

From the Department of Clinical Science, Intervention and Technology
Division of Pediatrics
Karolinska Institutet, Stockholm, Sweden

Fetal exposure to neurotropic drugs - neonatal effects and long-term outcome

Lisa Forsberg



**Karolinska
Institutet**

Stockholm 2016

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Published by Karolinska Institutet

Printed by Eprint AB 2016

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ISBN 978-91-7676-197-7

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Karolinska Institutet

Institutionen för klinisk vetenskap intervention och teknik,
Enheten för pediatrik

Fetal exposure to neurotropic drugs - neonatal effects and long-term outcome

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet
offentligen försvaras på engelska i föreläsningssal C1:87, Karolinska Universitets-
sjukhuset, Huddinge.

Fredagen den 26 februari, kl. 10.00

av

Lisa Forsberg

leg.läkare

Huvudhandledare

Med dr Katarina Wide
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik
Enheten för pediatrik

Bihandledare

Docent Lars Navér
Karolinska Institutet
Institutionen för klinisk vetenskap,
intervention och teknik
Enheten för pediatrik

Professor Lars L Gustafsson
Karolinska Institutet
Institutionen för laboriemedicin
Avdelningen för klinisk farmakologi

Fakultetsopponent

Professor Tim Oberlander
The University of British Columbia
Faculty of Medicine
Maternal and Child Health
School of Population and Public Health

Betygsnämnd

Docent Anna-Karin Edstedt Bonamy
Karolinska Institutet
Institutionen för medicin, Solna
Enheten för Klinisk Epidemiologi

Professor Inger Sundström Poromaa
Uppsala Universitet
Institutionen för kvinnors och barns
hälsa, Obstetrik och gynekologi

Professor Morten Andersen
Karolinska Institutet
Institutionen för medicin, Solna
Centrum för Läkemedelsepidemiologi

Stockholm 2016

ABSTRACT

Chronic illness in pregnant women is common. In epilepsy, bipolar disorder (BD) or major depressive disorder (MDD), pharmacotherapy is often necessary. Some neurotropic drugs may have negative effects on children exposed *in utero*. The aim of this thesis was to describe how neurotropic drugs and/or maternal chronic illness during pregnancy may influence the health of the child, both in the neonatal period and long-term outcome, with emphasis on neurodevelopment. In study I, we investigated school results at age 16 in children born to women with epilepsy (WWE), with or without antiepileptic drugs (AED) during pregnancy. Study II and study III aimed at describing neonatal morbidity in infants prenatally exposed to antidepressant drugs. In study IV we studied neonatal and long-term outcome of children born to mothers with severe mood disorders, mostly BD.

Methods: In study I, national health care and education registers as well as maternal care records were used to compare final grades of children of WWE with the rest of the population. Study II was a retrospective, hospital-based study of patient records of women treated with antidepressants in late pregnancy and their children. Information on neonatal diagnoses, maternal use of antidepressant drugs and scoring according to Neonatal Abstinence Score (NAS) was used. In study III, we used the Medical Birth Register, the Prescribed Drug Register and two neonatal quality registers to obtain data on maternal use of antidepressants, maternal health and infant morbidity (diagnoses, admission to neonatal care unit (NCU) and interventions). In study IV, information on maternal health during and after pregnancy was obtained from patient records and at a structured interview. At age 4 to 5 years, the children were assessed by a psychologist with a cognitive test (WPPSI-III).

Results: In study I, we observed an increased risk of not receiving a final grade from compulsory school for children exposed to ≥ 2 AED during pregnancy, adjusted odds ratio (OR) 2.99 (95 % confidence interval [CI] 2.14–4.17), but no increased risk for children born to mothers with untreated epilepsy or exposed to AED in monotherapy. In study II, 22 % of 205 infants assessed with NAS had signs of mild neonatal abstinence and 3 % of severe abstinence. Among a total of 741 040 infants included in study III, 22 507 (3 %) were exposed to antidepressants during pregnancy. Thirteen percent of exposed infants were admitted to NCU compared to 8 % in the population, adjusted OR 1.5 (95 % CI 1.4-1.6). Respiratory disorders, persistent pulmonary hypertension and hypoglycemia were more common after maternal use of selective serotonin reuptake inhibitors. In study IV, there were no statistically significant differences in IQ between children born to women with mood disorders with lithium use during pregnancy (n=20), children born to mothers with mood disorders but no lithium use during pregnancy (n=8) and children born to mothers with no mood disorders (n=11).

Conclusions: Neurotropic drugs during pregnancy can be associated to adverse outcomes in exposed children. Infants exposed to antidepressants have a moderately increased risk of being admitted to NCU. AED polytherapy during pregnancy may be associated to a worsened neurodevelopmental outcome but a causal connection is not established. Lithium exposure during pregnancy was not associated to adverse cognitive outcome at preschool age in our cohort.

LIST OF PUBLICATIONS

- I. **Forsberg L**, Wide K, Kallen B. School performance at age 16 in children exposed to antiepileptic drugs in utero- a population-based study. *Epilepsia*. 2011;52(2):364-9.
- II **Forsberg L**, Naver L, Gustafsson LL, Wide K. Neonatal Adaptation in Infants Prenatally Exposed to Antidepressants- Clinical Monitoring Using Neonatal Abstinence Score. *PLoS One*. 2014;9(11):e111327.
- III Nörby U, **Forsberg L**, Wide K, Sjörs G, Winbladh B, Källén K. Neonatal care after maternal use of antidepressant drugs during pregnancy (submitted manuscript).
- IV **Forsberg L**, Adler M, Römer Ek I, Ljungdahl M, Navér L, Gustafsson LL, Berglund G, Chotigasatien A, Hammar U, Böhm B, Wide K. Neonatal health and cognitive outcome at preschool age in children with intrauterine exposure to maternal mood disorders and lithium (manuscript).

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LIST OF ABBREVIATIONS

AED	Antiepileptic Drugs
ADHD	Attention Deficit Hyperactivity Disorder
AUDIT	Alcohol Use Disorders Identification Test
BD	Bipolar Disorders
BDI	Bipolar Disorder type I
BDII	Bipolar Disorder type II
BMI	Body Mass Index
CBZ	Carbamazepin
CI	Confidence Interval
CM	Congenital Malformations
CNS	Central Nervous System
CPAP	Continuous Positive Airway Pressure
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
DUDIT	Drug Use Disorders Identification Test
FAS	Fetal Alcohol Syndrome
FGA	First Generation Antipsychotics
FSIQ	Full Scale Intelligence Quotient
GA	Gestational Age
GAD	Generalized Anxiety Disorder
ICD	International Classification of Diseases
ICH	Intracerebral Hemorrhage
IQ	Intelligence Quotient
LC	Leaving Certificate
LTG	Lamotrigine
MBR	Medical Birth Register
MDD	Major Depressive Disorder
MMD	Maternal Mood Disorder
NAS	Neonatal Abstinence Score
NCU	Neonatal Care Unit
NNH	Number Needed to Harm
NPR	The National Patient Register
OR	Odds Ratio
PDR	Prescribed Drug Register
PHQ-9	Patient Health Questionnaire 9
PHT	Phenytoin
PIN	Personal Identification Number
PIQ	Performance Intelligence Quotient
PNAS	Poor Neonatal Adaptation Syndrome

PPD	Post-partum Depression
PPHN	Persistent Pulmonary Hypertension in the Newborn
PPP	Post-partum Psychosis
PRS	Perinatal Revision South Register
PSQ	Processing Speed Quotient
RDS	Respiratory Distress Syndrome
SCB	Statistiska Centralbyrån (Statistics Sweden)
SD	Standard Deviation
SeGA	Second Generation Antipsychotics
SNQ	Swedish Neonatal Quality Register
SNRI	Serotonin Noradrenaline Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants
TSH	Thyroid Stimulating Hormone
VIQ	Verbal Intelligence Quotient
VPA	Valproic acid
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence, 3rd edition
WWE	Women with epilepsy

I INTRODUCTION

1.1 Principles of teratology

Teratology is defined as ‘*the study of malformations or serious deviations from the normal type in developing organisms*’ (1), i.e. the pathology of embryology. James Wilson introduced six important principles of teratology (2). These principles, which still hold great relevance today (3), include:

1. *Susceptibility to teratogenesis depends on the genotype of the conceptus and the manner in which this interacts with environmental factors.*
2. *Susceptibility to teratogenic agents varies with the developmental stage at the time of exposure.*
3. *Teratogenic agents act in specific ways (mechanisms) on developing cells and tissues to initiate abnormal embryogenesis (pathogenesis).*
4. *The final manifestations of abnormal development are death, malformation, growth retardation, and functional disorder.*
5. *The access of adverse environmental influences to developing tissues depends on the nature of the influences (agent).*
6. *Manifestations of deviant development increase in degree as dosage increases from the no-effect to the totally lethal level (2).*

Teratology research aims to investigate how different maternal, pregnancy-related and environmental factors, in association to fetal factors, can negatively affect the development of the fetus. One important subgenre in this field is the study of pharmacological agents during pregnancy and how they affect the offspring. With the study of drugs during pregnancy also comes the inevitable study of the underlying conditions that are the indications for drug treatment and how that may impact the fetus.

Teratology research is often associated to the study of congenital malformations (CM). The studies included in this thesis do not specifically study CM, but rather focus on other outcomes such as neonatal morbidity and long-term health and development of children prenatally exposed to neurotropic medications and maternal psychiatric disorders or epilepsy. These outcomes are included in Wilson’s principle number four.

The American Food and Drug Administration classifies risks associated to drugs used during pregnancy and lactation. This system was recently changed and the new classification system provides information on drugs where the balance between risks associated to maternal illness as well as risks associated to the drugs are presented (4). Approximately half of all pregnancies in the US are

unplanned, which makes information on teratological properties of drugs an important matter not only for the pregnant population, but rather all women of child-bearing potential (5). In Sweden, an information database about risks of birth defects and adverse effects of drugs used during pregnancy, based on Medical Birth Register (MBR) data, is widely used clinically (6).

1.1.1 Congenital malformations

In 1961, William G McBride wrote a letter in *The Lancet* on observing a cluster of severe limb deformities in infants with intrauterine exposure to the drug thalidomide, used against pregnancy related nausea and vomiting (7). This was the start of a scandal with enormous human, societal and legal ramifications. It was also the start of intense research activity regarding drugs during pregnancy in general and drugs acting on the central nervous system (CNS) specifically (8). Surveillance of CM with birth/pregnancy registers was initiated, both drug specific registers such as the Lithium Register (9) and nation-wide registers, for example the Swedish MBR (10). Population-based registers have the advantage of providing malformation data on a non-exposed population which is highly relevant since major CMs are seen in 2-4 % of all infants (11). Only approximately 5 % of all CM in the US are caused by environmentally associated teratogen agents (11). Ninety four percent of all CM occur in low and middle income countries (12).

1.1.2 Pregnancy outcome and neonatal effects

Besides structural CM, other important outcomes often studied in pregnant women with specific conditions or exposures are miscarriage or perinatal death, fetal growth, gestational length and Apgar score. Gestational length is a major determinant of neonatal and subsequent health of the child (12-14). Neonatal morbidity in infants prenatally exposed to drugs can be due to toxic effects of the drug, where the neonatal effect is similar to the pharmacological effects seen in treated patients, for example sedation after benzodiazepine or lithium exposure (15, 16). The effects may also be caused by the discontinuation of the drug that occurs at the delivery, neonatal opioid abstinence is a typical example of this mechanism (17).

1.1.3 Long-term neurodevelopment

The brain is the target organ for many drugs and non-pharmacological substances that readily passes over the placenta, for example antidepressants, antiepileptic drugs or ethanol. Since the brain develops throughout the pregnancy, the influence of potential toxins must be evaluated with not only first

trimester use in mind (as is often the case with CM) (18). The immature and developing brain may also be more sensitive to these substances compared to the adult brain. Fetal Alcohol Syndrome (FAS) is a well-known example (19, 20) and the increasing evidence of the negative effect on intelligence seen in children prenatally exposed to valproic acid (VPA) another one (21, 22).

1.1.4 Considerations on lactation

The studies included in this thesis do not directly address lactation and drug use. However, use of pharmacological agents during pregnancy and breast-feeding are often discussed together in the literature as well as in the clinical situation. Lactation data for many drugs are limited. Milk:plasma ratio is of limited use if not infant blood/urine levels in nursed infants have been measured, to establish the relative dose that is being distributed to the infant (23). Several factors must be considered when clinical advice on breast-feeding and drugs are given: the benefits of breast-feeding to formula feeding, the potential negative effects of the drug distributed via breast milk and the risks for the mother should she refrain from the medication. The decision to breast-feed or not may not be binary. In some cases, high peak levels can be avoided through careful timing of drug administration in relation to infant meals, in others, certain types of medication may be preferable to others within a drug class (24). Careful monitoring of the infant, sometimes with infant plasma levels, may be needed if breast-feeding is combined with certain drugs, for example lithium (25, 26).

1.2 Chronic illness during pregnancy

Treating pregnant women with chronic conditions is a delicate medical task. Besides deep knowledge on how to treat the disease in question, it also requires insight into how pregnancy may change the course of illness, how pregnancy can affect pharmacodynamics and pharmacokinetics of drugs used for treatment and how the illness and/or treatment options may affect the unborn child. The negative effects of a drug- or a poorly controlled maternal illness- varies with the stage of the pregnancy. In some cases, associations to other risk factors may need to be considered, for example a higher incidence of smoking in women with depression (8). Pregnant women with a complex medical history often require multidisciplinary teams working together to ensure optimal care during pregnancy. Ideally, the pregnancy is planned, the maternal health status as good as possible at the start of the pregnancy and unsuitable drugs phased out and replaced before conception (27). Some women

may without consulting their doctor quit their medication once they become aware of the pregnancy. This may in the case of serious illnesses have dire consequences and is best avoided by preconception counseling (28).

1.2.1 Epilepsy

Epilepsy, a neurological condition defined by recurrent, unprovoked seizures, affect about 0.5- 0.9 % of the population (29). An estimated 0.3 to 0.4 % of pregnant women have epilepsy and the majority of them use antiepileptic drugs (AED) during pregnancy (30). The absolute risk for status epilepticus, stillbirth or maternal death is very low, but studies indicate increased maternal mortality compared to the rest of the population (31-33). Pregnancy has previously been considered neutral with regard to seizure frequency (27, 34) but a recent study indicate that being pregnant *per se* impairs seizure control in women with epilepsy (WWE) (35). Untreated epilepsy does not entail an increased risk of major malformations but is associated to impaired seizure control (36).

1.2.2 Depression and anxiety disorders

Major depressive disorder (MDD) is a common, potentially serious condition involving depressed mood but also an array of other symptoms. The diagnostic criteria according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) are summarized in Figure 1 (37). A global study ranked depression as the fourth leading cause of disease burden (38). Depression during pregnancy is a significant clinical problem. The prevalence varies greatly depending on disease definition and method of assessment (39-41). A systematic review found point prevalence of major and minor depression during the first trimester to be 11 %, dropping to 8.5 % in the second and third trimester (41). Some studies suggest that up to 18 % of all women have a depressive episode during pregnancy (41).

Anxiety disorders are also common in society (42). Generalized anxiety disorder (GAD) is the most common form of anxiety disorder in a primary care setting, whereas phobias are the most frequent forms in the general population (42, 43). There is a large overlap between GAD and MDD, especially if lower diagnostic thresholds are applied (43). Anxiety disorders also include panic disorder, phobias including social phobia and agoraphobia, obsessive compulsive disorder and posttraumatic stress disorder (42). See figure 2 for definition of GAD (37). Anxiety disorders are also common during pregnancy (40, 44). High level of anxiety during pregnancy has been linked to postnatal depression and there is generally an overlap between anxiety and depressive symptoms (39).

- A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. Symptoms 1-8 should be present nearly every day.
 - 1. Depressed mood most of the day. By self-report or observed by others.
 - 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day. By self-report or observed by others.
 - 3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite.
 - 4. Insomnia or hypersomnia.
 - 5. Psychomotor agitation or retardation (observed by others).
 - 6. Fatigue or loss of energy.
 - 7. Feelings of worthlessness or excessive or inappropriate guilt.
 - 8. Diminished ability to think or concentrate, or indecisiveness.
 - 9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
- B. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
- C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
- D. The occurrence of the major depressive episode is not better explained by other mental disorder.
- E. There has never been a manic episode or a hypomanic episode. (Note: all criteria except 'E' are included in the diagnostic criteria for major depressive episode included in bipolar disorders).

Figure 1. DSM-5 diagnostic criteria for Major Depressive Disorder (37)

- A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities.
- B. The individual finds it difficult to control the worry.
- C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
 - 1. Restlessness or feeling keyed up or on the edge.
 - 2. Being easily fatigued.
 - 3. Difficulty concentrating or mind going blank.
 - 4. Irritability.
 - 5. Muscle tension.
 - 6. Sleep disturbance.
- D. The anxiety, worry or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas.
- E. The disturbance is not attributable to the physiological effects of a substance or to another medical condition.
- F. The disturbance is not better explained by another mental disorder.

Figure 2. DSM-5 diagnostic criteria for Generalized Anxiety Disorder (37)

Depression is treated with pharmacotherapy, psychotherapy or a combination of the two. Selective serotonin reuptake inhibitors (SSRI) are the most commonly prescribed antidepressants (45-47). Antidepressants are first line treatment for moderate to severe depression. Several forms of psychotherapy are recommended, either as single treatment for mild (to moderate) forms of depression or in combination with pharmacotherapy (48, 49). Cognitive Behavioral Therapy has so far the largest body of evidence but Interpersonal Therapy and short-term psychodynamic therapy are also effective treatment options (50, 51).

Untreated mood or anxiety disorders during pregnancy involve risks to the mother as well as to the fetus. MDD, without exposure to antidepressants, have been linked to low birth weight and prematurity as well as neonatal symptoms in some but not all studies (52, 53). Also, maternal stress or negative life events have been associated to lower birth weight, lower gestational age and changed response to painful stimulus in the infant (54, 55). The long-term neurodevelopmental effects associated to untreated maternal mood or anxiety disorders or prenatal exposure to antidepressants are not yet fully described. There are no conclusive evidence of negative effects (52).

1.2.2.1 Post-partum depression and post-partum psychosis

Post-partum depression (PPD) is often preceded by depression during pregnancy (39). The risk of MDD is however higher post-partum compared to before delivery and compared to the female population in general (40). Inadequately treated PPD poses several risks for the mother and the infant, for example insecure mother-infant attachment (39, 56). Post-partum psychosis (PPP) is a rare but serious condition that is potentially life threatening to both mother and child (57). Properly diagnosed and treated PPP has a better long-term prognosis compared to other psychotic conditions but there is an increased risk of mania, depression or a second episode of PPP (58, 59).

1.2.3 Bipolar disorders

Bipolar disorders (BD) are a spectrum of disorders involving episodes of depression, mania, hypomania and/or mixed episodes. Bipolar disorders are divided into subgroups, the most important ones being bipolar disorder I (BDI) and bipolar disorder II (BDII) (37). BDI always include at least one episode of mania, while BDII involves at least one hypomanic episode and at least one major depressive episode (37, 49, 60). A worldwide meta-analysis found a point prevalence of 0.7 % (60), another survey a 12-month-prevalence of 1.5 % for bipolar spectrum disorders, 0.4 % for BDI and 0.3 % for BDII (61). Figure 3 and 4 describe diagnostic criteria in DSM-5 for hypomanic or manic

- A. A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
- B. During the period of mood disturbance and increased energy or activity, ≥ 3 of the following symptoms (4 if mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:
 - 1. Inflated self-esteem or grandiosity.
 - 2. Decreased need for sleep.
 - 3. More talkative than usual or pressure to keep talking.
 - 4. Flight of ideas or subjective experience that thoughts are racing.
 - 5. Distractibility as reported or observed.
 - 6. Increase in goal-directed activity or psychomotor agitation.
 - 7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments).
- C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational function or to necessitate hospitalization or there are psychotic features.
- D. The disturbance is not attributable to the physiological effects of a substance or to another medical condition.

Figure 3. DSM-5 diagnostic criteria for Manic Episode (37)

- A. A distinct period of abnormally and persistently elevated, expansive or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.
- B. During the period of mood disturbance and increased energy and activity, ≥ 3 of the following symptoms (4 if mood is only irritable) have persisted and represent a noticeable change from usual behavior:
 - 1. Inflated self-esteem or grandiosity.
 - 2. Decreased need for sleep
 - 3. More talkative than usual or pressure to keep talking.
 - 4. Flight of ideas or subjective experience that thoughts are racing.
 - 5. Distractibility as reported or observed.
 - 6. Increase in goal-directed activity or psychomotor agitation.
 - 7. Excessive involvement in activities that have a high potential for painful consequences.
- C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.
- D. The disturbance in mood and the change in functioning are observable by others.
- E. The mood disturbance is not severe enough to cause marked impairment in social or occupational function or to necessitate hospitalization. Psychotic features=manic episode.
- F. The disturbance is not attributable to the physiological effects of a substance or to another medical condition.

Figure 4. DSM-5 diagnostic criteria for Hypomanic Episode

episode. Diagnostic criteria for major depressive episode included in BDI or BDII are listed in figure 1 (37).

Clinical management of pregnant women with BD poses similar treatment dilemmas as in the case of unipolar depression. However, the risks associated to the untreated illness are generally higher due to an often more severe condition and special attentiveness related to PPD or PPP is necessary (62). It has been demonstrated that women with BD are not protected against recurrence in mood episodes by their pregnancy but continuous mood stabilizing treatment is effective (63-65).

1.3 Neurotropic drugs during pregnancy

Mood stabilizing drugs, AED, antidepressants and antipsychotic drugs are examples of neurotropic drugs, meaning substances with an affinity to the CNS. These drugs are of utmost interest during pregnancy, partly due to the fact that some of them are commonly prescribed in women of childbearing potential and partly due to the fact that neurotropic drugs may have unwanted and unpredictable effects on the immature, fetal brain (66). Below follows a brief presentation of the drugs studied in the included papers.

1.3.1 Antiepileptic drugs

AED are used to prevent seizures in patients with epilepsy but also as mood stabilizing drugs in bipolar disorders. A large collaborative European database study showed that 0.5 % of all pregnant women dispensed a prescription for an AED during pregnancy (67). The corresponding figure in Sweden 2007 was 0.3 % (45).

Many of the older AED have been associated to an increased risk of major CM, especially VPA, carbamazepine (CBZ) and certain polytherapy combinations (68-72). Use of topiramate, a newer AED, in the first trimester has also been linked to increased risk of CM (73, 74).

A large overview by Källén et al concluded that there was no large increase of neonatal morbidity (excluding CM) associated to AED in general. However, VPA exposure increased the risk of preterm birth and neonatal diagnoses (8).

Exposure to AED during pregnancy may have a negative impact on neurodevelopment. Many studies have linked VPA to autism or lower IQ (31,

75-79). CBZ has also been extensively studied but most studies have failed to show any effect on global cognitive abilities (79-82). Phenytoin (PHT) has been reported to have a negative influence on cognition (83, 84). Lamotrigine (LTG) does not seem to have a negative effect on neurodevelopment and levetiracetam is not yet adequately investigated (85). Polytherapy have also been associated to negative neurodevelopmental effects (81, 83, 86). This association may however be particularly difficult to investigate due to many different drug combinations and potential confounding by indication. Many studies of neurodevelopment and intrauterine exposure to AED have a relatively short follow-up period to evaluation and have limited power. Register studies, such as study I, is an important contribution to this field of research.

1.3.2 Antidepressant drugs

At present, around 4 % of pregnant women in Sweden and 6 % in the US undergo treatment with antidepressant drugs (87-89) and this use is increasing (46, 88). However, the prescription of antidepressants is reduced during pregnancy compared to the months before and after pregnancy (45, 46).

1.3.2.1 Selective serotonin reuptake inhibitors

SSRI are the most commonly used antidepressant drugs during pregnancy (45, 90). They are prescribed for both depression and anxiety disorders. For most SSRI, there have been no association to major malformations although there have been conflicting reports about the risk of congenital heart defects after first trimester exposure to paroxetine, in some instances also fluoxetine (91-95). A recent meta-analysis concluded a slightly increased risk of major cardiac malformation after use of paroxetine, odds ratio (OR) 1.28 (95 % confidence interval [CI] 1.11-1.47) (96).

Late pregnancy exposure to SSRI have been linked to an increased neonatal morbidity in numerous studies. The associated outcomes include respiratory distress, hypoglycemia and CNS effects, including seizures, as well as pre-term birth, low birth weight and low Apgar scores (8, 90, 97-102). The neonatal symptoms, also called poor neonatal adaptation syndrome (PNAS), are mostly transient but may require neonatal care (103-105). Proposed mechanism are withdrawal effects (98, 106) or serotonergic overstimulation syndrome (98). Pharmacogenetic variations in mother and/or fetus may contribute (107). Maternal depression in itself has been linked to poor neonatal adaptation (52, 53) and efforts have been made to account for maternal illness in the study of potential pharmacological effects. In one study an increased risk of

respiratory disorders in infants exposed to SSRI was seen, even when comparisons were made to infants exposed to equal levels of maternal depression (108). SSRI exposure *in utero* has also been linked to persistent pulmonary hypertension in the newborn (PPHN), a rare but potentially serious condition (109, 110). Admittance rates to neonatal care in SSRI-exposed infants have not yet been described in a Swedish material and the severity of PPHN in this group needs to be further described in large cohorts. In study III, we aimed at increasing the knowledge on neonatal morbidity after intrauterine exposure to antidepressants.

There are some studies of long-term neurodevelopment in children prenatally exposed to antidepressants and the majority of them have found similar cognitive development in exposed children compared to non-exposed peers, although subtle differences have been described (111-113). A study investigating child behavior reported that current maternal mood had an effect on externalizing behavior of the child at four years of age but exposure to SSRI was not an important determinant (114). A Swedish, register-based case-control study found an association between autism spectrum disorders without intellectual disability and maternal antidepressant drug use during pregnancy. A causal relationship is however not established (115).

1.3.2.2 Serotonin noradrenaline reuptake inhibitors and other newer antidepressants

Serotonin noradrenaline reuptake inhibitors (SNRI) have a broader effect on neurotransmitters than SSRI and are often used as therapeutic alternatives to SSRI (49). Mirtazapine, venlafaxine and mianserin have both serotonin and noradrenaline inhibitory features whereas reboxetine is a selective noradrenaline reuptake inhibitor. Exposure during pregnancy to these four drugs were associated to similar neonatal morbidity as SSRI exposure; preterm birth and hypoglycemia (116). No increased risk of malformations has been reported (116-118). Similar rates of transient neonatal symptoms were found after venlafaxine and SSRI exposure (107).

Bupropion is a second line antidepressant treatment, but also an effective pharmacological tool in smoking cessation, possibly also in pregnant women (119). Although data are limited, an increased risk of cardiac malformations after first trimester exposure has been reported (120, 121).

1.3.2.3 Tricyclic antidepressants

Prior to the introduction of SSRI, tricyclic antidepressants (TCA) were first

line of treatment for MDD. SSRI have a more favorable side effect profile and therefore, today, dominate the field (48). However, TCA remain as first line of treatment in severe, acute depression (48, 49). During recent years, the prescription of TCA have remained relatively unchanged in pregnant patients whereas a large increase of prescription of SSRI has been reported (46).

Clomipramine use during early pregnancy has been associated to an increased risk of cardiac malformations (8, 90). Neonatal morbidity, similar to that observed after SSRI/SNRI exposure, have been reported after TCA exposure in late pregnancy (8, 122). A tendency towards worsened neonatal outcome, including neonatal diagnoses, prematurity and low birth weight, has been described after TCA exposure compared to SSRI exposure, but this may be due to confounding by indication (8).

1.3.3 Mood stabilizing drugs

The treatment for BD focuses on acute stabilization, which means to bring a depressed or manic patient towards euthymic (stable) mood, and maintenance treatment, in which the goals are relapse prevention and reduction of mood disorder symptoms. In bipolar depression, antidepressants have not been found as effective as in unipolar depression and the treatment is challenging (123). Lithium is the most established maintenance treatment and have been found effective in numerous studies (124). Side effects include negative effects on renal function, disturbances of the thyroid and parathyroid glands and weight gain. Lithium have a rather narrow therapeutic window and therapeutic drug monitoring is necessary (125). AED, for example LTG, can be used for mood stabilization but has less robust evidence compared to lithium (123). AED and pregnancy are discussed in section 1.3.1. Antipsychotic drugs have sound evidence in the treatment of manic episodes but less in mood relapse prevention (123). Psychoeducation is also an important part of the therapeutic interventions in BD (126).

1.3.3.1 Lithium

Lithium completely passes over the placenta and umbilical cord concentrations are similar to those in maternal blood (16). CM, especially cardiac malformations and specifically Ebstein's anomaly, a cardiac anomaly involving the tricuspid valve, have been linked to lithium exposure during pregnancy. Reports during the 1970's described increased risks but later studies have modified this substantially and it is still debated whether first trimester exposure to lithium in therapeutic doses constitutes an increased risk of cardiac malformations (125, 127-131).

Increased risk of preterm delivery has been described in women with BD, regardless of exposure to mood stabilizers (129, 131). Infants exposed to lithium were found heavier than non-exposed infants in one study (132) but this was not repeated in a larger study (131). Neonatal morbidity related to fetal exposure to lithium has also been reported but the prevalence is not known. Lithium exposure has been associated to neonatal adaptation difficulties and symptoms such as poor muscle tone, lower Apgar score, cyanosis, hypothyroidism, neonatal diabetes insipidus, hypoglycemia, heart rhythm disturbances and respiratory disturbances (16, 133). Close surveillance of maternal serum lithium levels during pregnancy is of great importance for the safety of both mother and infant (16).

Current knowledge on long-term outcome after prenatal lithium exposure is limited. A study of 60 lithium-exposed children reported no difference in neurodevelopmental outcome compared to their non-exposed siblings, however evaluation was based on maternal report only (134). Developmental milestones in 21 children were reported similar to a control group (132). A systematic evaluation of 15 children exposed to lithium *in utero* revealed no adverse effect on cognition or neurological development (135). High quality evaluations of neonatal and long-term outcome of children prenatally exposed to maternal BD and lithium are needed.

1.3.3.2 Antipsychotic drugs

Antipsychotic drugs, especially second generation antipsychotics (SeGA), are increasingly being used in BD and MDD (136). A recently published meta-analysis reported an increased risk of CM (no specific pattern) and prematurity in SeGA exposed infants (137). Patients who use SeGA have a risk of substantial weight gain, insulin resistance and other metabolic side effects related to the medication (136). Increased risks of maternal gestational diabetes and neonatal respiratory disorders have been described after maternal use of antipsychotics (first generation antipsychotics, FGA, and SeGA) (138, 139). Other types of neonatal behavioral signs, such as extrapyramidal signs, have been reported after exposure to both FGA and SeGA. These may not be as quickly resolving as PNAS reported after antidepressant exposure (140).

1.3.4 Other neurotropic drugs

In patients with psychiatric illnesses such as depression, anxiety disorders or BD, polypharmacy is common (141). In addition to antidepressants or mood stabilizers, other neurotropic agents such as pain medication, hypnotics or sedatives are used in the pregnant population (45, 142).

1.3.4.1 Hypnotics and sedatives

Benzodiazepines can be used as both sedatives/anxiolytics and hypnotics. They are commonly prescribed in combination with antidepressants. Prescription of benzodiazepines was seen in 1.5 % of all pregnancies in a Norwegian register study (15). Exposure to benzodiazepines *in utero* has been linked to preterm birth, intrauterine growth restriction and PNAS (143) but no certain association to CM, although more than expected numbers of alimentary tract malformations have raised concern (143, 144). The combination of SSRI and benzodiazepines was in one study associated to an increased risk of cardiac malformations (145) but another study could not replicate the association (8).

Hypnotic benzodiazepine receptor agonists are often grouped together with benzodiazepines but have also been evaluated separately in pregnant women. They do not seem to increase the risk of CM (142).

Antihistamines are commonly used against nausea and vomiting during pregnancy but also have soporific properties which make them suitable for insomnia treatment in pregnant women. Antihistamines during the first trimester does not increase the risk of CM (146) and carries no risk for adverse delivery outcome according to Swedish register data (147).

2. AIMS

2.1 General aims of the thesis

The studies included in this thesis aimed at describing how neurotropic drugs and maternal chronic illness during pregnancy influence the health of the offspring, both neonatal and long-term outcome, with emphasis on neuro-development.

2.1.1 Study I

We aimed to investigate academic achievement (school grades) at age 16 in children prenatally exposed to maternal epilepsy with or without antiepileptic drug exposure during pregnancy and compare them to non-exposed peers.

2.1.2 Study II

Study II aimed to describe neonatal health in infants born to mothers who had used an antidepressant, SSRI or SNRI, during late pregnancy. We specifically studied neonatal diagnoses and behavioral scoring according to the Finnegan/Neonatal Abstinence Score and made comparisons between infants exposed to different antidepressant drugs.

2.1.3 Study III

The aim of the study was to describe the severity of neonatal complications after fetal exposure to antidepressant drugs in a nation-wide, register-based cohort. The studied outcomes were admissions to neonatal care units, length of stay, neonatal diagnoses and interventions.

2.1.4 Study IV

We aimed at describing cognitive development and general health at pre-school age in children prenatally exposed to maternal mood disorder, mainly bipolar disorder, with or without lithium exposure during pregnancy and compare them to unexposed children. Maternal psychiatric symptoms and neonatal health were also studied.

3. METHODS

3.1 The register-based studies

In studies I and III we have combined information from national registers on health care (I and III) and education (study I) to answer our research questions. The included registers and study methods are described below.

3.1.1 Registers

Sweden have a long tradition of collecting information about the health as well as the social and financial situation of its citizens in population-based registers (148). The National Board of Health and Welfare ('Socialstyrelsen') is generally responsible for registers concerning health and the health care sector. Statistics Sweden ('Statistiska Centralbyrån', SCB) compile large amounts of information on population and welfare, economical matters, regions and environment, education and many other subjects (149). Registers can be used for research purposes after application to the Regional Board of Ethics and the register holder. Linkage between different registers can be made using the personal identification number (PIN), a unique 10-digit number that all inhabitants of Sweden receive, either at birth or after immigration (150).

3.1.1.1 The National Patient Register

The National Patient Register (NPR) was founded by the National Board of Health and Welfare in 1964 and initially described inpatient care for psychiatric and somatic care in parts of the country. The coverage of the register increased gradually and in 1987, after a major revision, all counties of Sweden started reporting data on inpatient care (151). In 1983, approx. 85 % of all inpatient somatic care was reported to the register and in 2011, the coverage for somatic, inpatient care was almost 100 % (152). Since 2001, the register also contains information on public and private outpatient care. Primary care is not recorded in the NPR. The register contains information on main diagnosis, secondary diagnosis, length of hospital stay, procedures and age and sex of the patient (151).

3.1.1.2 The Prescribed Drug Register

The Prescribed Drug Register (PDR) contains information on drugs prescribed and dispensed in ambulatory care in Sweden, covering more than 99 % of these prescriptions (153). This includes information on dose, substance and brand as well as PIN, age and sex of the patient and information about

the prescriber (154). In Sweden, epidemiological studies on drug use during pregnancy have extracted drug information from the MBR, available since 1995, or the PDR, available since July 2005. The agreement between the PDR and the MBR is better for drugs used in chronic illnesses compared to short term treatments. The agreement for AED were 69 % and for antidepressants 60 % (45).

3.1.1.3 The Medical Birth Register

The MBR in Sweden was founded in 1973. It contains information on almost all pregnancies and deliveries in Sweden, only 0.5-3 % are missing completely (10). The information is extracted from the patient records filled out at the antenatal care clinics, delivery units and pediatric clinics. It contains information on maternal health and social situation during pregnancy and include for example smoking habits, body mass index (BMI), maternal age, mode of delivery, Apgar score of the infant, anthropometric data, gestational age (GA) and diagnostic codes according to the International Classification of Disease (ICD) for mother and infant. From 1995 and onward, information on maternal medication at the first visit to the antenatal care clinic and at GA 32 was included and computerized (10).

3.1.1.4 The Swedish Neonatal Quality Register

The Swedish Neonatal Quality Register (SNQ) started in 2000 in order to provide detailed information on neonatal care for the purpose of improving care and facilitating research. By 2004, 21 out of then 34 neonatal units reported all their patients to the register (155). It contains information on newborn infants admitted to a neonatal ward at birth or within 28 days of birth. Today, all 37 neonatal units in Sweden are included. The register contains medical information on diagnoses, procedures, feeding, respiratory support, pharmacological treatments, duration of stay and many other variables (156, 157). Diagnostic criteria are predefined (155).

3.1.1.5 The Perinatal Revision South Register

The Perinatal Revision South (PRS) database comprises obstetric and neonatal data from all maternity units in the southern Swedish region. PRS was established in 1995 with quality assurance of perinatal and neonatal care as the main purpose (158). In 1995, there were 11 obstetrical units but since then, four of them have closed. Neonatal data are sent from all seven neonatal units in the region. Since 2005, all data are sent electronically and since 2012, PRS data are included in SNQ (159).

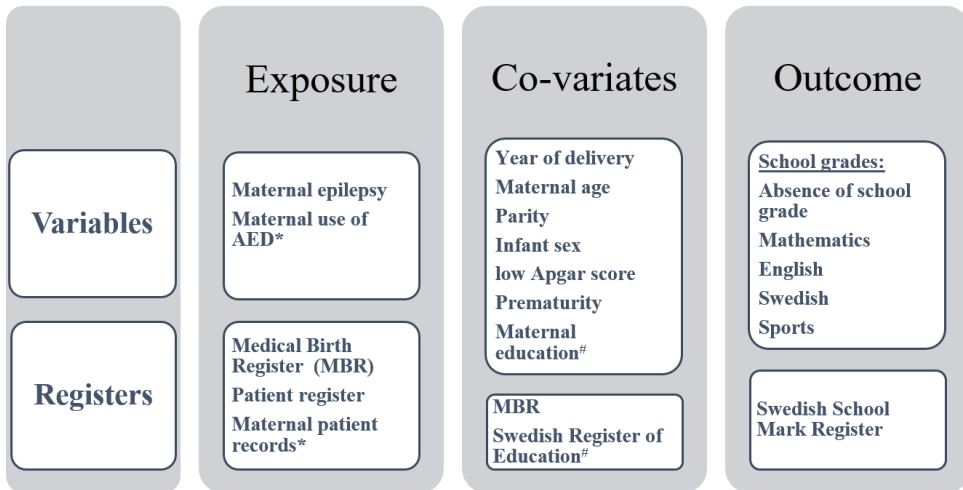


Figure 5. Patients and data collection in study I.

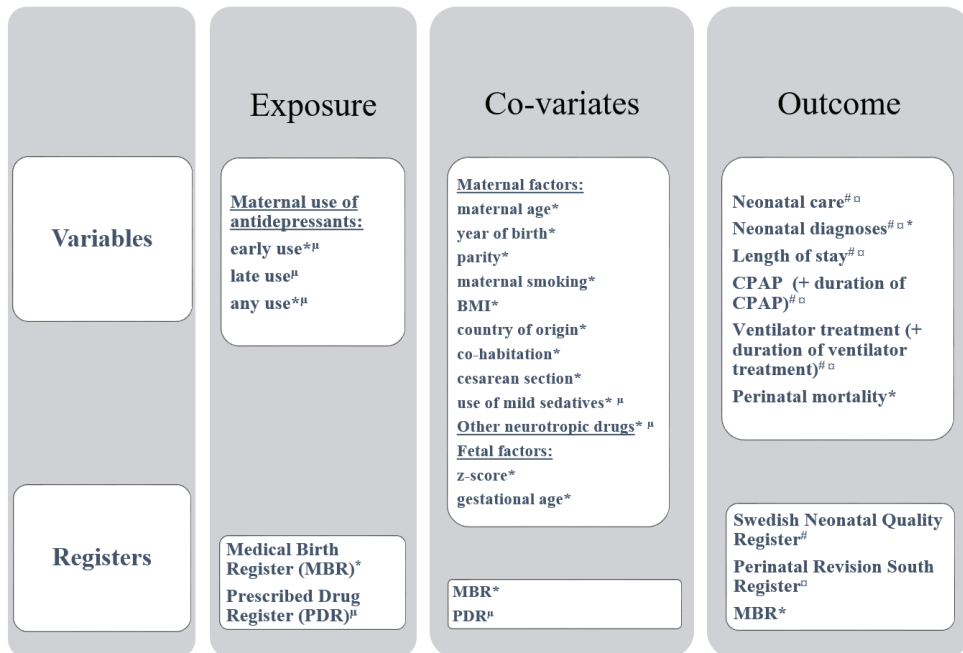


Figure 6. Patients and data collection in study III.

3.1.1.6 The Swedish School Mark Register

The Swedish National Agency for Education compile statistics from all Swedish schools on grades from compulsory school as well as upper secondary school and adult education. This has been done since 1988 and is published once per year. Information from the register can, after application to Statistics Sweden, be available for research purposes. The register holds information on grades in specific subjects as well as on leaving certificates (LC)/final grades (160).

3.1.1.7 The Swedish Register of Education

This register contains information on highest level of education attained by all residents of Sweden, aged 20-74 years. It started in 1985 and is since then updated once per year. The level of education is divided into six levels: 1=primary and lower secondary education less than 9 years, 2= primary and lower secondary education, 9 (or 10) years, 3=upper secondary education (2-3 years), 4=post-secondary education <2 years, 5=post-secondary education ≥ 2 years, 6=postgraduate program (161).

3.1.2 Patients and data collection

Exposures, co-variates and outcomes analyzed in the two register-based studies (I and III) as well as data sources are summarized in figure 5 and 6.

3.1.2.1 Study I

In study I, the MBR and the NPR were used to identify WWE who had been giving birth during 1973 to 1986. Women with a diagnostic code of epilepsy (ICD code) and hospital care in the NPR between 1973 and 1989 were identified as WWE. WWE who had been included in a clinical study at South Hospital in Stockholm, conducted 1984-1995 and women with a diagnosis of epilepsy in the MBR were also included (80). The children of WWE were compared to the rest of the population.

Information on maternal use of AED during the first trimester of the pregnancy was retrieved from the maternal care records. Variables relating to delivery and baseline maternal data were added from the MBR and maternal education level from the Swedish Register of Education. Information on the outcome, the school grades at the end of compulsory school at approx. 16 years of age, was taken from the Swedish School Mark Register. The different registers were linked together with a combination of mother's date of birth, date of delivery, delivery hospital, infant sex and birth weight which gives a full identity without the use of PIN.

3.1.2.2 Study III

The study population consisted of all singleton, live births in Sweden, registered in the MBR between 1 July, 2006 and 31 December, 2012. Using PIN for linkage, we could add information on maternal drug use during pregnancy from the PDR and the MBR. Data on neonatal outcomes were collected from the SNQ, the PRS and the MBR.

The studied antidepressant agents were divided into the following subgroups based on their pharmacological properties: SSRI, TCA, SNRI, mirtazapine/mianserin and other antidepressants, (moclobemide, bupropion, reboxetin and agomelatin). The use of antidepressants was allocated into *any use*: drugs dispensed 1 month before and at any time during the pregnancy, *late use*: drugs dispensed during the last 90 days of the pregnancy and *early use only*: drugs dispensed 1 month before and during pregnancy but not for the last 90 days of the pregnancy.

The neonatal outcomes studied included information from both ‘checkboxes’ and ICD-codes from SNQ and PRS as well as ICD-codes from the MBR. Since SNQ only contains information on infants admitted to a neonatal care unit (NCU), the inclusion of information from the MBR meant that we also had information on children with neonatal morbidity who remained in the maternity ward. Of course, the outcome ‘neonatal care’, length of stay and information on ventilator/CPAP (Continuous Positive Airway Pressure) was only available for children admitted to NCU.

3.1.3 Statistical methods

3.1.3.1 Study I

We compared children of WWE to all other children in the cohort using the Mantel-Haenszel analysis and adjusting for child’s year of birth, maternal age, parity and maternal level of education. Risks were expressed as OR, and 95 % CI were estimated using Miettinen’s method. Two ORs were compared as two-tailed z tests based on the estimated variances.

3.1.3.2 Study III

Logistic regression analyses were used to compare dichotomous outcomes. In the different analyses, we compared any antidepressant versus no use, the individual antidepressant substances versus no use, or late use versus early use only. Multivariate analyses were performed with ‘maternal’ and ‘fetal’ factors included, presented in Figure 6. Differences regarding the length of stay at the neonatal unit, the number of days on ventilator or CPAP respectively, were evaluated using Mann-Whitney U tests or Kruskal-Wallis tests

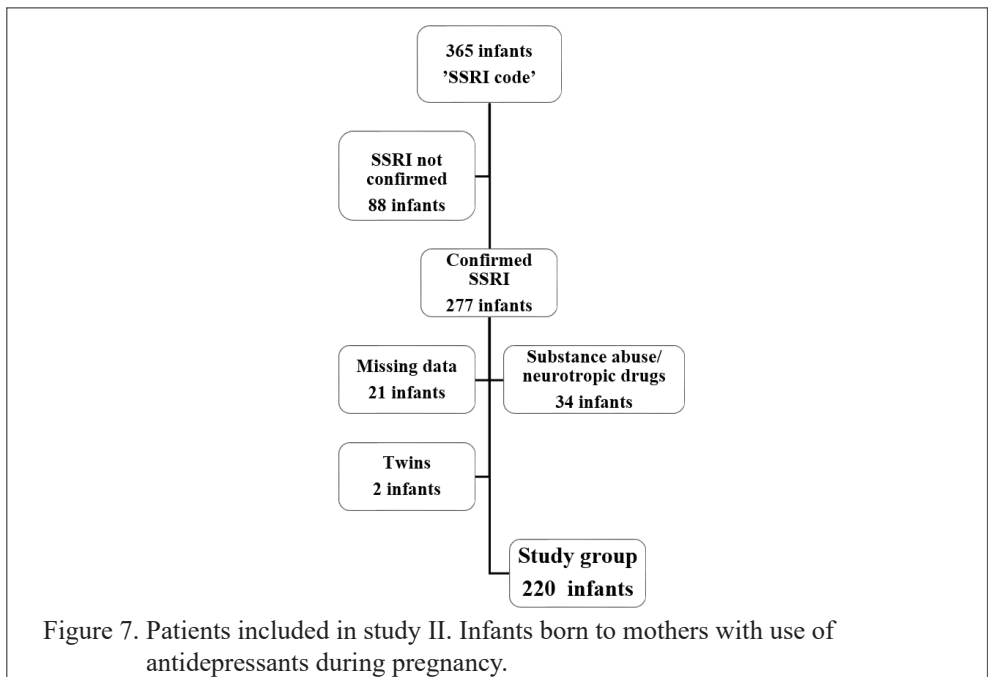
(non-parametric tests). Statistical analyses were made using SPSS (version 22) and GaussTM (Aptech Systems Inc., Maple Valley, WA, USA, <http://www.aptech.com>, version 10).

3.2 The clinical cohort studies

Studies II and IV were clinical cohort studies. Mother-infant pairs were divided into groups by maternal illness or neurotropic drug use during pregnancy and studied with regard to neonatal (studies II and IV) and long-term health (study IV).

3.2.1 Study II

This study was a retrospective cohort study investigating neonatal health in children exposed to antidepressant drugs during pregnancy.



3.2.1.1 Patients

The study patients were identified in the integrated electronic patient record used in the delivery and prenatal care units as well as for outpatient maternal visits (Obstetrix 2.12.01.100, Siemens AG, Munich, Germany). Patients with diagnostic codes for psychiatric illness during pregnancy and exposure to fetus of pharmacological substances were selected as the study population. Wo-

men fulfilling these criteria and who had been giving birth at the Karolinska University Hospital Huddinge between 1 January, 2007 and 30 June, 2009 were included. Women with other relevant neurotropic medications (AED, lithium or opioids), substance abuse or missing data from large parts of the health care records were excluded. Final study population is described in figure 7.

3.2.1.2 Data collection

Data was collected from the electronic health care records on social situation, prenatal medication (antidepressants and other pharmacological substances), health status including obstetrical health and mode of delivery. The source of information in the health care records were the prenatal care visits where standardized forms are used and large amounts of information on maternal health is gathered. Antidepressant use was defined as the type of antidepressant used in the third trimester. Health care records were also scrutinized for information on neonatal health including, but not limited to, ICD codes for neonatal morbidity such as hypoglycemia (defined as a blood glucose level < 2.6 mmol/L), respiratory disorders and admittance to NCU.

3.2.1.2.1 Neonatal Abstinence Score

During the study period, all infants where the mother had reported antidepressant use during late pregnancy were routinely observed at the maternal ward for at least 72 hours and modified Finnegan score (Neonatal Abstinence Score, NAS) used regularly to detect signs of abstinence. NAS was originally developed to diagnose abstinence in infants prenatally exposed to opioids (162), but has also been used to assess neonatal symptoms in SSRI-exposed infants (163). A version re-translated into English from Swedish is showed in figure 8 (164). The assessment includes four categories: CNS, respiratory, gastrointestinal and ‘other symptoms’, maximum score 41 points. Neonatal abstinence was in this study classified as either mild (score ≥ 4 on ≥ 2 occasions) or severe (score ≥ 8 on ≥ 2 occasions).

3.2.1.3 Statistical methods

Logistic regression was used to compare dichotomous outcomes between the different types of antidepressant exposures in a multivariate model (neonatal care, hypoglycemia, respiratory diagnosis). Kruskal-Wallis was used to compare time to ‘peak score’ of NAS and blood glucose levels in hypoglycemic infants between the exposure groups. We used ordinal regression to compare the rates of ‘no abstinence’, ‘mild abstinence’ and ‘severe abstinence’. OR in ordinal regression describes the odds to move one step up on an ordinal scale. Statistical analyses were performed using StatisticaR 64, version 12 (Statsoft Scandinavia AB, Uppsala, Sweden).


	Time 									
CNS		Score								
Cry	Highpitched, possible to soothe	2								
	Highpitched, not possible to soothe	3								
Sleep	Sleeps < 3 h after feed	1								
	Sleeps < 2 h after feed	2								
	Sleeps < 1 h after feed	3								
Moro-reflex	Over active	2								
	Very over active	3								
Tremor	Moderate tremors disturbed	1								
	Severe tremors disturbed	2								
	Moderate tremors undisturbed	3								
	Severe tremors undisturbed	4								
	Scratch marks	1								
Tone	Increased muscle tone	2								
Seizures	Myoclonic jerks	3								
	Generalised seizures	5								
Respiratory										
Yawning	Frequent yawning >3-4/interval	1								
Nose	Congested nose	1								
Sneezing	>3-4 times/interval	1								
	Nasal flaring	2								
Tachypnea (>60/min)	No retractions	1								
	With retractions	2								
Gastrointestinal										
Sucking behaviour	Excessive sucking	1								
Feeding	Poor feeding	2								
Vomiting	Regurgitation	2								
	Projectile vomiting	3								
Stool	Loose	2								
	Watery	3								
Other symptoms										
	Sweating	1								
Fever	37.2-38.2° C	1								
	>38.2° C	2								
Colour	Mottling	1								
TOTAL SCORE										

Figure 8. Neonatal Abstinence Score. Modified from Finnegan to Swedish by I Sarman (164) here re-translated.

3.2.2 Study IV

This study was a clinical cohort study on neonatal health as well as cognitive and general health at preschool age in children born to women with severe mood disorders with or without lithium during pregnancy.

3.2.2.1 Patients

The cohort consisted of two groups of mother-child pairs: women with mood disorders (maternal mood disorder, MMD) and women without mood disorders (no MMD). The first group was further divided into two: with or without lithium use during pregnancy. Patients with mood disorders were recruited from the Affective Disorder Outpatient Clinic, Psychiatry Southwest, Stockholm. The children were born between 2006 and 2010 and the mothers were offered participation when the child was four to five years old. Women without mood disorders were identified through the electronic health care record *Obstetrix*® and offered to participate. They were matched for maternal age, child's date of birth and child's sex. Maternal psychiatric illness and/or treatment during pregnancy were exclusion criteria.

3.2.2.2 Data collection

Information on maternal psychiatric health during pregnancy, including pharmacotherapy, lithium serum levels and obstetrical information was obtained retrospectively from a clinical register held at the outpatient clinic and from patient records. Neonatal morbidity, diagnoses, laboratory measurements and treatments was collected from electronic health care records (*Obstetrix*®). Information on thyroid stimulating hormone (TSH) from the neonatal screening was obtained from the PKU register, Center for Inherited Metabolic Diseases, Karolinska University Hospital.

The prospective part of the study included one or two research visit(s) at Karolinska University Hospital Huddinge. A researcher performed a standardized interview with the mother regarding maternal and child health and the social situation of the family and distributed several self-evaluation questionnaires: PHQ-9 (current symptoms of depression), AUDIT (alcohol use disorders identification test) and DUDIT (drug use disorders identification test). At the same visit, the child was examined by a pediatrician and blood tests drawn (kidney- and thyroid tests). He or she was also evaluated by a child psychologist (blinded to exposure to maternal illness or medication), using the Wechsler Preschool and Primary Scale of Intelligence, 3rd edition (WPPSI-III). All children but one, who had recently been tested in a clinical setting by a different psychologist, were tested by the same psychologist.

3.2.2.2.1 Wechsler Preschool and Primary Scale of Intelligence, 3rd edition
WPPSI-III is a standardized psychological instrument used to evaluate cognition in children between the ages 2 years and 6 months to 7 years and 3 months. The test results are presented as Full Scale IQ, FSIQ, which consists of seven subtests (three verbal, three non-verbal subtests and one subtest also included in the processing speed quotient, PSQ), Verbal IQ, VIQ (three subtests), and Performance IQ, PIQ (three subtests on non-verbal problem solving). PSQ consists of the results from two subtests. WPPSI-III IQ values are tested in a normal population and mean values are 100, standard deviation (SD) 15 (165).

3.2.2.3 Statistical methods

Fisher's exact test was used for dichotomous outcomes, Kruskal-Wallis or Wilcoxon rank sum test for continuous variables. Spearman's correlations test was used in testing correlation between maternal and infant lithium concentration. In statistical testing of the WPPSI-III results we used regression models for PIQ. Due to non-ignorable missing data (three children had missing values for VIQ, four for FSIQ and seven children had missing values for PSQ) a Tobit regression model was used to analyze VIQ, FSIQ and PSQ. Using this model we assumed that the missing value was at most the same value as the lowest recorded value for that variable. We chose the confounders in the regression analyses by testing them in a separate model, one by one, against PIQ, VIQ, FSIQ and PSQ and including variables with a p-value < 0.2 in any of the analyses. In all other statistical tests of our results, a significance level of $p < 0.05$ was used. Data were analyzed using Stata (Statacorp, Texas, USA, version 13.1).

3.3 Ethical considerations

Research concerning personal information such as reproductive history, socioeconomic situation, psychiatric health and family situation are of a sensitive nature. All patient material in the presented studies have been handled with a high level of confidentiality, as stated in the ethical permits. In studies I and III, population-based registers containing large amounts of patient data have been linked together and analyzed without personal identification numbers in the analytic phase. In study II, patient records were scrutinized by one researcher (LF). No individual patient consent was given or requested in study II, in accordance with the ethical permit. In study IV, all women gave informed consent to their own study participation and all legal guardians of participating children gave informed consent to their child's participation.

Ethical permit, study number I: 2006/673-31/4, Regional Ethics Board, Stockholm, Sweden; study II: 2010/686-31/2, Regional Ethics Board, Stockholm, Sweden; study III: 2013/342, Regional Ethics Board, Lund, Sweden; study IV: 2011/96-31/2 and amendment 2011/1144-32, Regional Ethics Board, Stockholm, Sweden.

4. RESULTS

4.1 Intrauterine exposure to neurotropic drugs and neonatal effects

Study II, III and IV investigate how neurotropic drugs during pregnancy, especially the last part of the pregnancy, can affect neonatal morbidity. Study II and IV are smaller but more controlled cohorts whereas study III describes a large, population-based cohort. They all include children born to mothers with mood disorders or anxiety disorders.

In study II, the study population consists of 220 infants born to mothers with antidepressant medication during pregnancy. 77 were exposed to citalopram, 76 to sertraline, 34 to fluoxetine and 33 to ‘other antidepressants’ (escitalopram, n=13, venlafaxine, n=11, paroxetine, n=8, and duloxetine, n=1).

In study III, the study population consisted of 741040 singleton births, of which 22 507 (3.0 %) were exposed to antidepressants. The most common drug group was SSRI with 17 736 exposures (2.4 %).

The patient cohort in study IV were 24 mothers with MMD and their 28 children (one set of twins, three sibling pairs) and 11 no MMD mother-child pairs. 20 children had been exposed to lithium during pregnancy, 8 had been exposed to MMD but no lithium and 11 no MMD. There was no information on obstetrical care and the neonatal period in one mother-child pair (MMD + lithium group).

4.1.1 Neonatal care

In study II, we could describe an admittance rate to NCU of 13 %, with no statistically significant differences in admittance rates between infants exposed to citalopram, sertraline, fluoxetine or ‘other antidepressants’. We did not have a proper control group but data from SNQ showed an admittance rate for Karolinska University Hospital Huddinge for the years 2007-2009 of 10 %, this difference was not statistically significant in a univariate analysis, $p=0.16$.

After study II, we decided to move on to a nation-wide, register-based study of infants exposed to antidepressants *in utero*. In study III, SNQ in combination with MBR and PDR provided us with a dataset that had adequate power to find differences between exposed and non-exposed children but also pos-

sible drug-class specific effects. We made comparisons both between the exposed children and the non-exposed population as well as between infants exposed in early and late pregnancy. The latter analysis was an attempt to adjust for maternal psychiatric morbidity. In the analysis of early vs late exposure a significant heterogeneity was found between all five antidepressant groups, $p=0.002$. ORs were highest for TCA and SNRI exposed infants.

Table 1 describes neonatal care in infants exposed to antidepressants vs non-exposed infants. When antidepressant drug treatment was combined with other neurotropic drugs – most commonly opioids, neuroleptics or sedatives – 16 % of the neonates were admitted to NCU; OR 1.8 (95 % CI 1.7-1.9, adjusted for maternal factors). When early and late use of antidepressants were compared there was also significantly increased odds for neonatal care, OR 1.7 (95% CI 1.6-1.9, adjusted for maternal factors and use of other neurotropic drugs). Number needed to harm (NNH) was 15 (adjustment for maternal factors and use of other neurotropic drugs did not change the estimate).

Table 1. Neonatal care in infants exposed to antidepressants^A (regardless of timing of exposure) during pregnancy. Study III.

	Total	Neonatal care		Crude		Adjusted ^C	
	n	N	%	OR	95 % CI	OR	95 % CI
Patients without simultaneous exposure to other neurotropic drugs^B							
No antidepressant drug	671627	54059	8.0	1.0	Reference	1.0	Reference
Any antidepressant drug	15013	1931	12.9	1.7	1.6-1.8	1.5	1.4-1.6
SSRI	12516	1594	12.7	1.7	1.6-1.8	1.5	1.4-1.6
SNRI	999	155	15.5	2.1	1.8-2.5	1.7	1.4-2.0
TCA	455	53	11.6	1.5	1.1-2.0	1.4	1.0-1.8*
Mirtazapin/Mianserin	299	37	12.4	1.6	1.1-2.3	1.5	1.0-2.1*
Combinations or changes of therapy	617	83	13.5	1.8	1.4-2.3	1.6	1.3-2.0
Patients with simultaneous exposure to other neurotropic drugs^B							
No antidepressant drugs	46906	5151	11.0	1.4	1.4-1.4	1.2	1.2-1.3
Any antidepressant drugs	7494	1240	16.5	2.3	2.1-2.4	1.8	1.7-1.9
SSRI	5220	843	16.1	2.2	2.0-2.4	1.8	1.6-1.9
SNRI	683	118	17.3	2.4	2.0-2.9	1.8	1.5-2.2
TCA	410	85	20.7	3.0	2.4-3.8	2.3	1.8-3.0
Mirtazapin/Mianserin	278	37	13.3	1.8	1.2-2.5	1.4	1.0-2.0*
Combinations or changes of therapy	818	147	18.0	2.5	2.1-3.0	2.0	1.7-2.4

^AExposure information obtained from self-reported use in early pregnancy or any prescription during pregnancy or 1 month before.

^BAntiepileptics (N03A), opioids (N02A), psycholeptics (N05) and centrally acting sympathomimetics (N06BA).

^CAdjusted to maternal factors (maternal age, year of birth, primiparity, maternal smoking, BMI, mother born in Sweden, cohabiting with the child's father, cesarean section and use of mild sedatives during pregnancy).

*The lower CI95% of 1.0 is statistically significant ($p<0.05$).

Duration of neonatal care was significantly shorter for infants exposed to antidepressants compared to non-exposed infants ($p < 0.001$).

In study IV, 3/19 infants in the MMD and lithium group were admitted to NCU, 3/8 infants in the MMD and no lithium group and 2/11 in the no MMD group, these differences were not statistically significant ($p = 0.5$). Among full-term infants only, there were NCU admissions in 2/18 in the MMD and lithium group, 0/5 in the MMD and no lithium group and 1/10 in the no MMD group.

4.1.2 Neonatal Abstinence Score

In study II, NAS scoring was performed in 205 infants out of 220 exposed to antidepressants. Mild abstinence/maladaptation (score 4 and above on at least two occasions) was seen in 22 % and severe (score 8 and above on at least two occasions) in only 3 %. There were no statistically significant differences in occurrence of mild or severe abstinence between the different types of antidepressant exposure ($p = 0.85$, ordinal regression, adjusted for infant sex and 5 min Apgar).

4.1.3 Neonatal morbidity

In study II, III and IV, several diagnoses or groups of diagnoses have been studied in infants prenatally exposed to neurotropic medications.

4.1.3.1 Hypoglycemia

In study II hypoglycemia was seen in 19 % of all study subjects (42 patients), significantly more prevalent in infants exposed to fluoxetine (35 %) compared to citalopram (11 %), multiple regression model adjusting for GA, 5 min Apgar, maternal smoking, infant sex, $p = 0.01$. In study IV, neonatal hypoglycemia was seen in 2/18 children in the group exposed to MMD and lithium, 2/8 in the MMD and no lithium group and 1/11 in the no MMD group, $p = 0.84$.

In study III, the incidence of hypoglycemia was 4 % in infants prenatally exposed to SSRI compared to 2.4 % in the general population, OR 1.3 (95 % CI 1.2-1.4, adjusted for maternal factors and use of neurotropic drugs). Adjusted OR, late use vs early use only of SSRI for hypoglycemia was 1.5 (95 % CI 1.3-1.7). In the comparison between late and early use, there was also an increased risk of feeding difficulties, adjusted OR 1.7 (95 % CI 1.3-2.3).

4.1.3.2 Respiratory disorders

In study II, a respiratory diagnosis was seen in 14 out of 220 infants (6 %), no significant differences between the exposure groups ($p= 1.0$, logistic regression adjusting for 5 min Apgar and GA). In study IV, three children exposed to MMD and no lithium and one child born to a mother with no MMD had a respiratory diagnosis. All four children were born preterm (one pair of twins).

There was an increased risk of respiratory diagnoses in infants prenatally exposed to SSRI in study III. Transient tachypnea and other respiratory diagnoses (not including meconium aspiration syndrome, PPHN or respiratory distress syndrome (RDS)) was more common in SSRI-exposed infants compared to the general population, OR 1.7 (95 % CI 1.6-1.9, adjusted for maternal factors and use of neurotropic drugs) and in early vs late use, OR 1.7 (95 % CI 1.5-2.0, adjusted as above). RDS was not more common in SSRI-exposed infants compared to non-exposed, OR 1.0 (95 % CI 0.8-1.2, adjusted as above). CPAP treatment was more common in SSRI-exposed infants compared to non-exposed, OR 1.5 (95 % CI, 1.4-1.6, adjusted as above).

4.1.3.3 Persistent pulmonary hypertension

PPHN was more common both when comparing SSRI-exposure to non-exposure; OR 1.3 (95 % CI 1.0-1.6, adjusted as above) and treatment during late vs early pregnancy; OR 2.1 (95 % CI 1.3-3.2, adjusted as above). The corresponding NNH was 285, comparing late and early exposure, adjusted for maternal factors and neurotropic drugs. Restricting the analysis to full-term infants, the association between SSRI, late vs early use, and PPHN was even more pronounced; OR 2.6 (95 % CI 1.4-4.8). NNH was however larger, 322, due to lower absolute risk. The mortality rate among infants with PPHN was 3.4 % (3/89) for SSRI-exposed and 8.3 % (171/2051) for non-exposed infants. This difference was not statistically significant, OR 0.4 (95 % CI 0.1-1.2).

4.1.3.4 CNS-related disorders

In study II, where NAS was used to assess poor neonatal adaptation in exposed infants, CNS-related symptoms accounted for 67 % of the scoring points in the group with severe abstinence and 58% in the group with mild abstinence.

In study III, separate analyses were made for CNS-related disorders (seizures, muscle tone disturbances, withdrawal symptoms, disturbances of cerebral status, hypoxic ischemic encephalopathy) and intracerebral hemorrhage (ICH). CNS-related disorders were more common both when SSRI-exposed infants were compared to non-exposed as well as in the comparison of early vs late use, in the latter analysis; OR 2.0 (95 % CI 1.3-3.1, adjusted for ma-

ternal factors and neurotropic drugs). There was no increased risk of ICH in any of the analyses.

4.1.3.5 Thyroid disorders

In study IV, TSH levels from the neonatal screening was available for 38/39 children. None of the children had abnormal values. In the child with a missing value in the neonatal screening, a normal TSH (3.8 μ U/ml) was analyzed in the neonatal period. TSH analysis due to maternal lithium treatment was done in another 7 cases (no neonatal data in one child) and among them, one child had a TSH of 37 μ U/ml at two hours of age, but the result was normalized 48 hours later. All other values were within normal limits.

4.1.3.6 Drug concentration measurements

Study IV was the only study where drug concentration measurements of mother and child were available. Lithium concentrations were repeatedly measured during pregnancy, see section 4.3.2. Sixteen infants (out of totally 20 mother-child pairs with lithium during any part of the pregnancy) were exposed to lithium during the third part of the pregnancy. In seven of these infants, lithium serum concentrations were analyzed in umbilical cord blood samples and for two of them, measurements were repeated during the neonatal period. Cord blood lithium concentrations ranged between 0.28 and 1.57 mmol/L, median 0.6 mmol/L. In one child exposed to lithium, no cord blood was sampled but serum lithium concentration was 0.6 mmol/L two hours after birth. In the eight infants with neonatal blood samples available, last maternal samples before delivery were between 0.26 and 0.8 mmol/L. Correlation between last maternal sample and cord blood value of lithium was low, $R=0.25$ ($p=0.58$).

4.2 Intrauterine exposure to neurotropic drugs and effects on long-term development

Two of the included studies aim to describe the potential effects of neurotropic drugs on long-term development of the exposed child, with special emphasis on neurodevelopment. In study I, this is investigated through school performance, measured by final grades from last year of compulsory school and in study IV by psychological testing and parental interview.

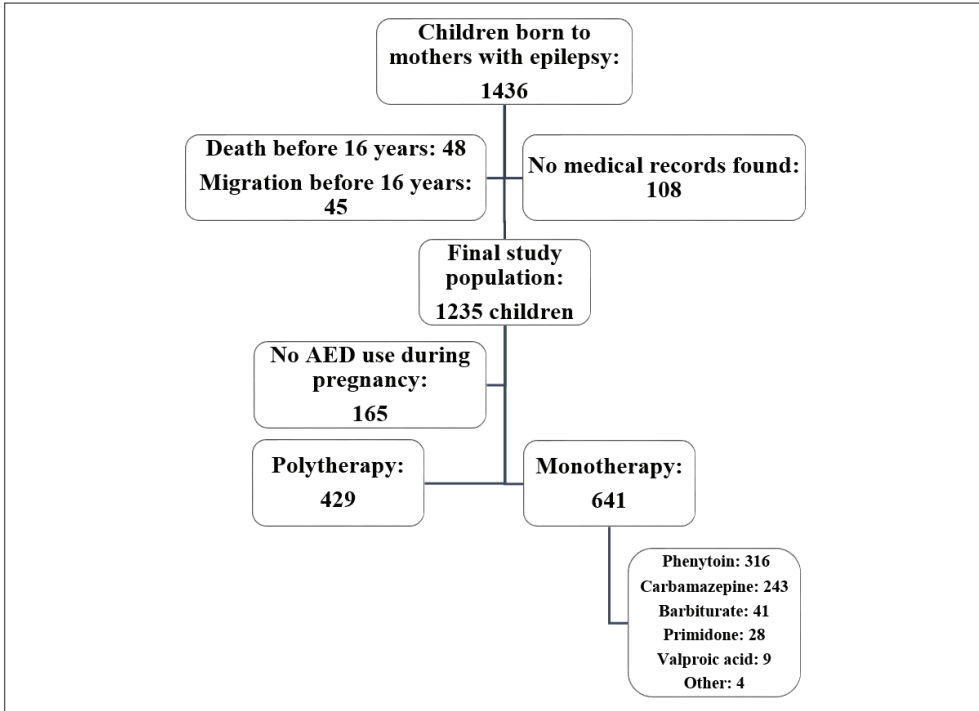


Figure 9. Patient material in study I. Children born to mothers with epilepsy, 1973 to 1986.

4.2.1 Antiepileptic drugs and school performance

Figure 9 describes the study population of study I. The final study population consisted of 1235 children born to WWE and 1 307 083 children born during the same study period to mothers with no record of epilepsy.

The school results of the study population is analyzed with regard to not getting a LC and school grades in English, Swedish, Mathematics and Sports, the latter divided into passed, passed with excellence and not passed, see Table 2 and 3. To not receive a LC means to have no grade in any subject, in most cases indicative of very high level of absence or special school attendance.

In Mathematics, English and Swedish, children exposed to CBZ had statistically significant lower odds of receiving a ‘pass with excellence’ compared to those exposed to PHT.

Table 2. Maternal epilepsy and use of antiepileptic drugs (AEDs). Odds ratios with 95 % confidence intervals (95% CI) for not getting a leaving certificate (LC) from compulsory school. Study I.

Study group	Mother with epilepsy		Population		Risk estimate	
	No LC	LC	No LC	LC	OR	95 % CI
All children	80	1 263	36 569	1 270 514	1.79	1.43-2.24
Excluding congenital malformations	70	1 201	33 821	1 227 492	1.72	1.35-2.18
Boys*	43	604	18 707	627 530	1.96	1.44-2.67
Girls*	27	597	15 101	599 962	1.43	0.97-2.09
No AED*	8	150	33 821	1 227 492	1.52	0.66-2.99
Any AED*	59	953	33 821	1 227 492	1.87	1.44-2.44
Monotherapy*	24	590	33 821	1 227 492	1.19	0.79-1.80
Polytherapy*	35	368	33 821	1 227 492	2.99	2.14-4.17

* All excluding children with congenital malformations

ORs adjusted for child's year of birth, maternal age, parity and maternal education level

Table 3. Maternal epilepsy and use of AEDs and odds ratio (OR) and 95% confidence interval (95 % CI) for "not passed" and "passed with excellence" in Mathematics, English, Swedish and Sports, study I.

Study group	Not passed	Passed	Passed with excellence	OR (95% CI) for not passed	OR (95% CI) for passed with excellence
Mathematics					
Population	200 988	543 034	444 704	1.0 (reference)	1.0 (reference)
<i>Maternal epilepsy</i>					
No drugs	40	82	38	1.44 (0.98-2.13)	0.64 (0.43-0.94)
Monotherapy	116	313	156	1.35 (1.06-1.71)	0.70 (0.57-0.85)
Polytherapy	107	171	87	1.62 (1.20-2.09)	0.67 (0.52-0.87)
English					
Population	167 112	511 850	507 977	1.0 (reference)	1.0 (reference)
<i>Maternal epilepsy</i>					
No drugs	29	76	55	1.32 (0.85-2.04)	0.79 (0.56-1.12)
Monotherapy	87	296	203	1.07 (0.83-1.38)	0.70 (0.58-0.84)
Polytherapy	84	174	105	1.41 (1.08-1.85)	0.70 (0.55-0.89)
Swedish					
Population	177 179	505 486	496 871	1.0 (reference)	1.0 (reference)
<i>Maternal epilepsy</i>					
No drugs	31	81	47	1.23 (0.78-1.95)	0.66 (0.72-0.95)
Monotherapy	99	298	187	1.23 (0.96-1.57)	0.66 (0.55-0.80)
Polytherapy	91	179	94	1.37 (1.05-1.78)	0.63 (0.49-0.80)
Sports					
Population	136 591	491 615	552 169	1.0 (reference)	1.0 (reference)
<i>Maternal epilepsy</i>					
No drugs	26	75	59	1.28 (0.81-2.03)	0.73 (0.52-1.03)
Monotherapy	77	270	224	1.09 (0.84-1.42)	0.71 (0.59-0.85)
Polytherapy	71	178	108	1.37 (1.03-1.81)	0.62 (0.49-0.78)

Children with congenital malformations were excluded from the analysis.

ORs adjusted for child's year of birth, maternal age, parity and maternal education level

4.2.2 Lithium, maternal mood disorders and general health

In study IV, fifteen of the included 39 children had a physical or developmental disorder according to the parental interview. There were five cases of asthma, all with intermittent treatment, four born to mothers with MMD (n=28) and one in the control group (n=11). Two children (one in each exposure group) had allergies. Three children in the MMD group had dermatological conditions. Two children had ear problems (one in each exposure group). Three children, all in the MMD and lithium group, had speech/language difficulties and were seen by a speech therapist. Two of these children (both of whom did not have Swedish as a first language) had low or no result on the verbal tests in WPPSI-III but one child had seen the speech therapist due to pronunciation difficulties and had a high VIQ. One child exposed to MMD and no lithium had been diagnosed with ADHD (Attention Deficit Hyperactivity Disorder) and one child in the control group had an unclassified neurological condition with gross and fine motor difficulties.

4.2.3 Lithium, maternal mood disorders and psychological test results

Results from the WPPSI-III test were available for all 39 participating children. The crude results are summarized in table 4 and the statistical models (linear regression models and Tobit regression models) in table 5. Table 5 both include a statistical model comparing the different exposure groups and a model comparing the results of the different groups to IQ 100.

There were no statistically significant differences between children exposed to MMD (with or without lithium) and the 'control' group when PIQ, VIQ and FSIQ were compared. PSQ results were significantly lower for children exposed to MMD with (p= 0.05, crude analysis) and without lithium (p= 0.04, crude analysis) compared to children not exposed to MMD.

Table 4. Cognitive evaluation of children divided into groups by MMD- with (n=20) and without (n=8) lithium during pregnancy- and no MMD (n=11). Wechsler Preschool and Primary Scale of Intelligence- 3rd edition, at age 4 to 5 years. Descriptive data, study IV.

	Mood disorder		No mood disorder
	Lithium during pregnancy <i>Median, IQR</i>	No lithium during pregnancy <i>Median, IQR</i>	<i>Median, IQR</i>
Age at testing (months)	50 (49 to 56)	54 (52 to 58)	54 (53 to 63)
Performance Intelligence Quotient (PIQ)	103.5 (97-122)	99.5 (91-107.5)	112 (101-125)
<i>n</i>	20	8	11
Verbal Intelligence Quotient (VIQ)	113 (101.5-118)	106 (100-115)	104 (95-114)
<i>n</i>	19	7	11
Processing Speed Quotient (PSQ)	92.5 (77.5-97)	85 (81.5-91)	91 (88-104)
<i>n</i>	14	7	11
Full scale Intelligence Quotient (FSIQ)	107.5 (99.5-116.5)	98 (93.5-110)	109 (98-118)
<i>n</i>	18	7	11

IQR= Interquartile Range, 25th to 75th percentile

4.3 Maternal health and risk factors

Maternal health and maternal risk factors relevant to infant/child health was, to some extent, described in all the included studies.

4.3.1 Baseline data and risk factors in participating mothers

In study I, all ORs presented above are adjusted for maternal age, parity, maternal level of education and child's year of birth.

Study II contains information on several maternal risk factors for neonatal morbidity, including BMI, maternal smoking and age. Cigarette smoking in early pregnancy was seen in 13 % of the women included in the study, compared to 4.7 to 5.4 % for pregnant women in the entire Stockholm area, 2007-2009. BMI was higher in the cohort, 24.4 kg/m², compared to all women who gave birth in the Stockholm area 2007-2009 (23.8-23.9 kg/m²). Note that the catchment area of Karolinska University Hospital Huddinge is demographically different compared to the rest of Stockholm County.

In contrast to study II, study III contain information on both women with antidepressants and women without antidepressants during pregnancy. To summarize background data (table 1 in the paper), women with antidepressants were more likely to be over 35 years of age (OR 1.3, 95 % CI 1.3-1.4), smokers (OR 2.7, 95 % CI 2.6-2.8) and obese (OR 1.6, 95 % CI 1.5-1.7) but less likely to be born in a non-Nordic country (OR 0.5 95 % CI 0.5-0.5).

Table 5. Cognitive evaluation of children, divided into groups by maternal mood disorder (MMD)- with (n=20) and without (n=8) lithium (Li) during pregnancy- and no MMD (n=11). Wechsler Preschool and Primary Scale of Intelligence- 3rd edition, at age 4 to 5 years. Statistical model analyses, study IV.

	Performance Intelligence Quotient (PIQ)	Verbal Intelligence Quotient (VIQ)	Processing Speed Quotient (PSQ)	Full scale Intelligence Quotient (FSIQ)
Estimated mean values according to Tobit model (mean, 95 % confidence interval)				
MMD	Li 105.9 (98.9 to 112.8)	106.6 (97.9 to 115.4)	87.5 (82.7 to 92.3)	107.4 (101.9 to 112.8)
	No Li [‡] 100.0 (88.8 to 110.7)	101.9 (88.1 to 115.8)	85.1 (77.7 to 92.5)	101.1 (92.5 to 109.7)
No MMD	113.7 (104.4 to 123.1)	107.1 (95.4 to 118.8)	95.4 (89.2 to 101.6)	108.8 (101.6 to 116.1)
Comparison between children of mothers with mood disorder with and without lithium during pregnancy, children born to mothers with no mood disorder and IQ 100				
Tobit model (VIQ, PSQ, FSIQ)	MMD and Li (p-value)	p=0.10	p=0.13	p=0.01*
Linear regression model (PIQ)	MMD, no Li (p-value)	p=0.96	p=0.78	p=0.80
	No MMD (p-value)	p=0.005*	p=0.29	p=0.02*
Comparison between children of mothers with mood disorder with and without lithium during pregnancy and children born to mothers with no mood disorder				
Crude analysis	MMD and Li (coeff., vs no MMD; p-value)	-7.9; p = 0.18	-0.5; 0.95	-1.5; 0.74
	MMD, no Li (coeff., vs no MMD; p-value)	-14.0; 0.06	-5.2; 0.57	-7.7; 0.17
Multiple regression (adjusted for prematurity)	MMD and Li (coeff., vs no MMD; p-value)	-8.0; 0.16	-1.4; 0.85	-1.6; 0.72
	MMD, no Li (coeff., vs no MMD; p-value)	-9.5; 0.20	-0.9; 0.92	-4.9; 0.39
Multiple regression (adjusted for maternal level of education and social problems)	MMD and Li (coeff., vs no MMD; p-value)	-7.6; 0.19	0.6; 0.93	-1.0; 0.81
	MMD, no Li (coeff., vs no MMD; p-value)	-13.3; 0.08	0.9; 0.92	-6.0; 0.30

[‡]No Li=no lithium during pregnancy

*significantly higher than IQ 100

[‡]significantly lower than IQ 100

Study IV also contains information on risk factors for the subsequent health of the child. Table 1 in the manuscript describes maternal characteristics for the three exposure groups. There were no mothers in any of the groups who smoked cigarettes during pregnancy (asked at research interview). Seventeen out of twenty in the lithium and MMD group and all mothers in the other two groups lived with the father of the child at the time of delivery. Among women with mood disorder, 67 % (18/27) had a post-secondary education, compared to 55 % (6/11) in the no MMD group. Polypharmacy was common in the MMD group, 15/27 women had two or more neurotropic drugs during pregnancy. None of the other types of drug exposure (LTG, antipsychotic drugs, hypnotics, antidepressants, antihistamines, benzodiazepines and other pharmacological substances) were associated to significantly lower child PIQ.

4.3.2 .Maternal psychiatric health during pregnancy

Table 6 summarizes information on psychiatric health during and after pregnancy for the mothers included in study IV. The majority of the participating mothers in the MMD groups, 25/27, had BD I or II. Two women had recurrent depression. Nine patients in the MMD and lithium group had episodes of depression during pregnancy, two of them also had an episode of hypomania. In the MMD and no lithium group, one mother had an episode of hypomania and one had a depressive episode during pregnancy.

In the 20 women who were treated with lithium during some part of pregnancy, a total of 183 lithium serum level values were measured during pregnancy, ranging between 0.07 and 1.3 mmol/L. Mean value 0.47 mmol/L, SD 0.20, median 0.4 mmol/L. Maternal lithium concentrations during pregnancy are summarized in figure 10.

4.3.3 Maternal psychiatric health at follow up

In study IV, median time in mood disorder episode after delivery was 8 months for women with MMD and no lithium during pregnancy compared to median 1 month for the MMD and lithium group, approaching statistical significance, $p=0.06$. The results for the depression scale PHQ-9 also indicated a more favorable situation for the women using lithium prenatally compared to the MMD and no lithium group, see table 6, but this was not statistically significant, $p=0.12$.

Table 6. Summary of maternal psychiatric symptoms and care during and after pregnancy, study IV.

	Mood disorder (n=27)		No mood disorder (n=11)
	Lithium during pregnancy (n=20)	No lithium during pregnancy (n=7)*	
Main psychiatric diagnosis			
Bipolar disorder type I <i>n</i>	11	3	0
Bipolar disorder type II <i>n</i>	7	3	0
Recurrent depressive episodes <i>n</i>	1	1	0
Missing data <i>n</i>	1	0	0
Psychiatric co-morbidity	3**	1***	0
Social problems [#] <i>n</i>	7	5	3
Patients with mood episodes during pregnancy <i>n</i>			
Depressive episodes	9	1	0##
Manic episodes	0	0	0##
Hypomanic episodes	2	1	0##
Mixed episodes	0	0	0##
Hospital care (psychiatric) during pregnancy <i>n</i>	3	0	0##
Number of mood disorder episodes after delivery [□] <i>Median (min. to max.)</i>	0.5 (0 to 15)	2 (1 to 28)	0 (0 to 1)
Time in episode(s) after delivery, months <i>Median (min. to max.)</i>	1 (0 to 30)	8 (1.5 to 17)	0 (0 to 2.5)
Mood disorder episodes after delivery[□] <i>n</i>			
Depressive episodes	9	7	1
Manic episodes	1	1	0
Hypomanic episodes	6	1	0
Mixed episodes	3	1	0
Hospital care (psychiatric) after delivery <i>n</i>	6	2	0
Current level of depressive symptoms (PHQ 9) <i>Mean (SD) (range)</i>	5.0 (6.5) (0 to 24)	8.4 (5.9) (1 to 16)	2.5 (2.7) (0 to 9)

* This group included 7 pregnancies, 8 deliveries (one woman had twins)
 **ADHD, borderline personality disorder, other psychiatric co-morbidity
 ***ADHD
 # Significant social problems in occupational situation/economic situation/ housing/ relationships/ own children's situation/ contacts with authorities.
 ## Not applicable. Mood disorder during pregnancy was an exclusion criteria for this group
 □ Occurrence of mood disorder episodes after delivery, until time of interview (4 to 5 years after delivery), 1=1 patient with episode

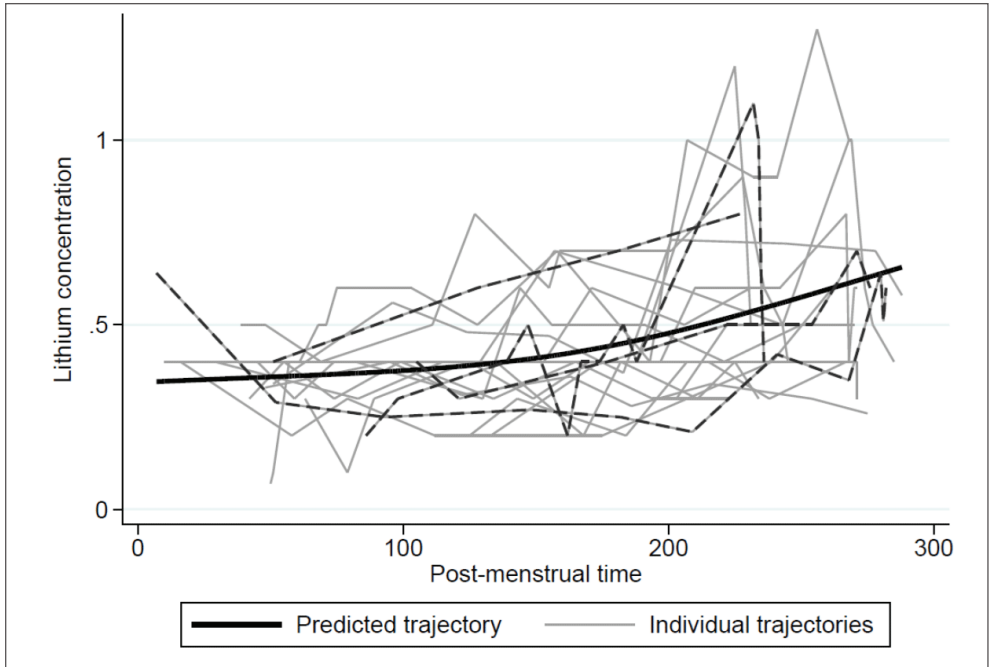


Figure 10. Maternal lithium concentrations (mmol/L) in the twenty women using lithium during any part of the pregnancy, by post-menstrual time (days), study IV. The grey and dotted lines are individual women's serum concentrations, the black line the predicted trajectory of all patients.

5. DISCUSSION

5.1 General discussion

Neurotropic drugs during pregnancy is a research area that attracts attention, and rightfully so. Pregnant women, just like all other patients, deserve evidence-based care for physical and mental illnesses and effective treatment options should be evaluated for this specific group. However, this is a lot easier said than done. Out of concern for the fetus, pregnant women are often reluctant to continue or initiate drug therapy during pregnancy. Health care professionals sometimes apply the ‘better safe than sorry’ approach to pregnant women and advise against pharmacotherapy during pregnancy. This may, in the case of mild conditions where pregnancy data on the drug are limited (or include known negative effects), be correct. In the case of potentially serious conditions such as epilepsy or bipolar disorder, advice to abstain from pharmacotherapy during pregnancy may have severe consequences for both mother and child (64, 68). On the other hand, some drugs have teratogenic properties and exposure during pregnancy can have lifelong ramifications. This delicate balance is something that clinicians treating pregnant women with chronic illnesses are dealing with on a daily basis. For a researcher within this field, all results must be interpreted with this balance in mind. A vast majority of the research performed on humans on pharmacological substances and pregnancy are observational studies with many methodological challenges. Randomized controlled trials are often described as impossible to perform in a pregnant population but some authors conclude that they are ethical and feasible in women with depression (166).

5.2 Discussion on neurotropic drugs and neonatal effects

In studies II, III and IV, we aimed at further describing neonatal adaptation difficulties in infants prenatally exposed to antidepressants or mood stabilizing drugs. Study II showed that a majority of all infants born to mothers with SSRI or SNRI treatment during pregnancy are healthy in the neonatal period. Seventy one percent received the diagnostic code ‘healthy infant’ in the discharge examination from the maternal ward. Only 3 % developed a severe abstinence syndrome and 22 % had signs of mild abstinence, the symptoms mainly arising from the CNS. Other studies have shown slightly higher prevalence of PNAS in infants with intrauterine SSRI/SNRI exposure (163, 167). The relatively low prevalence of PNAS and low admittance rate to NCU (13 %) in this study might be due to our exclusion of women using other neurotropic medications and women with substance abuse. In study III

we were able to compare infants exposed to antidepressants with unexposed infants in a large, population-based cohort. This comparison has been done previously in Swedish, register-based studies (90, 168) but never before with the additional information that the neonatal quality register SNQ and PRS can provide. MBR does not include data on NCU admission, length of stay and duration of CPAP treatment. We also increased the precision in the assessment of exposure by using the PDR (169).

We observed an increased risk of admission to NCU in all groups exposed to antidepressant drugs, with the highest proportion of neonatal care after exposure to SNRI or TCA in late pregnancy, 25 and 27 %, respectively. Since the median duration of NCU stay for the exposed infants was almost one week, we believe that they were admitted due to substantial neonatal problems and not only as a precaution. CPAP treatment was more common in exposed infants than in the non-exposed and the duration of treatment was the same in both groups. The higher risk of admittance to NCU in exposed vs non-exposed infants remained largely unchanged after adjustment for GA and intrauterine growth, indicating that the association between exposure to antidepressants and neonatal morbidity is not primarily mediated via preterm birth or intrauterine growth restriction. In fact, the ORs were in most cases more pronounced when restricting the analysis to full-term infants only. However, study III as well as other studies have described an association between antidepressants during pregnancy and prematurity (90, 97). That means that the negative influence of the prenatal drug exposure on neonatal morbidity can be mediated both through preterm birth, which is highly associated to all neonatal morbidity, and the drug effect itself which is more pronounced in full-term infants.

Untreated depression and anxiety disorders have, just like antidepressant agents, in some studies been linked to adverse neonatal outcomes such as neonatal adaptation difficulties, preterm birth and lower Apgar scores (44, 53, 170-172). The analysis of late vs early exposure was an attempt to account for the underlying psychiatric condition. The increased odds of neonatal care after antidepressant use in late pregnancy suggest a true association with pharmacotherapy. Today, there seem to be consensus that antidepressants in fact are causing PNAS (98, 167, 173), but *how much* of this condition that can be attributed to the underlying maternal depression or anxiety disorder might be difficult to establish until a study with randomization is performed. Preclinical data such as animal studies on several species (66) and studies on human embryos and placentas describe several effects after exposure to SSRI and maternal depression, including modifications of gene expression in placentas of depressed women with SSRI treatment and altered embryo development

and protein expression in embryos exposed to fluoxetine (174, 175). These findings are of course very valuable, but epidemiological and clinical studies, such as the ones included in this thesis, are also needed in order to develop clinical guidelines.

The rate of neonatal hypoglycemia was surprisingly high in study II, 19 %. In study III, the incidence of hypoglycemia among infants exposed to SSRI was only 4 %, compared to 2.4 % in non-exposed, OR 1.3 (95 % CI 1.2-1.4), no vs any SSRI use, adjusted for maternal factors and neurotropic drugs. The discrepancy in absolute risks is due to differences in data collection in a study based on clinical records and a register-based study. In study II, neonatal charts from the maternity and/or neonatal ward were scrutinized and all infants with recorded blood glucose < 2.6 mmol/L were considered hypoglycemic. In study III, 'hypoglycemia' meant having the diagnostic code for hypoglycemia registered in SNQ and/or MBR, or checkbox checked in SNQ. We thereby conclude that the incidence of hypoglycemia may be underestimated in register-based studies. Other studies have also found an association between prenatal antidepressant exposure and hypoglycemia (176). However, hypoglycemia is fairly common in all infants, e.g. one study reported hypoglycemia in 12 % of full-term and 14 % of preterm infants (177). In observational studies such as study II and III, increased risk of hypoglycemia may also be due to detection bias. Jitteriness and tremor, caused by SSRI exposure, can be perceived as symptoms of hypoglycemia leading to the measurement of blood glucose, increasing the chance of detecting a low value. Hypoglycemia in infants is however a potentially serious condition (178, 179) and clinicians should be aware of the association and evaluate infants exposed to antidepressants accordingly.

In study II, we investigated neonatal symptoms in infants exposed to antidepressants during the last part of the pregnancy using health care records including information on NAS. Time to peak value of NAS was analyzed but failed to show any significant differences between the groups. Individual factors such as metabolic and transporter capacity of SSRI/SNRI in mother and child may be of greater influence than drug class in determining strength and duration of symptoms (105, 180, 181), but we cannot rule out that a larger group size and/or prospective data collection with more stringent evaluation of NAS would have given other results. Time to peak score varied between 2 and 90 hours. Our results therefore support the notion that PNAS occurs early and is usually of relatively short duration (163). However, if duration of stay at the maternal ward is very short, symptoms may arise after the family has left the hospital.

MMD and neurotropic medication during pregnancy are often described as important risk factors for adverse events in the neonatal period (16, 18, 176, 182, 183). In study IV we saw a relatively low incidence of neonatal morbidity, 20/27 infants exposed to MMD, where neonatal data was available, had a normal neonatal period. Three out of eight infants in the group with MMD but not exposed to lithium were admitted to NCU, all due to prematurity. One pair of twins, which is a major risk factor for prematurity, was included in this group. In previous studies, prematurity has been associated to maternal BD (129, 131). Our study found no cases of neonatal hypothyroidism after lithium exposure *in utero* but due to our small sample size we still advice measurement of thyroid hormones in the neonatal period in lithium-exposed infants. A correlation between maternal lithium concentrations and neonatal outcome has previously been described (16). The low neonatal morbidity in this cohort may partly be due to adequate therapeutic drug monitoring during pregnancy but also due to low incidence of maternal smoking and, for the most part, stable socio-economic conditions in the cohort.

Previous studies have described increased relative risks of PPHN after intra-uterine exposure to SSRI, but with low absolute risks (109, 110, 141, 184). In study III, we were able to confirm this association, primarily in full-term infants where the adjusted (maternal factors and use of neurotropic drugs) OR was 2.6 (95 % CI 1.4-4.8). We conclude that PPHN and SSRI exposure in late pregnancy are associated, most likely with a causal relationship. The absolute risks are however small, with NNH around 300. Obviously, awareness of this association may be beneficial to the SSRI-exposed infant in respiratory distress. On the other hand, from a research perspective, the incidence of PPHN may rise with increasing awareness of the condition in this patient group, due to the fact that early echocardiograms may detect milder cases of PPHN that otherwise might have been diagnosed as other types of respiratory or circulatory illnesses. This type of detection bias has been suggested regarding cardiac malformations in paroxetine-exposed infants (92). However, the mortality, need for ventilator treatment and duration of NCU care did not significantly differ between exposed and non-exposed infants with PPHN after adjustment for GA meaning that we did not detect milder cases in our cohort.

Caregivers that meet infants prenatally exposed to antidepressants or mood stabilizers need to be aware of symptoms that may arise and evaluate accordingly. The parents have a right to receive balanced information regarding these risks in order to be prepared for the fact that the infant may need prolonged observation after birth, either at a NCU or, in the vast majority of cases, in the maternity ward. NAS is sometimes used, however not validated in SSRI-exposed neonates (163). Other methods of evaluation have been suggested (105).

To prevent neonatal morbidity in children born to mothers with psychiatric illnesses it may be more relevant to address maternal health from several angles rather than focus on neurotropic medication alone. We saw a higher incidence of cigarette smoking and obesity in mothers with antidepressant treatment in study III and these factors were included in the ‘maternal factors’ that we adjusted for. Among women with antidepressants and other neurotropic medications during pregnancy, the incidence of smoking and obesity (BMI >30 kg/m²) were each around 20 %. Maternal obesity and smoking are associated to considerable child morbidity (185-189). Substantial efforts are made by maternity care units to inform mothers-to-be on the benefits of weight control and smoking cessation but there may be substantial health benefits for their future children (and, of course, the mothers themselves) if psychiatric or primary care health care providers also direct similar efforts towards women of childbearing potential, prior to pregnancy (190). And again, maternal psychiatric symptoms may have negative implications for the infant. Inadequately treated maternal depression during pregnancy increases the risk of PPD which can have negative effects on the newborn infant, including insecure mother-infant attachment (39, 56).

5.3 Discussion on neurotropic drugs and long-term outcome

In study IV we aimed at expanding our understanding of the long-term outcome of children born to mothers with BD or other severe mood disorders and exposure to mood stabilizing drugs during pregnancy, an area where information so far has been limited (132, 134, 135). Since lithium readily passes the placenta, has affinity for the CNS and is known to cause (resolving) neurotoxicity to the newborn infant (16, 191), there was enough biological plausibility that the immature brain could be affected by prenatal exposure to lithium in order to perform this study. On the other hand, preclinical data suggest a *neuroprotective* effect from lithium in the immature brain (192-194).

With the exception of PSQ results, we observed surprisingly high IQ scores for both the control group and the MMD exposed children, particularly in the lithium-exposed group. This can be interpreted as a result of the high proportion of well educated women in the cohort and we can speculate that there was a participation bias towards women with high education and stable social conditions, especially in the control group. The fact that we did not have the possibility to test the mothers’ IQ is a limitation of the study. The results for PSQ differed between both groups of children exposed to MMD and ‘controls’ after Tobit model analyses. The former groups also had PSQ results significantly below 100. PSQ results are difficult to interpret in children of

this age group. Processing speed is important with regard to working memory (195) but at this point, with a small sample size, missing data and a young cohort our interpretation of the results must be very cautious.

Our results in study I show an association between exposure to two or more AED during pregnancy and a significantly increased risk of not receiving a LC from compulsory school at age 16. No LC usually means that the child was not attending general school due to intellectual disability and the results suggest that exposure to polytherapy during fetal life may have negative effects on long-term neurodevelopment. These results are in accordance with previous clinical and preclinical studies that have demonstrated a negative effect on the development of the immature fetal brain exposed to several AED simultaneously *in utero* (196-198). There was also a tendency in all children born to WWE towards a decreased probability to receive high grades in Mathematics, Swedish, English and Sports, particularly in children exposed to CBZ. These results are more difficult to interpret, since a decreased chance of getting a high grade can be attributed to a multitude of factors. Residual confounding cannot be excluded. Most previous studies report that CBZ does not seem to have a negative effect on neurodevelopment but evidence is not entirely conclusive (22, 76, 81, 199).

Several methodological considerations are important in the assessment of neurodevelopment in children prenatally exposed to neurotropic drugs: 1) Controlling for important confounders, such as socioeconomic factors, parental IQ, parental health during and after pregnancy and factors related to the child, for example GA. 2) Follow up at an adequate age. The evaluation should be performed at an age where more subtle difficulties are detectable. 3) Standardized and quantifiable methods to assess child development and behavior are preferred over for example parental recall of developmental milestones and other subjective and crude measurements. The assessor should be blinded to exposure. In two of the included studies, I and IV, we investigated long-term neurodevelopment in children prenatally exposed to AED and mood stabilizing drugs, respectively. The methods used were different but provide examples on how the above mentioned methodological challenges can be addressed.

In study I, we used population-based registers which provided us with a large enough cohort and a long time to follow-up (16 years of age). However, registers are sometimes limited regarding the information they provide. We had information on maternal level of education but no other socio-economic factors and no information on parental IQ, which is an important determinant for intelligence (200). We also lacked data on severity of maternal illness and since

polytherapy in the mother can be associated to a more severe form of epilepsy and decreased maternal health, confounding by indication in children of women with polytherapy treatment cannot be ruled out. The main outcome we investigated, LC, is a fairly crude outcome that only tells us whether the child had a grade in any subject. The absence or presence of a LC does not reveal mild neurodevelopmental difficulties but has the advantage of describing an important functional outcome rather than test results.

In study IV, information on maternal health, social situation and drug treatment during and after pregnancy was available, obtained from the clinical register kept at the Affective Disorder Outpatient Clinic and from the maternal interview at the research visit. We were however limited by a fairly small sample size. The children were tested at age four to five which is an age where severe neurodevelopmental disturbances can be detected but milder difficulties may be hard to diagnose. Another methodological limitation of study IV was that children who did not perform well enough on the different subscales of WPPSI-III did not receive an IQ result for these subtests, resulting in non-ignorable missing data. A Tobit regression model was used to account for missing data and avoid overestimation of mean scores. Also, several of the women in the study had a large number of other neurotropic medications during pregnancy, making the interpretation of the results more difficult. This is however often the case in observational studies.

In Sweden and the other Scandinavian countries there are excellent opportunities to perform nation-wide epidemiological studies using the population-based health registers. But register studies can only provide us with some parts of the puzzle that this important and rapidly expanding research field entail. Animal studies and clinical cohort studies are other important contributions. But regardless of type of study, the most important thing is that the data are interpreted wisely. Cooperation between different parts of the medical field, for example psychiatry, pediatrics, pharmacology and obstetrics, is often crucial to plan and perform relevant and precise studies.

6. CONCLUSIONS

- Epilepsy, bipolar disorders, depression and anxiety disorders are common disorders among women of childbearing age. Pharmacotherapy is often necessary to ensure symptom control and good health, also during pregnancy.
- In study I, we conclude that prenatal exposure to several AED in utero is associated to a decreased chance of receiving a final grade from compulsory school. This suggests that polytherapy may have negative effects on neurodevelopment and should, if possible with maintained seizure control, be avoided in pregnant women.
- Study III, a large, population-based register study, demonstrated that infants born to mothers using SSRI and other antidepressants during pregnancy have a moderately increased risk of admittance to neonatal care. OR for neonatal care after use of antidepressants in late vs early pregnancy was 1.7 (95 % CI 1.6-1.9, adjusted estimate). SSRI during pregnancy was associated to increased risk of neonatal respiratory disorders, hypoglycemia and PPHN. The severity of the illness did not differ in SSRI-exposed and non-exposed infants with PPHN, after adjustment for gestational age.
- In study II, 205 infants born to mothers with use of SSRI/SNRI during late pregnancy were assessed with NAS/Finnegan score. Seventy four percent of these infants had no signs of neonatal abstinence/maladaptation symptoms. No significant differences were observed regarding the level of abstinence between the different antidepressant exposure groups.
- Study IV describe no significant association between prenatal exposure to lithium or maternal mood disorder and performance IQ, verbal IQ and full scale IQ at preschool age. None of the twenty infants exposed to lithium *in utero* developed neonatal thyroid disorder.

7. FUTURE PERSPECTIVES

Our studies show a need for further studies within this field of research. A larger clinical evaluation of children born to mothers with bipolar disorders and mood stabilizing drugs during pregnancy would be valuable, including psychological tests and parental interview. Since BD and co-morbid conditions such as ADHD may be passed on to the next generation, an evaluation of the children at school age or even beyond that, would be interesting. Collaboration between researchers in several domains, such as psychiatry, clinical pharmacology, psychology, obstetrics, pediatrics and child and adolescent psychiatry is necessary to ensure high quality in this type of study. Multicenter design is preferable to ensure adequate power.

Population-based registers are excellent data sources for epidemiological studies. To combine national databases such as MBR, PDR and NPR with a national quality register, similar to what we did in study III, might be of further interest. There is a national quality register on BD, Bipolär, which could be useful in answering questions about pregnancy and BD. Several questions on lithium and breastfeeding remain unanswered and this is also a potential research field. The neuroprotective effects of lithium that have been reported in animal studies have not yet been studied in humans and might be of great interest in other pediatric research areas.

A repeated study on school results and prenatal exposure to AED may also be interesting since many new drugs have been introduced since the time period during which the children in study I were born and the long-term effects of these drugs are not yet fully described. Adding data from the PDR would also contribute substantially to the study design. However, since PDR was introduced in 2005, it is not yet possible to perform an evaluation of final grades in compulsory school. Further, more detailed studies that relate maternal drug concentration measurements and cognition in children prenatally exposed to certain AED would be of value.

Another important area of research, bordering to the studies included in this thesis, is the understanding of *how* all the existing information on chronic illness, drugs and pregnancy is being used. Risk perceptions- how do women and health care providers perceive risks related to neurotropic medication and untreated maternal illness? Studies continue to be published in this field of research but how is this research used in clinical practice, and what are the effects?

8. POPULÄRVETENSKAPLIG SAMMANFATTNING

Sjukdomar som epilepsi, bipolär sjukdom samt depression- och ångesttillstånd leder till stort lidande och kan vara livshotande, även för kvinnor som är gravida. Att effektivt behandla dessa sjukdomar är givetvis viktigt. Obehandlade symptom, som t ex kramper eller djup depression kan ha allvarliga konsekvenser även för den gravida kvinnans ofödda barn. Dock kan läkemedelsbehandling under graviditet vara förenat med risker för fostret. Denna avhandling fokuserar på att beskriva hälsa i nyföddhetsperioden och hjärnans utveckling hos barn som under graviditeten exponerats för antidepressiva läkemedel, stämningsstabiliserande läkemedel som används vid bipolär sjukdom eller läkemedel mot epilepsi.

I studie I har vi använt nationella register som baseras på hela befolkningen för att undersöka slutbetyg i nionde klass hos barn till kvinnor med epilepsi som under graviditeten behandlats med epilepsiläkemedel. Barn till kvinnor som behandlats med två eller fler läkemedel under graviditeten hade en ökad risk att inte få något slutbetyg från grundskolan. I de flesta fall betyder avsaknad av skolbetyg att man inte kunnat gå i vanlig grundskola på grund av inlärningssvårigheter. Barn som hade exponerats för en sorts anti-epileptika hade inte signifikant ökad risk för att bli utan slutbetyg.

Exponering för depressionsläkemedlen SSRI (selektiva serotoninåterupptagshämmare) eller SNRI (serotonin- och noradrenalinåterupptagshämmare) i sen graviditet kan leda till utsättningssymtom ("abstinens") hos det nyfödda barnet. Studie II beskriver barn födda till mödrar som behandlats med antidepressiva läkemedel under sista delen av graviditeten. Milda utsättningssymtom sågs hos 22 % medan endast 3 % hade svåra utsättningssymtom. Det fanns ingen signifikant skillnad mellan olika sorters antidepressiva läkemedel avseende grad av utsättningssymtom. Knappt en femtedel av barnen hade lågt blodsocker.

I studie III undersöktes hälsa i nyföddhetsperioden hos barn som exponerats för antidepressiva i en större, registerbaserad undersökning. Vi studerade totalt 741 040 barn, varav 22 507 (3 %) hade exponerats för antidepressiva, framförallt SSRI, under graviditeten. Barn som exponerats för antidepressiva hade en måttligt ökad risk för inläggning på neonatalavdelning jämfört med icke exponerade barn, oddskvot 1,5 (95 % konfidensintervall 1,4-1,6). SSRI-exponerade barn hade måttligt ökad risk för andningsstörningar, symptom från centrala nervsystemet och lågt blodsocker.

Få studier har undersökt hur barn till kvinnor med bipolär sjukdom utvecklas. I studie IV undersöktes 28 barn till kvinnor med affektiv sjukdom (merparten hade bipolär sjukdom I eller II) samt 11 barn där mamman inte haft någon psykisk ohälsa under graviditeten. Vi fann inga statistiskt signifikanta skillnader gällande barnens IQ vid 4-5 års ålder. Resultaten för snabbhetsindex, en del av begåvningsundersökningen, var lägre hos barn till mödrar med affektiv sjukdom- med eller utan exponering för läkemedlet litium i fosterlivet- men dessa resultat är svårtolkade hos så små barn.

9. ACKNOWLEDGEMENTS

First and foremost I want to express my enormous gratitude towards *Katarina Wide*, my main supervisor. With generosity, warmth, endurance and a large amount of scientific curiosity you made our work possible. Without you- no thesis! I would also like to thank my co-supervisors: *Lars Navér* - you are always the voice of reason; always friendly and encouraging and your broad knowledge within the medical field is impressive. Also, full of great travel recommendations! *Lars L Gustafsson* - your enthusiasm and encouragement has been amazing. I have learned so much from your experienced scientific mind and fearless attitude towards, well, everything!

My warmest appreciation towards my mentors: *Linda Andersson* who provided me with a valuable outside perspective in the beginning of my time as a PhD-student and *Björn Fischler*, a highly valued colleague who have helped me navigate among feelings of panic, enthusiasm and stress.

I have had the privilege to work with a number of excellent researchers and would like to express my gratitude: *Bengt Källén*, whom I was fortunate enough to work with in the first published work- a true honor! *Mats Adler*, for your enormous work with our study on bipolar disorder and pregnancy. *Inger Römer Ek*, for sharing your enthusiasm, friendliness and experience in psychiatry and research. *Malin Ljungdahl*, for all the hard work with the study, for your help with my thesis but mostly, for being a wonderful friend. *Gunilla Berglund*, for your excellent skills as a children's psychologist, testing all the children in study IV. *Ylva Beckman*, *Titti Grådman*, *Boel Zachrisson* and all the other nurses at the Pediatric Neurology Unit who provided invaluable help with the kids in study IV. *Christina Sandell* at the delivery unit for helping me locate 'controls' for study IV. *Ulrika Nörby*, for being the most awesome co-writer, it has been so much fun working with you! *Karin Källén*, for inviting me into your study and generously answering questions on statistics and epidemiology. I would also like to thank all former and current members of the 'Magdalena study group', I wish you all the best with the important work ahead! Special thanks to *Gustaf Håkansson*, a colleague and friend with a wonderful scientific mind and to *Maria Altman* for research help as well as friendship and good advice.

Birger Winblad, *Synnöve Lindemalm*, *Leif Bertilsson*, *Ulf Diczfalusy*, *Anders Rane*, *Anders Helldén*, *Sofia Sergel*, *Birgitta Böhm*, *Ulf Hammar*, *Anna Chotigasatien*, *Clas Guthenberg*, *Josefin Nasiell*, *Karin Monsen Börjesson*,

Marie Bendix, Margareta Blomdahl Wetterholm and Jan Kowalski: thank you all for getting me started and continued in research, in different ways.

My warmest thanks to *Professor Gideon Koren* and his colleagues at Mot-herisk, Dep. Of Clinical Pharmacology and Toxicology, Sick Kids Hospital, Toronto who welcomed me for a very interesting research visit at their de-partment.

I would also like to express my appreciation towards all teachers and students at the Research School for clinicians in Epidemiology, Karolinska Institutet for generously sharing invaluable knowledge.

My sincere gratitude towards all participating mothers and children in the included studies.

I would also express my appreciation towards all institutions who have granted our research group financial means: *Stiftelsen Margaretahemmet, Stiftel-sen Samariten, the Swedish Research Council (2011-3440 and 2012-3466), Stiftelsen Majblomman, Mjölkdroppen, Lilla Barnets Fond and the Stockholm County Council (ALF project)*.

I am fortunate enough to have two great jobs; I am a pediatrician *and* a resea-cher. I want to express my gratitude towards the people who have made it pos-sible for me to combine the two: my former boss *Jan Ejderhamn* who, despite a very tough situation at Huddinge BUMM, gave me time off from clinical work to finish my thesis. *Fredrika Gauffin* and *Johan Kaarme*, my current superiors and the previous ones: *Wouk Stannervik, Nina Perrin, Svante Nor-gren, Mikael Lundvall* and *Åsa Eriksson*, thank you for encouragement and a research-friendly work environment. And a huge thanks to *all* wonderful colleagues at *Huddinge BUMM* who have been so patient with me coming and going...

I would also like to thank Head of Department Professor *Li Tsai*, Profes-sors and Directors of studies *Mats Blennow* and *Paul Gerdhem* and Professor *Claude Marcus*, Head of the Pediatric Division, CLINTEC for all the ent-husiastic encouragement. To all administrative staff at CLINTEC who have helped me with the endless practical matters of completing a PhD: thank you!

To all my amazing colleagues and friends at *Astrid Lindgrens Barnsjukhus*: thank you for being so supportive! An extra big thanks to *Mia Herthelius* (my wonderful clinical supervisor during my residency), *Anna Ek, Åsa Fowler, Karl Hildebrand, Silvia Malenicka, Viveka Nordberg, Jenny Svedenkrans,*

Lina Ljungholm, Eva Svensson, Sandra Götberg, Mona-Lisa Engman, Mikael Sundin, Emma Honkaniemi, Marie Sallamba, Ola Eklund, Afrodite Einberg, Faiza Menshi and many more. To *Ylva Tranaeus-Lindblad*, my sister-in-arms and great support: thank you and best of luck in two months (you will rock!).

Thank you *Kerstin Andersson* who painted the beautiful picture on the cover of my thesis and *Fredrik Holmström* who edited the photo of the painting. Special thanks to *Agneta Wittlock* for excellent help with the layout of the thesis.

To Mum and Dad, *Pia* and *Lars Forsberg*: thank you for being such wonderful parents and supporters. You have, always, backed me up and believed in me, no matter what I've been up to. To my sister *Nina*, my brother-in-law *John* and their children *Arvid*, *August* and *Tilde*: ni är bäst!! To my awesome, awesome friends: *Sofie*, *Linda*, *Anna S*, *Ramona*, *Tamara*, *Joanna*, *Emma J*, *Greta*, *Karin S*, *Åsa E*, *Jennifer*, *Mariann*, *Kit* and *Mela*. You bring me so much joy, sisterhood and support: thank you!! I will now, hopefully, be able to talk about something else than my upcoming dissertation. And finally, to *Mikael*, who has given me more love and support than I ever thought was possible: thank you, my love.

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