of bone, intracerebral hemorrhagia and scarring	DiSaia 1966; van Driel *et al*. 2002
Diethylstilbestrol	1st and 2nd trimesters	Vaginal adenocarcinoma	Mittendorf 1995
Ethanol	1st-3rd trimesters	Multiple organ malformations, characteristic facial features, impaired growth and mental retardation	Jones and Smith 1973
Fluconazole	1st trimester, high doses	Multiple birth defects, including craniofacial and skeletal defects	Pursley *et al*. 1996
Iodide	Gestational week 10 onwards	Hypothyroidism, goitre	Committee on Drugs, American Academy of Pediatrics 1982
Lithium	1st trimester	Malformations of the heart (Ebstein's anomaly)	Cohen *et al*. 1994
Methimazole	1st trimester 2nd and 3rd trimesters	Esophageal atresia, choanal atresia Fetal goitre and hypothyroidism	Clementi *et al*. 1999
Misoprostol	1st trimester	Limb defects, Möbius syndrome	Fonseca *et al*. 1991; Gonzalez *et al*. 1998; Pastuszak *et al*. 1998
Non-steroidal anti-inflammatory drugs	3rd trimester	Renal failure, premature closure of arteriovenous duct	Peruzzi *et al*. 1999; Butler-O'Hara and D'Angio 2002
Penicillamine	1st trimester	Connective tissue abnormality (loose skin)	Rosa 1986a
Phenytoin	1st trimester	Digital hypoplasia, craniofacial abnormalities	Holmes *et al*. 2001
Drugs acting on the renin-angiotensin system	2nd and 3rd trimesters	Fetal renal tubular dysplasia and renal failure	Brent and Beckman 1991; Barr 1994
Synthetic retinoids	Gestational weeks 4-7	Malformations of central nervous system, heart, face and thymus	Rosa 1986b; Lammer *et al*. 1988
Tetracyclines	2nd and 3rd trimesters	Staining of deciduous teeth	Cohlan 1977
Thalidomide	Gestational weeks 5-8	Limb deficiencies (phocomelia, amelia), multiple organ malformations	McBride 1961; Newman 1985
Valproic acid	1st trimester	Neural tube defects, multiple organ malformations	Clayton-Smith and Donnai 1995

2.1.5. Drug safety classifications during pregnancy

Drug safety classifications group drugs according to fetal safety. The classification is based on human experience, and when unavailable, on animal data. The purpose of these classifications is to give information to health care professionals about possible or established risk or safety of using drugs during pregnancy (Alvan *et al.* 1995; Doering *et al*. 2002). These classifications can also be used in epidemiological research to study drug choice during pregnancy. Significant differences exist between the established classification systems in the distribution of drugs into risk categories (Addis *et al.* 2000). The Swedish classification (Swedish System of Approved Drugs (FASS) 1993) differs considerably from the Food and Drug Administration (FDA) classification (Briggs *et al*. 2002), the latter having been criticized for being of questionable value in clinical settings (Friedman 1993; Sannerstedt *et al*. 1996; Uhl *et al*. 2002). The classification system adopted by the Australian Drug Evaluation Committee (ADEC 1996) is only slightly modified from the Swedish system (Addis et al. 2000) (Table 2). The recently established EU classification divides drugs into ten different categories, and also includes interactions with oral contraceptives and possible male-mediated effects (European Medicines Agency EMEA 2005). This classification is currently under review.

2. 2. Use of drugs during pregnancy

2. 2. 1. General aspects

For the vast majority of drugs, insufficient data exists for reliable assessment of fetal risk (Lo and Friedman 2002). While unnecessary and harmful drug treatments should be avoided during pregnancy, diseases requiring drug treatment must be treated adequately (Czeizel 2001). If left untreated, exacerbation of the mother's illness not only jeopardizes the mother's health but also the well-being of the fetus. According to several studies, drug use during pregnancy is extensive (Olesen *et al.* 1999a; de Vigan *et al.* 1999; Donati *et al*. 2000; Lacroix *et al*. 2000). However, differences in the study methods used to ascertain drug exposure, and heterogeneous categorization of drugs make comparisons of results difficult (Bonassi *et al*. 1994; Nordeng *et al*. 2001a). Socio-demographic factors associated with drug use include maternal illness, smoking, country of residence, education and parity (Buitendijk and Bracken 1991; Rubin *et al*. 1993; Bonassi *et al*. 1994; de Vigan *et al*. 1999), maternal illness obviously being the most important factor in determining drug use (Donati *et al*. 2000; Nordeng *et al.* 2001a).

2. 2. 2. Studies based on interviews

In studies based on interviews, use of OTC drugs and vitamins can be included in the assessment. A collaborative study, under the auspices of the World Health Organization (WHO), assessed drug use during pregnancy in several European countries, also including countries outside Europe (Collaborative Group of Drug Use in Pregnancy (CGDUP) 1991, 1992) (Table 3a). Of the nearly 15 000 women interviewed, 86% had taken at least one drug during pregnancy. The use of most drugs had increased from the first to the third trimester, and the use of drugs classified as potentially harmful or harmful (ADEC categorizations B3, C, D, X), had increased throughout pregnancy (CGDUP 1991) (Table 3b). The study also revealed a number of differences in drug-utilization profiles between countries, reflecting cultural differences in medical care and public health policies (CGDUP 1992).

Large differences between European countries were also found in a multicentre study focusing on first-trimester drug use, in which more than 1000 mothers of healthy newborns were interviewed after delivery (de Vigan *et al.* 1999). In this study, 36% of all women reported drug use during the first trimester, the rate varying from 23% to 50% according to the centre (de Vigan *et al.* 1999) (Table 3a). Two Italian studies showed relatively similar drug exposure profiles (Bonassi et al. 1994; Donati *et al*. 2000), differing from results derived from other European studies (Irl and Hasford 1997; Olesen *et al.* 1999a; de Vigan *et al*. 1999; Nordeng *et al.* 2001a) (Table 3a). A recently published study from Norway reported increasing use of most drug groups with progression of pregnancy (Nordeng *et al*. 2001a). The authors did, however, point out that the study material was collected during 1986-1988 and may not reflect today's practice of drug use in pregnancy (Nordeng *et al.* 2001a).

Table 2. Pregnancy safety classifications. FASS = Swedish classification, ADEC = Australian classification, FDA = American classification.

Classification	*Pregnancy category definition*
FASS	
A	Drugs taken by a large number of pregnant women with no proven increase in the frequency of malformations or other observed harmful effects on the fetus
B1	Limited experience in pregnant women, no increase observed in the frequency of malformations or other observed harmful effects on the fetus Animal studies reassuring
B2	Limited experience in pregnant women, no increase observed in the frequency of malformations or other harmful effects on the fetus Animal studies inadequate or lacking
B3	Limited experience in pregnant women, no increase observed in the frequency of malformations or other harmful effects on the fetus Animal studies have shown evidence of an increased occurrence of fetal damage
C	May cause pharmacological adverse effects on the fetus or neonate
D	Suspected or proven to cause malformations or other irreversible damage on the fetus
ADEC	
A-D	Categories A; B1, B2, B3, C, D similar to the FASS definitions
X	High risk of causing permanent damage to the fetus. Contraindicated in pregnancy
FDA	
A	Controlled studies fail to demonstrate a risk to the fetus in the first trimester. Fetal harm appears remote
B	No controlled studies in humans, animal studies indicate no risk. Well-controlled studies in humans show no risk, and animal studies show an adverse effect on the fetus
C	No controlled studies in women. Animal studies indicate risk or are lacking
D	Existing evidence of fetal risk in humans, benefits may outweigh risks in certain situations
X	Risk clearly outweighs any possible benefit. Contraindicated in pregnancy

Table 3a. Overview of most recent studies on drug use during pregnancy.

Country	Method	Study period	n	Percent of women taking drugs during pregnancy	Mean number of drugs taken	Most commonly used drug group [a]	(%)	Reference
	Studies based on prescriptions and registers							
Denmark	Pharmacy records	1991-1996	16 000	44 [b]	2.6	Anti-infectives Gynecological drugs Anti-asthmatic dugs	22 13[c] 8[c]	Olesen *et al*. 1999a
France	Prescriptions	1995-1996	1000	99	13.6	Gastrointestinal drugs Dermatological drugs Analgesics	69 63 62	Lacroix *et al*. 2000
	Studies based on interviews							
Several countries [d]	Interview and medical records	1987-1988	14 778	86 [e]	2.9	Anti-infectives Analgesics and anti-inflammatory drugs	19 17	Collaborative Group on Drug Use in Pregnancy 1991
USA	Interview (retrospective)	1981-1987	2 752	68 [f]	1.8	Analgesics (including NSAIDs) Antimicrobials Antihistamines	46 19 15	Rubin *et al*. 1993
Italy	Interview (retrospective)	1989-1990	3 268	83 [e]	2.2	Tocolytics Non-narcotic analgesics and NSAIDs Dermatologic drugs	23 9 8	Bonassi *et al*. 1994
Germany	Interview (prospective)	1995-1997	921	84 [e]	4.7	Gastrointestinal drugs Gynecological anti-infectives Cough and cold preparations	22 21 21	Irl and Hasford 1997
Europe [g]	Interview (retrospective)	1989-1992	1134	36 [f, h]	NA	Anti-infectives Antinauseant drugs Treatment for threatened abortion	12 11 6	de Vigan *et al*. 1999
Italy	Interview (retrospective)	1995-1996	9004	75 [e]	1.7	Tocolytics Treatment for threatened abortion Antimicrobials	20 12 5	Donati *et al*. 2000

N=Number of women included
NSAID= Non-steroidal anti-inflammatory drugs
N A= Not assessed
[a]Percentage of women using the drug (excluding vitamins and minerals)
[b]Excluding vitamin and mineral supplements and over-the counter (OTC) drugs
[c]Reported as percentage of all prescriptions
[d]Europe, Asia, Central and South America, Africa
[e]OTC drugs, vitamins and minerals included
[f]OTC drugs included
[g]Several countries in Europe
[h]Only first trimester use

2. 2. 3. Studies based on prescription and pharmacy registers

Register-based studies are cost-effective and allow large population-based samples to be analysed. In addition, recall bias present in studies based on interviews can be avoided. However, complete data on drug intake are lacking. Register-based studies include only prescription drugs, and therefore, the use of OTC drugs and herbal medicines can not be assessed.

No previous register-based studies investigating overall prescription drug use during pregnancy in the Finnish population have been published. In a large Danish study based on pharmacy records and including 16 000 pregnant women, 44% of the women received prescriptions for one or more drugs during pregnancy (Olesen *et al.* 1999a) (Table 3a). The majority of prescriptions (29%) were for antibiotics. Anti-epileptic drugs were prescribed in a constant manner throughout pregnancy, but no data were given regarding possible changes in utilization of drugs for other chronic illnesses such as asthma or diabetes (Olesen *et al.* 1999a).

2. 2. 4. Pharmacoepidemiological studies on drug use assessing fetal risk according to drug safety classifications

A study based on the material of their previous report (Olesen *et al.* 1999a) assessed potential risks related to drug use in pregnancy using the FASS classification (Olesen *et al*. 1999b). Prescriptions for drugs considered safe (category A) had increased, while prescriptions for potentially harmful drugs (categories B3, C and D in the study, see Table 2), filled by nearly 20% of pregnant women, were prescribed less often during the course of pregnancy (Olesen *et al.* 1999b) (Table 3b).

A recently published study from France showed that 99% of women received one or more prescription drugs during pregnancy, the average number of different drug preparations being 13.6 per woman (Lacroix *et al*. 2000). In this study, 59% of pregnant women had received one or more prescriptions for drugs belonging to FDA category D (positive evidence of human fetal risk but benefits in pregnant women deemed acceptable), and 1.6% had received prescriptions for drugs contraindicated in pregnancy (Lacroix *et al*. 2000) (Tables 3a and 3b). Furthermore, 78.9% of pregnant women had received prescriptions of drugs for which there were no data available for safety in pregnancy (Lacroix *et al*. 2000). The authors concluded that too many pregnant women are exposed to drugs with established or unknown risk, and emphasized the need for continuous monitoring of drug use during pregnancy.

Table 3b. Pharmaco-epidemiological studies assessing drug use during pregnancy according to safety classifications.

Country	Method	Study period	n	Drug safety classification used	Drug use according to safety categorization (%) [a]	Trends during pregnancy	Reference
Several countries [b]	Interview after delivery and medical records [c]	1987-1988	14 778	ADEC	B3 3 C 7 D 1 X -	Increasing trend in use of drugs in all categories with advancing pregnancy	Collaborative Group on Drug Use in Pregnancy 1991
Denmark	Pharmacy records	1991-1996	15 756	FASS	B3, C, or D 17.8	Increasing trend in prescriptions of safer drugs and decreasing trend in prescriptions of drugs with (potential) risks	Olesen *et al*. 1999b
France	Prescriptions	1995-1996	1000	FDA	A 80 B 95 C 85 D 59.3 X 1.6 No classification 78.9	N A	Lacroix *et al*. 2000

ADEC = Australian risk classification
FASS = Swedish classification
FDA = Food and Drug Administration classification
N A = not assessed
[a] Percentage of pregnant women using drugs in different safety categories. For clarification see Table 2
[b] Europe, Asia, Central and South America, Africa
[c] First trimester use

2. 3. Safety of the selective serotonin reuptake inhibitors during pregnancy

2. 3. 1. General aspects

The prevalence of major depression during pregnancy is approximately 10%, and up to 20% of pregnant women have definable depressive symptoms (O'Hara 1986; Gotlib *et al.* 1989; Pajulo *et al.* 2001; Burt and Stein 2002). Non-medical treatment is effective especially in mild and moderate major depression, but antidepressants are also often needed. The selective serotonin reuptake inhibitors (SSRIs: fluoxetine, citalopram, paroxetine, sertraline and fluvoxamine) are used primarily to treat depression and anxiety disorders (Masand and Gupta 1999). They have a favourable side-effect profile, and accordingly, are being used increasingly (Goldstein and Goodnick 1998). However, no epidemiologic studies evaluating the use of SSRIs in the pregnant population have been conducted. Several studies assessing the safety of SSRIs in pregnancy have been based on relatively small subject pools (Pastuszak *et al.* 1993; Chambers *et al.* 1996; Kulin *et al*. 1998; Chambers *et al*. 1999). Furthermore, study designs and methods for detecting adverse pregnancy outcome have varied, making it difficult to draw conclusions. If the safe use of an antidepressant during pregnancy has not been established, physicians may hesitate in prescribing it to pregnant women even when clearly indicated. Moreover, inadequate treatment of maternal major depression may lead to worsening of the condition, and discontinuation of maintenance antidepressant treatment is associated with high rates of relapse (Nonacs and Cohen 2002).

2. 3. 2. Risk of major malformations

No definitive evidence of an increased risk of malformations associated with the use of SSRI drugs has been reported to date. While most data concern fluoxetine and citalopram, less is known about paroxetine, sertraline and fluvoxamine. The rate of major malformations was no higher in infants exposed to fluoxetine in the first trimester than in the non-exposed control group in two studies based on prospectively collected exposure data (Pastuszak *et al*. 1993; Chambers *et al*. 1996). In one of these studies, the presence of three or more minor malformations was more common in the exposed infants than in non-exposed controls (Chambers *et al*. 1996). However, no pattern of malformations was recognized. The authors stated that, in general, infants with three or more minor malformations are at increased risk of having an associated major malformation (Chambers *et al*. 1996). As some major malformations may stay occult, such as defects in brain development, this finding could raise concerns of an associated developmental defect in the central nervous system, detected only later in life (Chambers *et al*. 1996). No increased risk of major malformations was

found in the fluoxetine pregnancy registry maintained by the manufacturer and including nearly 800 first-trimester exposures (Goldstein *et al*. 1997). However, the lost-to-follow-up percentage in that study was nearly 40% and may have biased the results. A large register-based study with exposure data collected prospectively to outcome did not reveal an increased risk of major malformations among infants exposed to SSRIs in the first trimester (Ericson *et al*. 1999). The majority of exposures were for citalopram (375 pregnant women). However, pregnancy terminations due to fetal malformation were not included (Ericson *et al.* 1999). Data evaluating the safety of the other SSRIs are less abundant, but no increased risk of major malformations has thus far emerged (Kulin *et al.* 1998; Chambers *et al*. 1999; Diav-Citrin *et al* 2002). Data on studies assessing SSRI safety during pregnancy are summarized in Table 4.

2. 3. 3. Preterm birth and low birth weight

Two studies based on relatively small numbers of subjects have suggested an increased risk of preterm birth (<37 gestational weeks) (Chambers *et al*.1996; Costei *et al*. 2002) or birth at or below 36 gestational weeks (Simon *et al*. 2002) in women using SSRIs during pregnancy (Table 4). A cohort study with 531 women exposed to SSRIs found that preterm birth was more common in the exposed cohort but also in the cohort using other antidepressants, when compared with the population-based control cohort (Ericson *et al*. 1999). Data were based on confirmed first, or early second-trimester exposure. A correlation between exposure to SSRIs and low birth weight (< 2500 g) has been proposed (Chambers *et al*. 1996). However, because of the small subject pool and the methodological limitations regarding the control cohort, no definitive conclusions can be made.

2. 3. 4. Neonatal complications

Several case reports and case series have described neonatal adverse events after prenatal SSRI exposure (Dahl *et al*.1997; Mohan and Moore 2000; Nordeng *et al*. 2001b; Stiskal *et al*. 2001). Typical symptoms include irritability, jitteriness, increased muscle tone and feeding problems and, less frequently, more severe symptoms manifesting as convulsions (Mohan and Moore 2000). The symptoms may be caused either by abrupt drug withdrawal or by a toxic serotonergic effect on the newborn (Isbister *et al*. 2001). Two controlled studies with small numbers of subjects found that admittance to special care nursery was more common in infants exposed late in pregnancy than in controls (Chambers *et al*. 1996; Cohen *et al*. 2000). In addition, in a prospective cohort study, neonatal complications necessitating intensive care treatment were observed in 12 of 55 new-borns

Table 4. Studies assessing safety of selective serotonin reuptake inhibitors during pregnancy.

Drug	Number of women exposed during 1st trimester/total number of exposed	Study design	Malformations	Observed increased risk of adverse perinatal outcome other than malformations	Reference
Fluoxetine	128	Prospective controlled study	-	-	Pastuszak *et al*. 1993
Fluoxetine	164/228	Prospective controlled study	Increased risk of minor malformations	Admittance to special care nursery and poor neonatal adaptation Preterm birth Lower birth weight	Chambers *et al*. 1996
Fluoxetine	796/2072	Prospective, historical control group	-	N A	Goldstein *et al*. 1997
Sertraline, paroxetine, fluvoxamine	267	Prospective controlled study	-	-	Kulin *et al*. 1998
Citalopram, paroxetine, sertraline	531	Register-based controlled cohort study with prospectively collected exposure data	-	Preterm birth	Ericson *et al*. 1999
Fluoxetine	11/64	Retrospective (medical records)	N A	Admittance to special care nursery	Cohen *et al*. 2000
Paroxetine	N A/55	Prospective controlled study	N A	Admittance to neonatal intensive care unit Preterm birth	Costei *et al*. 2002
Citalopram	10/11	Prospective controlled study	-	-	Heikkinen *et al*. 2002
Fluoxetine, Sertraline, paroxetine	N A/185	Retrospective (hospital and pharmacy records)	-	Birth at or before 36 weeks of gestation Lower mean birth weight Low Apgar score	Simon *et al*. 2002

- = not observed
N A = not assessed

exposed to paroxetine during the third trimester, compared with only three of 54 infants in the control group (Costei *et al*. 2002).

2. 3. 5. Long-term neurodevelopment

Major concerns of prenatal exposure to SSRI drugs include neonatal neurologic symptoms and possible adverse effects on the developing central nervous system. No conclusive evidence of increased risk of adverse long-term effects exists at present. Two studies assessing neurodevelopment in pre-school and school-age children and with partially overlapping study subjects did not find differences in global intelligence quotient (IQ) or language or behavioural development compared with non-exposed controls, or with children exposed to tricyclic antidepressants (Nulman *et al.* 1997, 2002). Furthermore, normal neurodevelopment was observed in a one-year follow-up of 11 infants exposed to citalopram during pregnancy in a prospective, controlled study (Heikkinen *et al*. 2002). Longer-term outcome was not, however, assessed.

2. 4. Risks associated with valproic acid use during pregnancy

2. 4. 1. Epilepsy and pregnancy

The population prevalence of epilepsy in Finland is 0.7% (The Social Insurance Institution in Finland KELA 2005) and similar figures have been reported in other countries (Bell and Sander 2001). The use of major anti-epileptic drugs (valproate, carbamazepine, phenytoin and phenobarbital) during pregnancy is associated with a two- to threefold increase in congenital malformations in the offspring (Lindhout *et al*. 1992; Yerby 1993). Studies involving women with a seizure history but no anti-epileptic drug treatment indicate that the risk is associated with anti-epileptic drug use rather than epilepsy itself or type of epilepsy (Jick and Terris 1997; Holmes *et al*. 2001). Anti-epileptic drugs differ in their mode of action and specificity on epilepsy type. Valproic acid is mainly used for generalized tonic-clonic seizures and partial seizures (Brodie and Dichter 1997; Feely 1999). Convulsive seizures may harm the fetus by maternal abdominal trauma or by reducing placental blood flow and impairing fetal oxygenation (Teramo *et al*. 1979; Zahn 1998). Consequently, avoidance of seizures is important also for the well-being of the fetus.

2. 4. 2. Risk of major malformations

An association between caudal neural tube defects (spina bifida) and fetal exposure to valproate was observed in 1982 in a case-control study (Robert and Guibaud 1982), and has subsequently been confirmed in cohort and other case-control studies (Omtzigt *et al* 1992; Samren *et al*. 1997, 1999; Canger *et al*. 1999; Arpino *et al*. 2000; Rodriguez-Pinilla *et al*. 2000). The estimated prevalence of spina bifida in children born after early fetal exposure to valproate is 1-2% (Lindhout and Schmidt 1986). In addition to a dose-dependent risk of major malformations with daily valproate doses above 1000 mg, an increased risk associated with polytherapy including valproate has been confirmed in several studies (Lindhout *et al*. 1992; Samren *et al*. 1997, 1999; Kaneko *et al*. 1999).

Other major malformations associated with valproate exposure include cardiac defects, urogenital malformations and skeletal and limb defects (Clayton-Smith and Donnai 1995; Arpino *et al*. 2000; Rodriguez-Pinilla *et al*. 2000). Occurrence of a specific valproate-related syndrome in children exposed to valproate *in utero* has been suggested, with characteristic facial dysmorphism, neural tube defects, cardiac and genitourinary malformations and developmental delay (DiLiberti *et al*. 1984; Christianson *et al*. 1994; Clayton-Smith and Donnai 1995). However, many of these malformations also occur after exposure to other anti-epileptics, thus lacking the relative specificity that neural tube defects have to valproate (Zahn *et al*. 1998).

Studies assessing valproate teratogenicity have frequently been limited by the small number of exposed pregnant women or by methodological issues concerning retrospective ascertainment of cases. Furthermore, characteristics of the control groups have varied between studies. The most recent epidemiological studies on valproate and malformations are summarized in Table 5.

2. 4. 3. Developmental delay

Several studies based on small numbers of cases suggest an increased risk of long-term neurocognitive sequelae among the offspring of mothers with epilepsy and anti-epileptic drug treatment (Granström and Gaily 1992; Scolnik *et al*. 1994). Psychosocial factors and seizure activity – rather than exposure to anti-epileptic drugs – have been speculated to play an important role in determining the level of cognitive development (Gaily *et al*. 1990). However, a number of case reports and case series have indicated increased risk of developmental delay after exposure to valproate *in utero* (DiLiberti *et al*. 1984; Clayton-Smith and Donnai 1995; Koch *et al*. 1996; Moore *et al*. 2000; Kozma 2001). Neonatal withdrawal symptoms are common after prenatal exposure to

valproate, and neurological symptoms observed in the newborn have been suggested to correlate with neurological dysfunction in pre-school-age children (Koch *et al*. 1996). One retrospective study comprising 400 schoolchildren assessed additional educational needs in a cohort of children of epileptic mothers (Adab *et al*. 2001); additional needs were reported more often in the group of children exposed to valproate monotherapy (n=56) than in non-exposed children (OR 3.4, 95% CI 1.63-7.10). No association was observed for exposure to carbamazepine (Adab *et al*. 2001). However, factors such as parents' socio-economic and educational status and seizure burden were not controlled and may have biased these observations (Adab *et al*. 2001).

2. 4. 4. Role of folic acid

Observational studies (Smithells *et al*. 1983; Milunsky *et al*. 1989) and randomized clinical trials (MRC Vitamin Study Research Group 1991; Czeizel and Dudas 1992; Berry *et al*.1999) have confirmed a protective role of maternal folic acid supplementation against neural tube defects in the general population. Whether the risk is reduced for epileptic women taking anti-epileptic drugs is unclear (American Academy of Neurology 1998). Several case reports have been published of infants born with neural tube defects after exposure to valproate despite the mother's folic acid supplementation (Craig *et al*. 1999; Duncan *et al*. 2001). However, a recent case-control study suggested that folic acid supplementation in pregnant women taking anticonvulsants (carbamazepine) may reduce the risk of neural tube defects (Hernandez-Diaz *et al*. 2001). In addition to the small number of exposed cases in that study, methodological problems included bias of recall and timing of exposure (Hernandez-Diaz *et al*. 2001). Animal studies suggest altered folate metabolism in valproic acid exposed embryos (Wegner and Nau 1992). In humans, enzyme-inducing anti-epileptics such as carbamazepine, phenytoin and phenobarbital, reduce serum or erythrocyte folate levels, whereas no reduction has been observed even after prolonged treatment with non-enzyme-inducing valproate (Kishi *et al*. 1997; Apeland *et al*. 2000).

Table 5. Epidemiological studies assessing valproate teratogenicity.

Country	Method	Study period	Number of pregnancies exposed to valproate/ other anti-epileptics	Prevalence of major malformations in valproate-exposed pregnancies (%)	Relative risk (95% CI)	Additional findings and comments	Reference
Several countries	Prospective Pooled data from five studies Non-epileptic control group	1971-1990	184/1221	8.7	4.9 (1.6-15.0) [a]	Increased risk with VPA doses above 1000mg Increased risk with polytherapy including VPA Pregnancy terminations due to major malformation included only in data from 2 centres	Samren *et al*. 1997
The Netherlands	Retrospective Non-epileptic control group	1972-1994	158/1411	5.7	4.1 (1.9-8.8)	Increased risk with VPA doses above 1000mg Increased risk with polytherapy including VPA Pregnancy terminations due to major malformation included	Samren *et al*. 1999
Several countries (Japan, Italy, Canada)	Prospective	1978-1991	167/983	11.1	No control group	Increased risk with VPA doses above 1000mg/day Increased risk with polytherapy including VPA	Kaneko *et al*. 1999
Italy	Prospective	1977-1996	44/ 517	15.9	No control group	Pregnancy terminations due to major malformations included	Canger *et al*. 1999

[a] Relative risk derived from a pooled analysis of 21 valproate-exposed children compared with non-exposed controls

2. 4. 5. Genetic susceptibility

Why the majority of children born to mothers using valproate during pregnancy are born healthy while others are severely handicapped is unknown. Genetic differences in maternal folic acid metabolism may increase the risk of fetal adverse effects associated with maternal anticonvulsant treatment (Dean *et al*. 1999). Several reports of sibling pairs with developmental defects consistent with valproate embryopathy are available in the literature (Di Liberti *et al*. 1984; Winter *et al*. 1987; Christianson *et al*. 1994; Espinasse *et al*. 1996; Janas *et al*. 1998; Kozma 2001), suggesting genetically determined susceptibility to valproate teratogenicity.

3. AIMS OF THE STUDY

The purpose of this research project was to study, mainly by using nationwide registers, use of prescription drugs during pregnancy, and possible fetal risks associated with gestational use of drugs.

Specific aims were:

1. To investigate the use of prescription drugs, irrespective of their teratogenic potential, in pregnant women.
2. To evaluate potential risks related to drug use during pregnancy by using drug classifications for safety during pregnancy.
3. To assess fetal and newborn risks related to prenatal exposure to selective serotonin reuptake inhibitors.
4. To describe and determine the aetiology of developmental defects and overlapping multiple malformations in three sets of siblings exposed to valproic acid *in utero*.

4. MATERIALS AND METHODS

4. 1. Definitions

4. 1. 1. Major malformations

The National Register of Congenital Malformations defines a major congenital malformation as a significant congenital structural anomaly, chromosomal defect or congenital hypothyroidism, using the exclusion list of minor congenital anomalies as specified in the European Surveillance of Congenital Anomalies (EUROCAT) definitions (EUROCAT 2005; National Research and Development Centre for Welfare and Health STAKES 2005).

4. 1. 2. Preterm birth

Preterm birth is defined as birth ending before 37 gestational weeks.

4. 1. 3. Small for gestational age

Small for gestational age is defined as birth weight of more than 2 standard deviations (SD) below the sex- and length-of-gestation-specific national standards (Pihkala *et al*. 1989).

4. 1. 4. Low birth weight

Low birth weight is defined as birth weight below 2500 g.

4. 2. Use of prescription drugs during pregnancy (Studies I and II)

4. 2. 1. Register data

The majority of the data in Studies I and II were derived from three nationwide registers (Tables 6 and 7).

Table 6. Summary of study materials and methods.

Study	Materials and methods	Focus	Number included in the study
I, II	Linkage of Maternal Grants Register Finnish Population Register Drug Reimbursement Register (including the Special Refund Register)	Use of prescription drugs during pregnancy Prescription of hazardous drugs during pregnancy	43 470 cases 43 470 controls
III	Data used in the study derived from a national joint project, linking the Medical Birth Register National Register of Congenital Malfomations National Register of Induced Abortions Finnish Cause-of-Death Statistics Drug Reimbursement Register (including the Special Refund Register)	Safety of selective serotonin reuptake inhibitors during pregnancy	1782 cases 1782 controls
IV	Evaluation of families and medical records	Aetiology of overlapping multiple malformations observed in all siblings	Three families with seven children

The Maternal Grants Register, maintained by the Social Insurance Institution of Finland (Kansaneläkelaitos, KELA), contains data on all women who have applied for maternal grants. Grants are provided when the mother has visited a maternity clinic before the end of the fourth month of pregnancy. Data were collected on all women applying for maternal grants in 1999. To rule out the influence of previous pregnancies or lactation on practice of drug use, women who had applied for maternity grants during the 24 months preceding the beginning of the pregnancy now studied were excluded; 43 470 pregnant women were thus included. The beginning of the first trimester was calculated by subtracting 40 weeks from the estimated delivery date recorded in the register data. After the child is born, the date of birth is added to the register, marking the end of pregnancy.

Controls were collected from the Finnish Population Register. For each pregnant woman, one female control was randomly selected from women matched by age and hospital district, who had not applied for a maternity grant during the period from 24 months before her case's pregnancy to the end of the year 2000.

The Drug Prescription Register maintained by KELA comprises data on 97%-98% of all reimbursed prescriptions (Finnish Statistics on Medicines 1999, 2003) (Table 7). In Finland, prescription-only medicines deemed necessary for the treatment of an illness are reimbursed under the Health

Insurance Scheme. Some OTC drugs are also reimbursable when prescribed by a physician. The Prescription Register contains a special code for specially refunded drug purchases. Patients with specified chronic diseases (about 50 diseases total) are entitled to special refunds for drug treatment costs. Every person entitled to special refunds is recorded in the Special Refund Register, KELA (Finnish Statistics on Medicines 1999). Drug purchases were recorded using the date of purchase, and drugs were coded according to the Anatomic Therapeutic Chemical (ATC) classification system, year 2000 (Finnish Statistics on Medicines 1999; ATC 2000).

Table 7. Data quality and coverage of the registers used in Studies I-III.

Register	Quality or coverage of data	Reference
Maternal Grants Register	All pregnant women applying for maternal grants	Statistical Yearbook of the Social Insurance Institution, Finland 2000
Finnish Population Register	All Finnish citizens and those with permanent residence in Finland	Population Register Centre 2005
Drug Reimbursement Register	97-98% coverage of all reimbursed prescriptions	Finnish Statistics on Medicines 1999, 2003
Medical Birth Register	Coverage close to 100% Data quality good	Teperi 1993; Gissler *et al*. 1995
National Register of Congenital Malformations	Data quality considered good	STAKES 2005
National Register of Induced Abortions	Coverage close to 100%	Gissler *et al*. 1996
Cause-of-Death Statistics Finland	Covers all deaths in Finland	Statistics Finland 2005

4. 2. 2. Study design

The linkage of all three registers was done using the unique identification number (coded in a concealed form for study purposes) assigned to all Finnish citizens and those with permanent residence in Finland. Claims data of the study population (cases and non-pregnant controls) were analysed in time periods of three months before pregnancy, during pregnancy (divided into three trimesters; weeks 0-12, 13-26 and 27 onwards) and three months post-partum.

4. 2. 2. 1. Categorization of drugs according to risk classification during pregnancy

Each fifth-level ATC code was linked to the corresponding pregnancy safety code using primarily the Swedish classification (FASS 1999, 2000). If there was no FASS categorization for a drug, the Australian classification (ADEC 1996) was used, and when neither existed, the American classification (FDA) was used (Briggs *et al*. 2002). Drugs were grouped as 'probably safe' (FASS and ADEC gategories A, B1 and B2, and FDA categories A and B), 'potentially harmful' (FASS and ADEC categories B3 and C, and FDA category C) and 'clearly harmful' (FASS category D, and ADEC and FDA categories D and X) (Table 2).

4.3. Risks associated with the selective serotonin reuptake inhibitors during pregnancy (Study III)

4. 3. 1. Register data

The majority of the data in Study III were derived from five nationwide registers (Tables 6 and 7).

Data were derived from a national joint project in Finland, established by three governmental organizations (STAKES, KELA and the Finnish National Agency for Medicines) for continuing surveillance of drug-related safety during pregnancy. In the project, the following registers have been linked by the unique identification number assigned to all citizens.

4. 3.1.1. Medical Birth Register

The Medical Birth Register collects maternal background data, maternal pregnancy-related medical data, delivery data (live births and stillbirths) and neonatal outcome data, including malformations, until the age of 7 days. All births of infants or fetuses with gestational age of at least 22 weeks or birth weight of 500 g or more are included in the register. Data for the register are collected from all maternity hospitals, and in the case of home births, from the assisting midwife or physician. The register data are forwarded to STAKES and missing data are supplemented by information from birth and death certificates.

4. 3. 1. 2. National Register of Congenital Malformations

The National Register of Congenital Malformations defines a major congenital anomaly as a significant congenital structural anomaly, chromosomal defect or congenital hypothyroidism, using the European Surveillance of Congenital Anomalies (EUROCAT) exclusion list of minor anomalies, as specified in the EUROCAT definitions (EUROCAT 2005; STAKES 2005). The registry collects information from the whole of Finland on all newborn infants with a birth defect, using several data sources (STAKES 2005). In case of a malformation, the delivery units are obliged to complete and forward a special data collection form to the Malformation Register. Data on diagnosis are also collected and confirmed from the Medical Birth Register, the Hospital Discharge Register and the Cause-of-Death Register and from cytogenetic laboratories until the age of one year (STAKES 2005). In addition to maternity hospitals, health care professionals in outpatient clinics, such as child welfare clinics, may provide cases that have been detected after discharge from the delivery unit to the register. All pregnancy terminations due to fetal malformation are also recorded in the register (Table 7).

4. 3. 1. 3. National Register of Induced Abortions

According to the national legislation in Finland, termination of pregnancy is allowed until the end of the 20th gestational week for social reasons, and until the end of the 24th gestational week if a serious fetal malformation has been detected. Notification of pregnancy termination must be sent to the registry within one month after the termination. The register covers more than 99% of induced abortions registered in the hospital records (Gissler *et al*. 1996) (Table 7).

4. 3. 1. 4. Drug Reimbursement Register

The Drug Reimbursement Register contains data on 97-98% of reimbursed prescription drug purchases, and data on chronic illnesses requiring continuous drug treatment (Finnish Statistics on Medicines 1999, 2003) (Table 7).

4. 3. 1. 5. Cause-of-Death Statistics

The Cause-of-Death Statistics complied by Statistics Finland includes information on all postnatal mortalities (Table 7).

4. 3. 2. Defining length of gestation and pregnancy trimesters in the national project database

The estimated length of gestation at delivery – based on the last menstrual period and ultrasound examination – is recorded in the Medical Birth Register. In the national joint project, the beginning of pregnancy has been defined by subtracting the number of days corresponding to gestation length from the date of birth. In the combined database, data on drug purchases have been collected during preconception (three months before pregnancy), each pregnancy trimester and three months postpartum. Pregnancy trimesters have been defined as 0-12 weeks (first trimester), 13-26 weeks (second trimester) and from week 27 onwards (third trimester). A total of 405 892 anonymous mother - child/ fetus- pairs have been registered in the database during the period of 1996-2001.

4. 3. 3. Study design

The study material was derived from the joint research project database described in 'Materials and Methods' 4.3.1. and covers the years 1996-2001. All data in the research register are anonymous.

Cases were defined as women who made at least one purchase of a SSRI drug (defined by the fourth level ATC code) from one month preceding pregnancy to the day when pregnancy ended (n=2077). Only singleton pregnancies were included in the study. Women with chronic illnesses requiring continuous medication (e.g. hypertension, epilepsy, psychosis) were excluded from the analysis (n=273). Another 22 cases were excluded because their matched pair in the control group had a chronic illness. After exclusion, a total of 1782 cases were remained.

Controls were women with no reimbursed drug purchases during the time period from one month before pregnancy to the end of pregnancy. They were first matched with cases by year of pregnancy ending, age, parity (no previous deliveries or one or more previous deliveries), geographical area (university hospital district), and social status. Matching was then done on a one-to-one basis by randomly selecting one control for each case from the case-specific matched control pool.

Low birth weight was defined as birth weight below 2500 g and was considered only in the analysis of birth register cases. Small for gestational age was defined as birth weight of more than 2 SD below the sex- and length-of-gestation-specific national standards (Pihkala *et al*. 1989) and was considered only in the analysis for birth register cases. In the Medical Birth Register, only 1-minute Apgar score is recorded. A low Apgar score was defined as a score < 7. The social class of the mother is recorded in the Medical Birth Register in a form modified from the coding system used by Statistics Finland (Statistics Finland 2005). In the study, a crude social distinction was used by grouping upper officials in one category and lower officials, workers, students and housewives in another category.

The study protocol was approved by the national health authorities, STAKES, and the Finnish Data Protection Authority in conjunction with establishment of the joint research project.

4. 4. Valproate embryopathy (Study IV)

In Study IV, three families were evaluated at a genetics clinic to determine the aetiology of multiple malformations and the developmental deficit among the siblings. In addition to clinical evaluation of the children and their parents, medical records of the children and their mothers were reviewed.

4. 5. Statistics (Studies I-III)

In Study I, pregnant women served as their own controls when assessing changes in the drug-purchasing pattern during each trimester, and they were also compared with matched controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by using Chi square cross-tabulation.

In Study II, changes in the drug-purchasing pattern between different trimesters were calculated by using the McNemar test (two-sided) on dichotomic variables (use or no use) for a time-dependent association. ORs and 95% CIs were calculated by cross-tabulation using the Chi square distribution. These tests were also used when comparing pregnant women with non-pregnant controls. Data were analysed with SPSS 8.0 for Windows.

In Study III, the McNemar test for categorical variables and paired t-tests for continuous variables were used in comparisons between one-to-one matched case-control pairs. In comparisons between different subgroups of cases and all controls, or cases with only first-trimester purchase(s), univariable analysis to study differences between proportions was performed using Chi square test or Fischer's exact test for dichotomous variables and t-test for continuous variables (all two-tailed). Variables found to differ between the study and control groups ($P<0.1$), and those that could be expected to confound the association between other independent variables and dependent variables, were included in the multivariable analysis. Logistic regression analysis was carried out applying major malformations, low Apgar score, treatment in special or intensive care unit, low birth weight and small for gestational age as dependent outcome variables. Independent variables in the model were purchase(s) of SSRIs, social status, smoking, artificial reproductive techniques (ART), previous deliveries, age and other purchased medications. All variables were entered simultaneously. Logistic regression analysis was performed between different subgroups of cases or between subgroups of cases and all controls. Crude and adjusted ORs and their 95% CIs were calculated. The statistical analyses were performed using SAS version 8.2 statistical software. Statistical significance was set at $P < 0.05$ (two-tailed).

5. RESULTS AND DISCUSSION

5. 1. Use of prescription drugs during pregnancy (Studies I and II)

5. 1. 1. Reimbursements during pregnancy and lactation (Study I)

Mean age of the 43 470 pregnant women and controls was 27.9 (range 15-50) years and mean length of gestation was 39.3 (range 22-44) weeks. The prevalence of chronic diseases entitling patients to special refunds of medicine costs was generally higher among the controls than in the pregnant women, with the exception of astma and thyroid insufficiency, which were equally common in both cohorts (Table 8).

During the period corresponding to pregnancy 20 083 pregnant women (46.2%) *versus* 23 985 controls (55.2%) purchased one or more drugs (OR 0.7, 95% CI 0.6-0.7). The mean number of different drugs bought during pregnancy was 2.1 in the pregnant cohort and 2.8 in the control cohort. Of the pregnant women, 5508 (12.7%) purchased three or more different drugs *versus* 10 012 (23.0%) controls (OR 0.5, 95% CI 0.5-0.5); this difference was statistically significant during all stages corresponding to pregnancy trimesters and three months post-partum. The most frequently purchased drugs during pregnancy were antibacterials for systemic use (ATC J01; 24.1% of pregnant women *vs*. 27.3% of controls), which were purchased by 9.6% of pregnant women during the first trimester. Gynecological anti-infectives were the second most frequently purchased drugs during pregnancy (ATC G01; 8.3% of pregnant women *vs*. 1.5% of controls). These drugs were purchased less often by controls than by pregnant women throughout pregnancy.

The use of overall prescription drugs during pregnancy, and the mean number of different drugs per user, were similar to that observed in another Scandinavian population-based study (Olesen *et al*. 1999a). Much higher numbers were reported in a study from France (Lacroix *et al*. 2000). In that study, 99% of pregnant women used one or more prescribed drugs, and the mean number of different drugs taken was 13.6 (Lacroix *et al*. 2000). The diverging observations reflect different drug-prescribing patterns between countries.

Table 8. Number and percentage of pregnant women and non-pregnant controls (43 470 each) entitled to special reimbursement of medicines for certain chronic diseases at the end of 1998.

Diagnosis	Pregnant women n (%)	Controls n (%)	Odds Ratio (95% CI)
Asthma and similar obstructive pulmonary diseases	1144 (2.6)	1113 (2.6)	1.0 (0.9 -1.1)
Thyroid insufficiency	357 (0.8)	316 (0.7)	1.1 (1.0 -1.3)
Epilepsy	309 (0.7)	531 (1.2)	0.6 (0.5 -0.7)
Rheumatoid arthritis and comparable diseases	231 (0.5)	300 (0.7)	0.8 (0.6 -0.9)
Diabetes mellitus	208 (0.5)	298 (0.7)	0.7 (0.6 -0.8)
Hypertension	191 (0.4)	285 (0.7)	0.7 (0.6 -0.8)
Ulcerative colitis and Crohn´s disease	163 (0.4)	212 (0.5)	0.8 (0.6 -0.9)
Severe psychotic and other severe mental disorders	89 (0.2)	427 (1.0)	0.2 (0.2 -0.3)

The use of systemic antibacterials has been similar to our observations in several studies (Olesen *et al*. 1999a; Andrade *et al*. 2004; Schirm *et al*. 2004). However, in a French study covering a cohort of 1000 women, more than 50% received a prescription for antimicrobial agents during pregnancy (Lacroix *et al*. 2000). Although many of the older preparations in this group are considered safe during pregnancy, recent data suggest that trimethoprim exposure in early pregnancy may be associated with an increased teratogenic risk (Hernandez-Diaz *et al*. 2000, 2001). Several of the gynecological anti-infectives in Finland are OTC drugs and their use may have been even more extensive than seen in our study, which included only prescription drugs. Much higher percentages have been reported in studies from France and Germany (Lacroix *et al*. 2000; Egen-Lappe and Hasford 2004). Persistent bacterial vaginosis is a known risk factor for preterm delivery and, consequently, infant morbidity and mortality. However, routine screening and treatment have not proven beneficial (Kekki *et al*. 2001).

Antidepressants were purchased by fewer pregnant women than by controls in all time periods concerned, but serious psychiatric disorders were also less common in the pregnant cohort (Table 8). Of the pregnant women, 1.4% purchased antidepressants during the preconception period, the proportion declining to 0.7% in the first trimester and to 0.3% in the third trimester, and increasing again during lactation (to 0.7%). A statistically significant reduction was also observed in the

number of women purchasing several other drug groups during the first trimester as compared with three months' preconception. These included drugs for peptic ulcer (ATC A02; 0.9% *vs*. 0.6%), sex hormones and modulators of the genital system (G03; 5.4% *vs*. 4.2%), systemic antimicrobials (J01; 12.1% *vs*. 9.6%) , systemic antimycotics (J02; 1.9% *vs*. 0.7%), anti-inflammatory drugs (M01; 5.1% vs. 1.9%) and antipsychotics, anxiolytes, hypnotics and sedatives (N05; 1.1% *vs*. 0.9%), nasal preparations (R01; 3.1% *vs*. 2.0%), cough and cold preparations (R05; 2.7% *vs*. 1.5%) and systemic antihistamines (R06; 1.9% *vs*. 0.8%). Fewer pregnant women than non-pregnant controls purchased these drugs during each trimester and the post-partum period, except for sex hormones and modulators of the genital system which were purchased by a larger number of pregnant women during the first trimester (OR 1.1, 95% CI 1.0-1.2), and antimicrobials which were purchased more abundantly by mothers than by controls during lactation (OR 2.3, 95% CI 2.2-2.4).

A recent study from the US based on drug-dispensing data reported that altogether 3.6% of women used antidepressants during pregnancy, 2.7% of them in the first trimester, showing a declining trend with advancing pregnancy (Andrade *et al*. 2004). Furthermore, another recent study from the US based on interviews reported that approximately 1% of pregnant women had used SSRI drugs during pregnancy (Refuerzo *et al*. 2005). By contrast, in a study from Europe, less than 0.3% of women interviewed during pregnancy reported using antidepressants (Headley *et al*. 2004). Besides cultural differences, one possible explanation is that women are unwilling to report the use of psychotropic drugs.

Treatment of chronic illnesses requiring drug therapy continued during pregnancy. Chronic asthma was diagnosed at similar rates in pregnant women and in non-pregnant controls (Table 8), and the number of women receiving asthma medications throughout the study period corresponding to pregnancy did not differ between the two cohorts. A small decline in pregnant users of anti-asthmatic drugs occurred in the first trimester, but the number increased again in the second trimester (Figure 1). The frequency of epilepsy treatment was similar during the preconception period, all stages of pregnancy, and lactation (Figure 1). Insulin was responsible for the increase in drug reimbursements for diabetes during pregnancy.

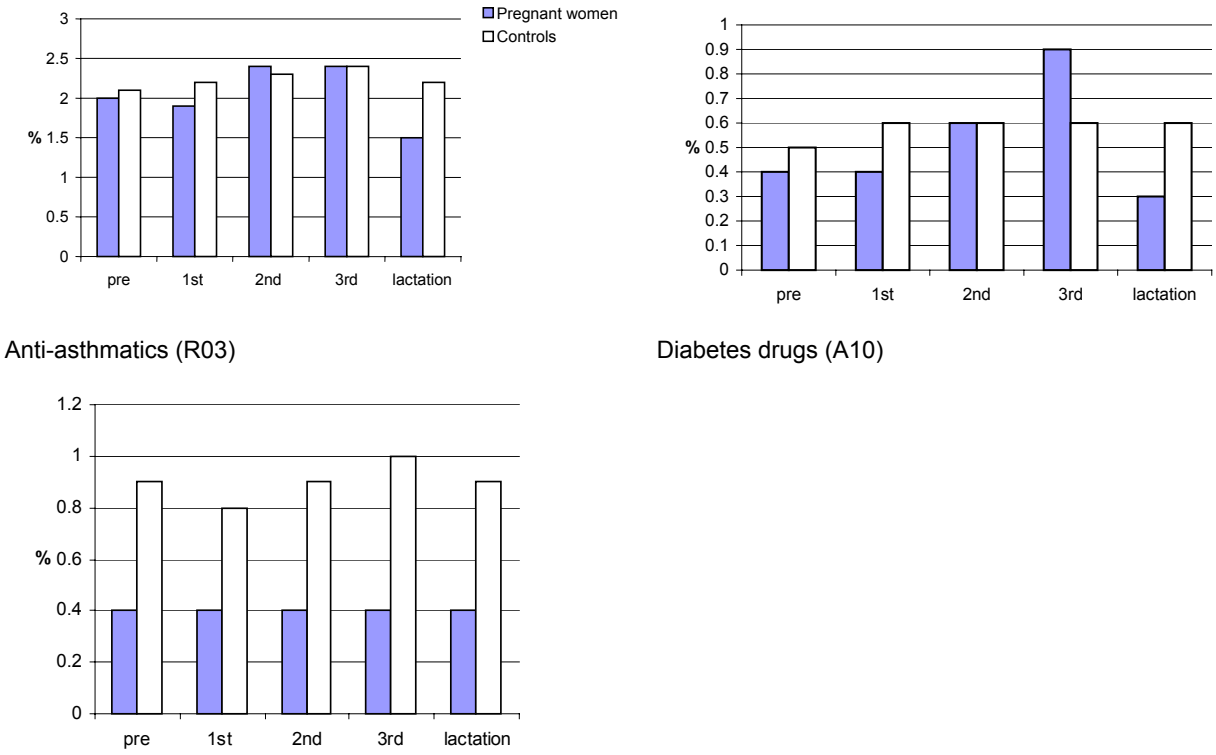


Figure 1. Percentage of pregnant women and non-pregnant controls (43 470 each) purchasing drugs for selected chronic diseases. Each second-level ATC code was recorded only once per person. Time periods: pre= preconception, 1st= first trimester, 2nd= second trimester, 3rd= third trimester.

Relatively few other studies have investigated the pattern of drug use for treating chronic illnesses, such as asthma, epilepsy or diabetes, during pregnancy. Drug treatment of asthma remained fairly constant throughout pregnancy in a register-based Danish study (Olesen *et al*. 1999b), consistent with our findings. Although large epidemiological studies are scant, existing data do not indicate a major risk for congenital malformations or other adverse outcomes with maternal exposure to commonly used asthma medications (Källen *et al*. 1999; Jadad *et al*. 2000; Gluck and Gluck 2005). Furthermore, untreated asthma requiring drug treatment presents a definite risk to the pregnancy and the fetus (Namazy and Schatz 2004). As in our study, anti-epileptic drugs were prescribed in a constant manner throughout pregnancy in one interview-based (Rubin *et al*. 1993) and three register-based (Olesen *et al*. 1999b; Andrade *et al*. 2004; Egen-Lappe and Hasford 2004) studies. All traditionally used anti-epileptics are known teratogens, but adequate treatment of epilepsy presents a smaller risk to the fetus than does untreated epilepsy (Yerby 2000). In the present study the use of insulin increased throughout pregnancy. Similar results were reported in another study based on prescription data (Egen-Lappe and Hasford 2004). This is in accordance with generally accepted guidelines to use insulin instead of oral antidiabetics during pregnancy, and indicates rational prescribing of drugs.

5. 1. 2. Reimbursements according to drug safety categorization (Study II)

A total of 562 different active substances according to the ATC code were recorded in the two cohorts, and a pregnancy safety categorization was identified for 528 drugs (94%). The majority of drugs were categorized according to the FASS classification (76.2% of all different active substances recorded), and the rest were categorized according to the ADEC classification (8.6%) and the FDA classification (9.1%).

During overall pregnancy, 8853 women (20.4 %) purchased at least one drug that was classified as *potentially harmful*, *versus* 15 562 of non-pregnant controls (35.8%) (Figure 2). The number of pregnant women purchasing potentially harmful drugs during the first trimester was lower than during the preconception period (11.2% *vs*. 17.9%; OR 0.6, 95% CI 0.6-0.6; P<0.05) (Figure 3a). The decline continued from the first to the second trimester (OR 0.7, 95% CI 0.7-0.7; P<0.05) but no difference was present between the second and third trimesters (P=0.2) (Figure 3a). The majority of potentially harmful drugs purchased in the preconception period were non-steroidal anti-inflammatory drugs (NSAIDs) and drugs for infertility treatment. In the first trimester, pivmecillinam was the most frequently purchased drug classified as potentially harmful (1.4% of all pregnant women), followed by chorionic gonadotropin (0.8%) and clomiphene (0.7%). Ibuprofene, fluconazole, and nasal fluticasone – all grouped as potentially harmful – were each purchased by 0.6% of pregnant women.

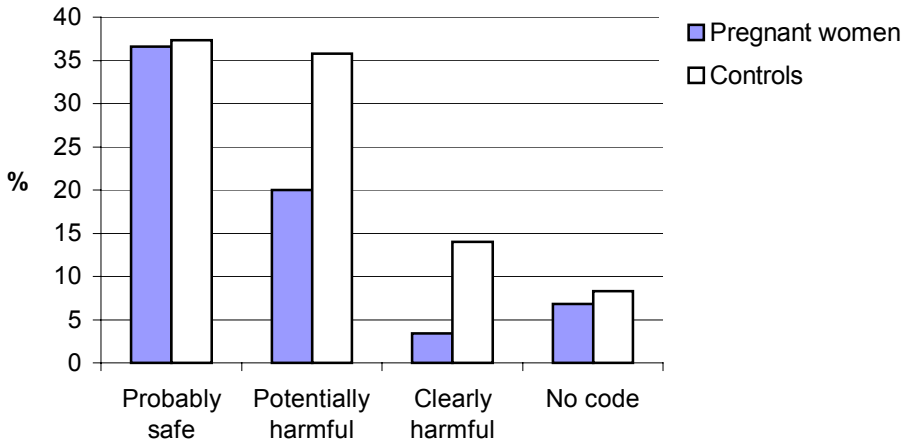
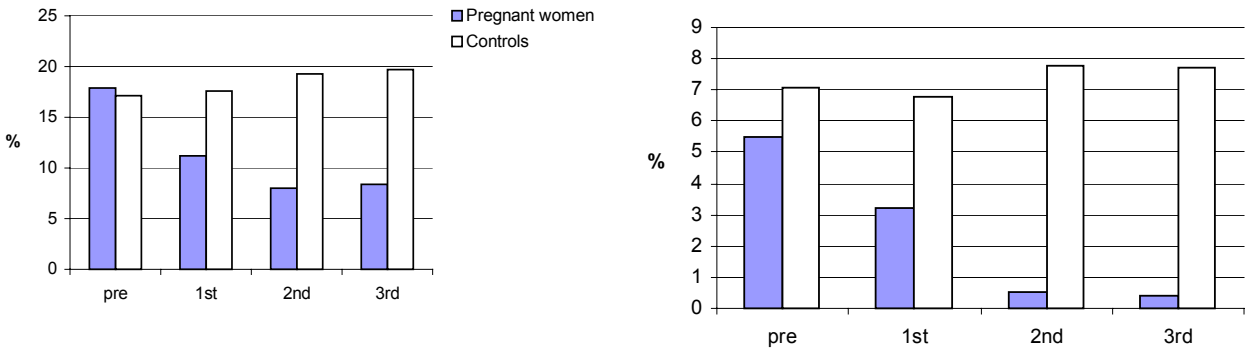


Figure 2. Percentage of pregnant women and non-pregnant controls (43 470 each) purchasing drugs grouped as probably safe, potentially harmful and clearly harmful during pregnancy.

Regular use of NSAIDs at the time of conception or in early pregnancy has been associated with an increased risk of miscarriage in a carefully conducted cohort study (Li *et al*. 2003). Furthermore, prostaglandin inhibition may affect fertility by interfering with normal ovarian follicular

development and ovulation (Killick and Elstein 1987; Stone *et al*. 2002). The regular use of NSAIDs should therefore be avoided already in the preconception period. Due to the register-based design in our study, considerable overestimation of exposure to infertility drugs during organogenesis is likely, as these drugs are used to stimulate ovulation, and consequently, exposure occurs before pregnancy begins. Pivmecillinam is categorized as potentially harmful because of its capacity to lower serum carnitine levels (FASS 1999). However, no adverse effects on the fetus have been reported, and pivmecillinam is considered safe for use in pregnancy in clinical practice (Christensen 2001). Furthermore, existing data do not indicate a major risk of congenital malformations or other adverse outcomes with maternal exposure to commonly used allergy or asthma medications (Kalter and Warkany 1983b; Källen *et al*. 1999; National Heart, Lung and Blood Institute: National Asthma Education and Prevention Program Asthma and Pregnancy Working Group 2005).



a. **b.**

Figure 3a and b. Percentage of pregnant women and non-pregnant controls (43 470 each) purchasing drugs grouped as *potentially harmful* (a) and *clearly harmful* (b). Time periods correspond to preconception (3 months before first trimester) and pregnancy trimesters.

One or more drugs classified as *clearly harmful* were purchased by 1478 women (3.4%) during overall pregnancy, compared with 6075 non-pregnant controls (14%) (Figure 2). The number of pregnant women purchasing clearly harmful drugs was lower during the first trimester than during the preconception period (3.2% *vs*. 5.5%; OR 0.6, 95% CI 0.5-0.6; P<0.05), declining further from the first to the second trimester (OR 0.1, 95% CI 0.1-0.2; P<0.05) (Figure 3b). No difference was present between the second and third trimesters (P=0.9) (Figure 3b). During preconception the most commonly purchased clearly harmful drugs were doxycycline (2.1% of all pregnant women), follitropin alpha or beta (1.6%), estradiol (0.4%) and norethisterone (0.4%). During the first trimester the most commonly purchased clearly harmful drugs were follitropin alpha or beta (1.4%), doxycycline (0.6%), estradiol (0.4%), carbamazepine (0.2%), menotropin (0.2%) and valproate (0.1%). The use of carbamazepine and valproate remained constant throughout pregnancy. Twenty-

one women purchased tetracyclines in the second trimester. Three women purchased isotretinoin in the preconception period, and one during each pregnancy trimester.

As discussed previously, infertility treatments are used to induce ovulation and are therefore used prior to conception, and consequently, are not likely to affect embryonic development. Tetracyclines do not increase risk of major malformations when used in early pregnancy, but they may cause discoloration of deciduous teeth when used after 16th week of pregnancy (Cohlan 1977; Webster and Freeman 2003). Isotretinoin is a major teratogen, with first-trimester exposure leading to a 40% risk of abortion and a 25-30% risk of major malformations in newborns (Lammer *et al*.1988). An increased risk of developmental delay even in the absence of detectable major malformations has also been observed (Adams and Lammer 1993; Coberly *et al*. 1996; Kalter 2003). Furthermore, due to the relatively long half-life of isotretinoin, exposure shortly before or at conception may increase risk as well (Nulman *et al*. 1998).

A Danish study based on registers and FASS categorization of drugs reported that 18% of pregnant women were exposed to potentially or clearly harmful drugs during pregnancy (Olesen *et al*.1999b). In that study, the proportion of prescriptions for drugs classified as potentially harmful decreased during pregnancy, similarly to our findings. A French study based on prescriptions found that 59% of pregnant women purchased drugs known to be harmful according to the FDA categorization and 1.6% purchased drugs that were absolutely contraindicated (Lacroix *et al*. 2000). A register-based study from the US and covering over 150 000 deliveries found that 1.1% of pregnant women purchased drugs categorized as contraindicated during pregnancy; however, when female reproductive hormones were excluded, the proportion declined to 0.1% (Andrade *et al*. 2004). Another register-based study from the US reported that 0.3% of pregnant women filled prescriptions for contraindicated drugs during the first trimester (Cooper *et al*. 2004). Moreover, the FDA classification classifies some benzodiazepines as contraindicated, even though at present these drugs are not considered teratogenic (McElhatton 1994; Ornoy *et al*. 1998; Webster and Freeman 2003). A Dutch study based on pharmacy record data and the Australian risk classification disclosed that 10% of prescriptions for pregnant women belonged to the potentially harmful group (including recognized teratogens), compared with 49% of prescriptions for non-pregnant women (Schirm *et al*. 2004). The majority of prescriptions for pregnant women considered potentially harmful in that study were for psycholeptics (N05), psychoanaleptics (N06) and NSAIDs (M01) (Schirm et al. 2004).

5. 1. 2. 1. Polytherapy

A total of 107 (0.2%) pregnant women purchased 10 or more different drugs during the period of pregnancy (mean 12.0, range 10-28), and 29 (0.1%) purchased five or more drugs during each trimester. In this subgroup of 107 women, drugs most frequently purchased during pregnancy (defined by the third-level ATC code) were dermal corticosteroids (85% of pregnant women), decongestants and other nasal preparations for topical use (74%), adrenergic inhalants (67%), other inhaled drugs for obstructive airway diseases (63%), penicillins (62%), other beta-lactam antibacterials (59%), gynecological anti-infectives (50%), anxiolytics (38%), corticosteroids for systemic use (38%), antihistamines (32%), and NSAIDs (31%). Accordingly, the drug groups responsible for multidrug use were relatively innocent. At present, no evidence exists that drugs from any of these drug groups would pose any appreciable teratogenic risk (Koren *et al*. 1998; Kalter 2003; Webster and Freeman 2003; Gilbert *et al*. 2005). The use of systemic corticosteroids in certain situations is well-founded, but anxiolytics and NSAIDs are probably prescribed and used with less well-defined indications.

The number of pregnant women purchasing two or more anti-epileptic drugs concurrently was 23 (7.4% of the 309 pregnant women with an epilepsy diagnosis) during the preconception period, remaining essentially the same throughout the pregnancy trimesters. Among the 21 anti-epileptic drug combinations purchased, 7 contained valproic acid and 4 included three different anti-epileptics. Polytherapy may increase teratogenic risk considerably, and the principal goal in epilepsy treatment during pregnancy should be monotherapy (Pennell 2003). All women with epilepsy who are planning a pregnancy are recommended to take folic acid supplementation (Wald *et al*. 2001; Yerby 2003). Because folic acid is not reimbursable in Finland, the frequency of folic acid supplementation in this subgroup of pregnant women could not be analysed.

5. 2. Safety of selective serotonin reuptake inhibitors (SSRIs) during pregnancy (Study III)

5. 2. 1. General characteristics of the study population

Women with SSRI purchases and their matched controls numbered 1782 each. The mean age of the women in both cohorts at delivery was 30.0 years (SD 0.7). There were more than twice as many tobacco smokers in the cohort of women with SSRI purchases than in the cohort of controls ($P<0.0001$). Similarly, pregnancy induced by artificial reproductive techniques was six times more

common in women with SSRI purchases (P<0.0001). The mean length of gestation was shorter (P<0.0001), and the mean birth weight slightly lower (P<0.0001) in SSRI-exposed women. The rates of perinatal death, Caesarean section and total number of malformations in offspring of SSRI users did not differ statistically significantly from those in the control group.

5. 2. 2. First-trimester exposure and major malformations

A total of 1398 mother-infant/fetus pairs were recorded with at least one SSRI drug purchase during one month preceding pregnancy or in the first trimester. These mothers had 57 infants or fetuses with major malformations, compared with 62 in the control cohort (n=1782). The difference in malformation rate between the exposed and nonexposed cohorts was not statistically significant (P= 0.4, adjusted OR 1.0, 95% CI 0.6-1.7). Moreover, when cases with first-trimester SSRI purchase(s) were compared to their matched controls (n=1398), the malformation rate did not differ between the two groups (P=1.0). The occurrence of major malformations was not independently associated with any of the confounding variables considered in the logistic model. The confounders considered in the logistic analysis were age (<20 or >40 *vs*. ≥20 and ≤40), social status (low *vs*. high), smoking (yes *vs*. no), previous pregnancies (yes *vs*. no) and other reimbursed medications (yes *vs*. no).

Citalopram was the most frequently purchased SSRI drug during the first trimester (554 women), followed by fluoxetine (525 women). In a subgroup analysis of individual SSRIs, major malformations were more common only in fetuses or infants of women with fluoxetine exposure in the first trimester compared with all control women with no drug purchases (P=0.03). After adjusting for confounders (age, smoking, low social status, parity and purchases of reimbursed drugs other than SSRIs), the association was almost statistically significant (OR 1.7, 95% CI 0.9-3.3). Women with fluoxetine exposure during the first trimester had 29 infants or fetuses with major malformations (5.5%), compared with 62 out of 1782 in the control group (3.5%). There were 12 isolated cardiovascular malformations in infants of fluoxetine-exposed women; the prevalence was thus 23 per 1000 newborns. This is nearly threefold the prevalence of cardiovascular malformations in Finland (8 per 1000 newborns). Of the isolated cardiovascular malformations in fluoxetine-exposed women, eight were ventricular septal defects (VSDs). In addition to isolated cardiovascular malformations, two cardiovascular malformations were recorded in four infants with chromosomal abnormalities (all 21 trisomies), and four cases were recorded with urinary tract malformations. After excluding chromosomal abnormalities, there were 25 malformations in the fluoxetine-exposed pregnancies (4.8%) and 52 in the control cohort (2.9 %).

Prospective studies on first-trimester fluoxetine exposure have been published without evidence of increased risk of major malformations (Pastuszak *et al*. 1993; Chambers *et al*. 1996; Hendrick *et al*. 2003). However, numbers in the cohorts have been relatively small, and the samples may not have been representative of the population overall. The fluoxetine pregnancy registry maintained by the manufacturer reported nearly 800 first-trimester exposures with no suggestion of increased risk (Goldstein *et al*. 1997). However, post-marketing surveillance data are based on spontaneous reporting and have serious limitations due to the high percentage of cases lost to follow-up, making definitive conclusions difficult.

Similarly to fluoxetine, previous studies have not identified an increased risk of malformations with other SSRIs (Kulin *et al*. 1998; Ericson *et al*. 1999; Diav-Citrin *et al*. 2002). Quite recently, however, two preliminary reports have suggested an association between first-trimester paroxetine exposure and cardiovascular malformations (Diav-Citrin *et al*. 2005; GlaxoSmithKline Clinical Trial Register 2005). In one of these studies, most of the cardiovascular malformations were VSDs (GlaxoSmithKline Clinical Trial Register 2005), consistent with the malformations present in the fluoxetine-exposed cohort in the present study. The similar pattern of malformations raises some concerns about the teratogenic potential of these drugs.

5. 2. 3. Continuous exposure during pregnancy and small for gestational age, low birth weight and preterm birth

While during the period covering preconception and the first trimester the total number of SSRI users was 1398, the number of women purchasing one or more SSRI drugs during the second and third trimesters or during each trimester was 360. Small for gestational age was more common in infants born to mothers with continuous exposure (n=360) than in infants of mothers with no SSRI purchases (n=1779) (P= 0.001, adjusted OR 2.4, 95% CI 1.1-5.3). To avoid possible bias related to the underlying illness, women with continuous exposure were compared with women with only first-trimester exposure (n=1010). A considerable difference in the frequency of small for gestational age, reaching almost statistical significance, was found between the two groups (P=0.08, adjusted OR 1.9, 95% CI 1.0-3.8). Mean birth weight and mean length of gestation did not differ between the continuous-exposure group and those exposed only during the first trimester. Low birth weight was no more common in the exposed cohort than in the non-exposed control cohort (P=0.3), or in the cohort exposed only during the first trimester (P=1.0, adjusted OR 1.0, 95% CI 0.5-2.0).

The results suggest but do not confirm a drug-specific risk of small for gestational age. One previous study based on a small cohort has suggested an increased risk of small for gestational age in full-term infants after exposure to fluoxetine in late pregnancy (Chambers *et al*. 1996), but in a large register-based study no such risk was observed (Källen 2004). One previous study with a small number of cases and no control group suggested an increased risk of low birth weight with high doses of fluoxetine (Hendrick *et al*. 2003). Furthermore, a Swedish study recently reported a twofold increase in the rate of low birth weight in infants exposed to SSRIs during the second or third trimester compared with a population-based control cohort (Källen 2004). Those results differ from our findings and are difficult to explain because both studies had large numbers of cases, and confounding factors, including smoking, were controlled for. In the Swedish study, a risk of similar magnitude was found in pregnancies with exposure to tricyclic antidepressants, suggesting a role of residual confounding linked to the disease rather than a drug-specific effect (Källen 2004).

No increased risk of preterm birth (<37 gestational weeks) (P=0.2, adjusted OR 0.7, 95% CI 0.3-1.3) was found, and there were no births earlier than or at 32 gestational weeks in the continuous-exposure cohort. Three previous studies have suggested an increased risk of preterm birth in women using SSRIs during pregnancy (Chambers *et al*. 1996; Simon *et al*. 2002; Källen 2004). The first of these studies, a prospective cohort study based on cases collected by Teratology Information Services, found a relative risk of 4.8 for preterm birth after fluoxetine exposure (Chambers *et al*. 1996). In that study, mean age of exposed mothers was higher than in the non-exposed control group. In addition, women using antidepressants were more likely to smoke and use alcohol, both factors which may increase the risk for preterm birth (Ohmi *et al*. 2002; Lemoine *et al*. 2003). A controlled study based on medical records reported birth at or below 36 gestational weeks being more common in the exposed cohort (OR 4.4) (Simon *et al*. 2002). However, both of these studies were based on relatively small cohorts. A large study based on registry data and prospectively collected interviews found a statistically significant increased risk for preterm birth after adjustment for confounders (OR 2.0), but the same risk was observed in pregnancies exposed to tricyclic antidepressants (Källen 2004).

5. 2. 4. Third-trimester exposure and neonatal outcome

A total of 597 women purchased SSRIs during the third trimester. Compared with those with only first-trimester exposure, no difference was observed between these cohorts in the mode of delivery (vaginal or Caesarean section) (P=0.6). Low Apgar score was more common in infants of women using SSRIs in the third trimester than those exposed only in the first trimester (P=0.05, adjusted

OR 1.6, 95% CI 1.0-2.4). Similarly, treatment in special or intensive care units was more common in infants exposed in the third trimester (15.7% vs. 11.2%) (P=0.009), and this association remained statistically significant after adjusting for confounding variables (OR 1.6, 95% CI 1.1-2.2).

The results are in agreement with previous studies of increased risk of neonatal problems and need for neonatal special or intensive care unit treatment or low Apgar score (Chambers *et al*. 1996; Costei *et al*. 2002; Laine *et al*. 2003; Källen 2004; Oberlander *et al*. 2004). The largest of these studies, based on prospectively collected exposure data, included a total of 985 women with antidepressant use, 558 of whom were exposed to SSRIs (Källen 2004). A twofold incresed risk of low Apgar score was found in neonates exposed to SSRIs *in utero* compared with a population-based control cohort (Källen 2004). A limitation in the study was that in nearly 40% of the exposed women, timing of exposure could not be confirmed. Several case reports and case series have also suggested an association between SSRI exposure in late pregnancy and neonatal respiratory difficulties or central nervous system excitation (Mohan and Moore 2000; Nordeng *et al*. 2001b). One recent case report described a neonate with severe adverse effects, including tremor and rigidity, who was genotyped to be a poor metabolizer of CYP2D6, the enzyme responsible for paroxetine metabolism (Laine *et al*. 2004). Contrary to these findings, one prospective study of 64 women using fluoxetine did not find an increased risk of any neonatal adverse effects examined, including low Apgar score and admittance to special or intensive care unit (Suri *et al*. 2004). In that study, depressive women using fuoxetine were compared with depressive women without medication and with non-depressive controls. Only non-smoking women with neither potentially harmful medications nor alcohol use were included in the study. No adverse effects in perinatal outcome, including preterm birth, low birth weight or low Apgar score, were correlated with fluoxetine exposure or to depression (Suri *et al*. 2004). The differing findings from previous studies may partly be explained by differences in study populations (Suri *et al*. 2004).

In the present study, diagnoses for the stay at neonatal special or intensive care unit (ICD-10 in the Birth Register) were unspecific and did not allow definite conclusions about the origin of neonatal problems. Furthermore, no data on duration of stay in these units were available. However, drug-induced withdrawal symptoms or drug toxicity in newborns are a likely explanation for the observed results.

Paroxetine exposure in late pregnancy has been associated with neonatal convulsions in a database analysis based on spontaneous reporting (Sanz *et al*. 2005). In the present study, treatment in special or intensive care unit was more common in the neonates exposed in the third pregnancy trimester to

other SSRIs than in the 64 neonates exposed to paroxetine (P=0.02); however, the numbers were too small to draw any definitive conclusions.

5.3. Valproate embryopathy (Study IV)

Three families with altogether seven children were examined clinically, and their medical records and photographs were carefully reviewed. The families had been referred to a genetics clinic to determine the aetiology of similar multiple malformations and developmental deficits in the siblings. One mother had had one generalized seizure at gestational week 36, and one mother had had two nocturnal generalized seizures of unknown duration at weeks 11 and 14; otherwise, all pregnancies had been uneventful. One child in each family had a normal karyotype, therefore, parental chromosomal abnormalities as aetiological factors could be excluded. The age of the children at assessment ranged from 13 months to 8 years.

Table 9. Signs and symptoms of fetal valproate syndrome in siblings.

Sign	Family A			Family B		Family C	
	Patient 1	Patient 2 [a]	Patient 3	Patient 4	Patient 5[a]	Patient 6 [a]	Patient 7 [a]
Facial dysmorphism	+	+	+	+	+	+	+
Malformations	Small fingernails	Cleft palate Trigono-cephaly Short phalanges Underriding third toe	Cleft palate Trigono-cephaly Multicystic dysplasia of kidney Inguinal hernias Underriding third toes Proximally placed thumbs	-	Inguinal hernias Duplex thumb	Unilateral kidney agenesis Tracheo-malacia Enlarged cerebral ventricles	Unilateral kidney agenesis Severe sensorineural hearing loss
Developmental delay	Moderate (verbal, motor)	Mild (verbal, motor)	Mild (motor)	Mild (verbal, visuomotor)	Moderate (verbal)	Moderate (overall)	Mild (motor)

[a] Normal karyotype

5. 3. 1. Facial dysmorphism and other malformations

All of the children had subtle but strikingly similar typical facial dysmorphism, including medial deficiency of the eyebrows, a broad nasal root, anteverted nares, a shallow philtrum and a long, thin upper lip (Table 9). Furthermore, two siblings had trigonocephaly, in one case necessitating cranioplasty at the age of 7 months, and both had a surgically corrected cleft palate (Patients 2 and 3). Four children in two families had hand and foot malformations, including an underriding third toe with and without short phalanges (two siblings), preaxial polydactyly and small fingernails. Two children from different families had inguinal hernias. Two siblings had unilateral renal agenesis (Patients 6 and 7), and one child had an unilateral non-functioning kidney (Table 9).

The typical facial dysmorphism, observed in all siblings, has been described previously in several reports (DiLiberti *et al*. 1984; Jäger-Roman *et al*. 1986; Winter *et al*. 1987; Ardinger *et al*. 1988; Clayton-Smith and Donnai 1995; Moore *et al*. 2000; Kozma 2001; Dean *et al*. 2002; Mawer *et al*. 2002). These features are typical of valproate embryopathy, but are not specific, as some of them are also seen after exposure to other anti-epileptic drugs (Moore *et al*. 2000). Trigonocephaly and cleft palate are both malformations that have previously been frequently described in valproate embryopathy (Kozma 2001; Wide *et al*. 2004; Vajda and Eadie 2005). Congenital limb malformations after exposure to valproate *in utero* have been observed in several case reports and case series (Winter *et al*. 1987; Verloes *et al*. 1990; Buntinx 1992; Clayton-Smith and Donnai 1995), and an association between exposure to valproate and limb malformations has been confirmed in a case-control study (Rodriquez-Pinilla *et al*. 2000). Inguinal hernia has been frequently observed in children exposed to valproate (Jäger-Roman *et al*. 1986; Kozma 2001). Kidney hypoplasia has been described in association with valproate embryopathy (Verloes *et al*. 1990), but neither renal agenesis nor severe sensorineural hearing loss, diagnosed in one of the children, has been reported earlier.

5. 3. 2. Neonatal withdrawal and developmental delay

Five of the seven children had neonatal withdrawal symptoms at or shortly after birth. One infant had convulsions necessitating drug treatment, and respiratory distress. Three infants were treated in a ventilator after birth, and one infant experienced transient tachypnoea with rapid spontaneous recovery. Moderate developmental delay had been confirmed in three children and mild developmental delay in four.

Neonatal withdrawal symptoms or drug toxicity have been reported to be frequent after valproate exposure *in utero* (Jäger-Roman *et al*. 1986; Koch *et al*. 1996; Ebbesen *et al*. 2000; Dean *et al*. 2002; Mawer *et al*. 2002). The severity of the symptoms may also be related to neurological dysfunction later in life (Koch *et al*. 1996; Hernandez-Diaz and de Abajo 2003).

Epilepsy might affect children's intellectual development by the neurotoxic effect of the anti-epileptic drug, by brain damage induced by maternal convulsions, or by hereditary causes (Gaily *et al*. 1990). In our study, no deficient intelligence was reported in any of the parents. The correlation between brief maternal convulsions – such as had been documented in two pregnancies – and neurodevelopment is controversial (Gaily *et al*. 1988, 1990; LaJoie and Moshe 2004). Furthermore, seizure history *per se* has not been shown to increase risk of cognitive dysfunction (Holmes *et al*. 2000). Several studies have suggested an increased risk of neurodevelopmental delay after exposure to valproate *in utero* (Koch *et al*. 1996; Adab *et al*. 2001; Dean *et al*. 2002; Adab *et al*. 2004; Gaily *et al*. 2004), but several confounding factors, including the severity of the disease and hereditary factors, may bias these results. One retrospective study based on data gathered by sending questionnaires to epileptic mothers found that children exposed to valproate had lower verbal intelligence quotient (IQ) than those exposed to other anti-epileptic drugs (Adab *et al*. 2004). However, the low response rate and the retrospective methodology used in that study may have biased the results (Adab *et al*. 2004). Another, carefully conducted prospective cohort study found lower verbal intelligence in valproate-exposed children than in non-exposed controls (Gaily *et al*. 2004). However, the results were confounded by low maternal education and polytherapy (Gaily *et al*. 2004). Both studies were based on relatively small numbers of exposed subjects. Developmental delay was observed in 28% of the 46 children exposed to valproate *in utero* in a retrospective, population-based study (Dean *et al*. 2002). After excluding affected children with a positive family history from the analysis, the rate of developmental delay declined but speech and language disorders remained more frequent in the valproate-exposed cohort than in non-exposed children (Dean *et al*. 2002). The results suggest that the interaction between fetal drug exposure and hereditary susceptibility factors is important (Dean *et al*. 2002). This is in accordance with a recent population-based study from Finland, in which inheritance and environmental factors were proposed to partly explain the increased prevalence of neurocognitive symptoms in children exposed to valproate *in utero* (Eriksson *et al*. 2005).

The characteristic facial dysmorphism may be a marker of underlying central nervous system dysfunction and developmental problems (Mawer *et al*. 2002; Adab *et al*. 2004). Several case reports and case series have suggested an association between autism and maternal exposure to valproate (Williams and Hersh 1997; Moore *et al*. 2000; Williams *et al*. 2001). In animal studies,

valproate exposure leads to a selective loss of neurons, affecting the development of motor cranial nerve nuclei, and a similar mechanism has been hypothesized for autistic humans (Rodier *et al*.1996). These observations highligt the direct neurotoxic potential of valproate.

5. 3. 3. Dose and polytherapy

In the present study, the daily dose of valproate in all pregnancies was relatively high, ranging from 1000 to 2500 mg. The dose was divided into two daily doses in four pregnancies, and in three daily doses in three pregnancies. Maternal serum valproate levels were within the reference range in all pregnancies. One of the children was also exposed to phenytoin *in utero* but only from 36 weeks onwards. Another child was exposed to valproate and vigabatrin throughout pregnancy.

A threshold dose of 1000 mg or more predicting increased risk of major malformations has been established in several studies (Omzigt *et al*. 1992; Kaneko *et al*. 1999; Samren *et al*. 1999: Mawer *et al*. 2002; Perucca 2005; Vajda and Eadie 2005). As teratogenesis is a threshold phenomenon, it is obvious that larger doses imply greater risk. However, individual hereditary factors in the mother and the fetus may exist, and therefore, caution is warranted when drawing conclusions about risks related to a given milligram dose.

The effect of phenytoin exposure *in utero* on neurodevelopment is controversial (Gaily *et al*. 1988; Scolnik *et al*. 1994; Dean *et al*. 2002), but it is unlikely that a one-week treatment would have a significant impact. Little is known about the teratogenic potential of vigabatrin because this drug is usually administered in conjunction with other anti-epileptic drugs (McCorry *et al*. 2004; Hunt and Morrow 2005). Several studies have observed an increased risk of major malformations with polytherapy including two or more anti-epileptic drugs (Lindhout *et al*. 1992; Kaneko *et al*. 1999; Samren *et al*. 1999; Kaaja *et al*. 2003; Pennel 2003; Wide *et al*. 2004).

5. 3. 4. Role of folic acid

No neural tube defects, which are among the most severe valproate-associated malformations, occurred in our patients. Periconceptional folic acid was used in only one pregnancy.

The prevalence of neural tube defects after early intrauterine valproate exposure is 2-5%, ten- to twentyfold that observed in the general population (Alsdorf and Wyszynski 2005). Periconceptional

supplementation with a 4-mg daily dose of folic acid reduces the recurrence of neural tube defects by 70% in infants of non-epileptic women (MRC Vitamin Study 1991). The effect of valproate on human folate is controversial but even prolonged valproate treatment may not influence serum or erythrocyte folate levels (Kishi *et al*. 1997; Apeland *et al*. 2000; Verrotti *et al*. 2000). Low serum folate levels were correlated with adverse outcome in one large, prospective study on epileptic women (Kaaja *et al*. 2003). At present, no conclusive evidence of the protective role of folic acid in pregnancies exposed to anti-epileptic drugs exists (Alsdorf and Wyszynski 2005).

5. 3. 5. Hereditary susceptibility

All of our patients had developmental defects characteristic of valproate embryopathy. One sibling in each family had a normal karyotype, therefore parental chromosomal abnormalities as aetiological factors could be excluded. Several affected sibling pairs have been described in the literature (Kozma 2001; Moore *et al*. 2000). Our seven patients with valproate embryopathy, representing all children in three families, strongly suggest the significance of hereditary factors in development of the embryopathy.

5. 3. 6. General aspects

Valproic acid crosses the placenta and higher concentrations have been observed in the fetus than in the mother (Nau *et al*. 1981; Kaneko *et al*. 1983; Nau *et al*. 1984). The teratogenicity of valproic acid has been established in several case-control and cohort studies (Omtzigt *et al*. 1992; Kaneko *et al*. 1999; Samren *et al*. 1999; Arpino *et al*. 2000; Rodriquez-Pinilla *et al*. 2000; Kaaja *et al*. 2003; Wide *et al*. 2004; Artama *et al*. 2005) and recently also in studies based on data from national and international pregnancy and epilepsy register databases (Vajda and Eadie 2005; Wyszynski *et al*. 2005).The risk of a major congenital malformation after exposure to valproate in early pregnancy is estimated to be two- to fourfold higher than that in the general population, but even higher numbers have been proposed (Alsdorf and Wyszynski 2005). In addition, minor malformations, including facial dysmorphism and digital anomalies, are frequently observed (Jäger-Roman *et al*. 1986; Clayton-Smith and Donnai 1995; Alsdorf and Wyszynski 2005). Some of the birth defects produced by valproate, such as caudal neural tube defects (spina bifida), characteristic facial features and radial ray defects, are more specific than those defects related to maternal use of other anti-epileptic drugs, suggesting that the teratogenic influence occurs along specific developmental pathways (Moore *et al*. 2000; Barrett and Richens 2003; Alsdorf and Wyszynski 2005). In general, only a

small proportion of exposed children are affected (Hunt and Morrow 2005). The mechanisms underlying susceptibility have not been established. In one study, maternal mutation in the methylenetetrahydrofolate reductase (MTHFR) was associated with adverse outcome in pregnancies of epileptic mothers using anticonvulsants (Dean *et al*. 1999). Generally, the 677 C > T mutation is associated with decreased activity of the MTHFR enzyme and has been suggested to be a genetic risk factor for neural tube defects, although the findings are controversial (Finnell *et al*. 2000, 2003). In another study, autoantibodies to folate receptors were found more frequently in sera of women with offspring with neural tube defects than in controls (Rothenberg *et al*. 2004). By binding to folate receptors, these autoantibodies may interfere with cellular uptake of folate (Rothenberg *et al*. 2004). These results are interesting given that neural tube defects are characteristic of valproate embryopathy. However, at present, the clinical relevance of these findings in pregnant women treated with anti-epileptic drugs is obscure.

5. 4. Methodological considerations

In Studies I-III, data were derived from population-based registers. The Drug Reimbursement Register covers claims data on 97%-98% of all reimbursed drugs (Finnish Statistics on Medicines 1999, 2003). Timing of exposure could be assessed by a period corresponding to each trimester, as the drugs to be reimbursed are delivered from pharmacies for a maximum period of three months at a time. Furthermore, pregnancy is confirmed by ultrasound before applying for maternal grants, adding to the reliability of the recorded length of gestation. A methodological problem in several other register-based studies is the lack of information on gestation length, which has been assessed indirectly (Andrade *et al*. 2004; Egen-Lappe and Hasford 2004; Schirm *et al*. 2004); this may interfere with the reliability of the estimation of drug use. In Studies I and II, the control group served not only as a point of comparison with the pregnant women but also reflected general trends in drug prescription and reimbursement policies.

Validation studies have revealed that data coverage of the Medical Birth Register and the National Register of Induced Abortions is close to 100%, and data quality of most variables has been reported to be good in both registers, showing 95% or better agreement with medical records (Teperi 1993; Gissler *et al*. 1995, 1996, 2004) (Table 7). In addition, the Medical Birth Register includes maternal background data, such as parity and tobacco smoking, which could be used in the analysis of Study III. However, no data on alcohol or street drug use, or on non-prescription drug use are available in the register and therefore could not be included. Contrary to register-based studies, studies based on

interviews allow collection of data on OTC drugs and vitamin use. However, problems with such studies include recall bias if the interview is done as late as after delivery (Czeizel *et al*. 2003). In addition, unfavourable pregnancy outcome may increase this bias (Rockenbauer *et al*. 2001).

All neonates are examined by a paediatrician before discharge from the hospital, and diagnoses of possible illness or malformations are recorded in the Medical Birth Register. By including data from the Register of Induced Abortions, all pregnancy terminations due to fetal malformation could be included in the analysis. The Malformation Register classifies a congenital anomaly as a major congenital structural anomaly, chromosomal defect or congenital hypothyroidism (STAKES 2005). Major anomalies in this register do not include hereditary diseases, tissue or organ dysfunction, developmental disabilities or congenital infections (STAKES 2005), and the registry uses the European Surveillance of Congenital Anomalies (EUROCAT 2005) definitions and guidelines to exclude minor anomalies. No validation studies are available on the accuracy of the Malformation Register, but its coverage is considered good (STAKES 2005). Data derived from the Malformation Register provided additional cases of malformations, which were detected after hospital discharge, and were therefore not reported in the Birth Register. It is therefore likely that virtually all malformations were recorded in our study. Only singleton pregnancies were included because twinning is known to increase the risk of several perinatal complications.

Even cohort studies with large numbers of subjects may be insufficient to detect rare outcomes such as specific organ system malformations (Olsen *et al*. 2002). Assuming a 3% baseline risk of major congenital malformations, a sample of 750 or more is needed to detect a twofold increase in risk. In these situations, a case-control approach may be more informative. In Study III, however, a cohort study design was chosen to allow the detection of different endpoints of possible developmental toxicity.

Study IV was based on clinical examination and reviewing of medical records and photographs of the families. Case reports and case series can be valuable for hypothesis generation and for testing in cohort or case-control studies. Furthermore, when considering rare events, such as specific congenital malformations or pattern of malformations, case series may – by providing clinical description of patients – yield additional information regarding already proven causality. Several factors, including timing of exposure, must be critically evaluated when causality between exposure and outcome is suspected. Because of the lack of a control group, the rate of adverse outcome could not be determined.

6. GENERAL DISCUSSION

According to the study results, prescription drug use during pregnancy is relatively common. However, a declining trend was observed in the use of several drug groups as pregnancy advanced. As expected, in chronic illnesses requiring treatment, drug therapy continued during pregnancy. In general, the findings seem to suggest rational drug prescription and drug use policy. However, the relatively frequent use of drugs during the first trimester highlights the importance of avoiding unnecessary treatments in women of child-bearing potential already before pregnancy.

Register-based studies provide a large, population-based data for analysis, and several sources of bias encountered in studies based on interviews can be avoided. On the other hand, data on actual drug intake, including timing and duration of exposure, are not available. Furthermore, due to possible non-compliance in drug intake, drug use may be overestimated. Studies assessing compliance in drug intake in pregnant women have shown that drugs used for chronic illnesses are nearly always taken, whereas compliance may be lower with short-term drug therapies (de Jong van der Berg *et al*. 1999; Olesen *et al*. 2001; Olsen *et al*. 2002). While it is therefore not possible to estimate drug use directly, the large numbers of subjects in register-based studies partly overcome this bias.

Our results confirm that drug safety classifications provide a very rough estimate of risk for adverse fetal effects. These classifications can be used in pharmacoepidemiological studies, but relying on classification in individual risk assessment may lead to oversimplification. Several drugs classified as harmful are only harmful during a critical period of fetal development (Kalter 2003). Accordingly, risk assessment should always be made individually in counselling situations, including careful evaluation of timing of exposure. In studies assessing drug use during pregnancy, the varying results reported for different countries may be partly due to different reimbursement regulations. However, cultural differences and differences in health policy issues are probably the important determining factors.

No statistically significant increased risk of major malformations, preterm birth or low birth weight was found in mothers using SSRIs. The study had 85% power to detect a twofold increase in major malformations. In the fluoxetine group, an increased risk of major malformations, mainly VSDs, was observed, but after adjusting for confounders the correlation was no longer statistically significant, suggesting that factors other than drug exposure may play a major role in adverse outcome. The preliminary findings of an association between paroxetine use and cardiovascular

malformations (Diav-Citrin *et al*. 2005; GlaxoSmithKline Clinical Trial Register 2005) raise some concern. On the other hand, while VSDs are recorded as major malformations, they often close spontaneously. The prevalence of non-complex malformations, such as VSDs, vary due to differences in methods and activity of ascertainment, whereas the prevalence of more serious malformations do not tend to vary (Bosi *et al*. 2003). In several reports, paroxetine exposure in the third trimester has been correlated with severe neonatal problems (Costei *et al*. 2002; Laine *et al*. 2004; Sanz *et al*. 2005). Because of the frequent occurrence of neonatal problems in this group, these children may be examined more thoroughly after birth than those not exposed, allowing less severe malformations – easily going undetected in the absence of symptoms – to be ascertained more frequently.

A statistically significant increased risk of treatment in neonatal special or intensive care units was found in children exposed to SSRIs in late pregnancy. Accordingly, pregnant women using SSRIs in the third trimester should deliver in hospitals where paediatric care is available immediately after birth.

The registers used in the present study did not include information on later neurodevelopment of the children. Two prospective studies with partially overlapping cases did not find differences in school-age children exposed to SSRIs in neurobehavioural performance or intelligence (Nulman *et al*. 1997, 2002). A study comparing children of depressed mothers with and without medication suggested subtle adverse effects in psychomotor development in children exposed to SSRIs *in utero* compared with non-exposed controls (Casper *et al*. 2003). The sample size was, however, small, and alcohol consumption in mothers using medication was more frequent than in the control group (Casper *et al*. 2003). In another small study, neonatal neurobehavioural differences were associated with SSRI exposure compared with non-exposed controls (Zeskind and Stephens 2004). Furthermore, diminished pain response has been observed in infants after exposure *in utero* to SSRIs (Oberlander *et al*. 2005). The possible long-term effects on neurodevelopment warrant further studies (Gentile 2005; Morrison *et al*. 2005; Moses-Kolko 2005; Ruchkin and Martin 2005). Animal studies suggest that early exposure can disrupt the normal maturation of the serotonin system and have long-lasting effects on behaviour (Maciag *et al*. 2005). On the other hand, duration of maternal depression correlates negatively with cognitive and language development in children (Nulman *et al*. 2002), emphasizing the need for careful balancing between the risks and benefits of treatment. Furthermore, abrupt discontinuation of treatment may lead to increased risk to the mother and should be avoided (Einarson *et al*. 2001).

The characteristic facial features of valproate embryopathy observed in all siblings and the typical malformations observed in most children of the three families strongly suggest hereditary susceptibility to valproate-induced adverse outcome. The developmental delay established in all of our valproate embryopathy patients further implicates valproate neurotoxicity, as no other factors were found to predispose to this adverse outcome. Valproate is considered a first-line anti-epileptic drug in generalized-onset and unclassifiable seizure disorders (McCorry *et al*. 2004) but is also used in combinations and other indications, including bipolar disorders and migraine prophylaxis (Viguera *et al*. 2002; Johannessen and Johannessen 2003; Spina and Perugi 2004). In epilepsy treatment, seizure control is essential. When possible, other alternatives for valproate should be considered before pregnancy, especially if previous children in the family have been affected. When valproate is used for indications other than epilepsy, a change to a safer drug treatment should be made when planning pregnancy.

7. SUMMARY AND CONCLUSIONS

An overall tendency towards diminished drug exposure during pregnancy was seen, but medication for chronic illnesses requiring treatment continued throughout pregnancy. The results are thus in line with rational drug use during pregnancy. However, although prescriptions for potentially or clearly harmful drugs decreased during the first and second trimesters, many women were exposed to these drugs during the period of organogenesis. When prescribing drugs to women of child-bearing potential, the safety of the drug in view of eventual pregnancy should be considered. Risk assessment must always be made on an individual basis. Drug safety classifications give a very crude estimate of risk and should be used only as general guidelines when planning treatment.

No statistically significant increase in the risk of major malformations was found after exposure to the SSRI-class of drugs in early pregnancy. Women with fluoxetine exposure in the first trimester were more likely to have malformed offspring; after adjusting for confounders, the association between drug exposure and malformations remained almost statistically significant (OR 1.7, 95% CI 0.9-3.3). Our findings support the previous reports and studies of increased risk of neonatal problems after exposure to SSRIs in the third trimester. We found a statistically and clinically significant increased risk for treatment in a neonatal special or intensive care unit after third-trimester exposure (adjusted OR 1.6, 95% CI 1.1-2.2). Our results do not, however, confirm previous findings of an SSRI-related risk of preterm birth or low birth weight. Nevertheless, SSRIs should be used in pregnancy only when clearly indicated. The SSRI drug dose should be the lowest that allows adequate treatment of the illness, and when possible, treatment should be discontinued two to three weeks before the expected delivery date. Due to the relatively common occurrence of neonatal problems, women using SSRIs should deliver in units where paediatrician consultation is available without significant delay.

While the mechanism of valproate teratogenicity remains unknown, genetic factors are probably important in determining the teratogenic potential of valproate. In addition to the established risk of major malformations, the risk of neurodevelopmental delay may be increased. Alternative anti-epileptic drugs should be considered before pregnancy, especially if previous offspring in the family have been affected. When valproate is used for indications other than epilepsy, a change to a safer drug treatment should be made already in the pregnancy-planning stages.

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