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PSYCHOTROPIC DRUG TREATMENT DURING PREGNANCY AND LACTATION

Effects on mother and child

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Psychotropic drug treatment during pregnancy and lactation - effects on mother and child

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To all of my family and for science towards evidence-based drug therapyin pregnancy and lactation

POPULAR SCIENCE SUMMARY OF THE THESIS

Psychiatric conditions such as depression, anxiety, bipolar and psychotic disorders are common in young adults and can end up life threatening if not correctly treated. Treating these disorders is particularly complicated during pregnancy and while breastfeeding. Potential adversities for the fetus and the infant need to be considered as well as recognizing that this is a sensitive period for the woman. This thesis focuses on describing the effects of antidepressant and antipsychotic medications used during pregnancy on the mother and infant, and the effects of lithium used during breastfeeding on the infant.

Study I was a randomized study on treatment with the antidepressant drug sertraline of moderate depression during pregnancy. The main objective, to examine the psychomotor development in the infants at two years of age, could unfortunately not be answered due to slow recruitment. Instead, we were allowed to explore the sertraline levels in blood in nine women during and after pregnancy and in seven of their infants. This is one of the largest studies to date in this field. The sertraline levels in the mothers' blood varied tenfold between the women, but the median maternal levels were 25-40% lower during pregnancy than one month after the delivery. The infants' levels of sertraline were around 25-33% of their mothers' and decreased rapidly in the first days of life. Some of the infants showed symptoms such as transient breathing disorders, jitteriness, and hypoglycaemia, but the symptoms were mild and fairly similar in infants to mothers treated with placebo.

In studies II and III we studied complications of treatment with antipsychotics during the pregnancy for the mother (study II) and the child (study III), using advanced statistical methods to study data on 1.3 million pregnancies extracted from the Swedish nationwide health registers. In 2677 (0.2%) of the pregnancies, the women had been treated with antipsychotics: 728 with first-generation antipsychotics, 1710 with the second-generation antipsychotics with an elevated risk for metabolic side-effects (olanzapine, clozapine, and quetiapine), and 541 with other second-generation antipsychotics (mainly aripiprazole and risperidone). The control group consisted of 34 492 women not treated with antipsychotics during, but before and/or after the pregnancy. Of the women treated with olanzapine, clozapine or quetiapine, 2.9% were diagnosed with gestational diabetes, compared to 1.2% of the untreated population, adjusted risk ratio 1.8 (95% confidence interval 1.3-2.4), indicating a moderate risk increase for gestational diabetes for the exposed women. These women were also at risk to give birth to infants that were large for gestational age. We also found that all women treated with antipsychotics during pregnancy had moderately increased risks to give birth through a caesarean section and for late to moderately preterm delivery, i.e. giving birth between pregnancy weeks 32-36. Study III showed that 19% of the infants exposed to antipsychotics in fetal life were admitted to neonatal care, compared to 8% of the unexposed infants, adjusted risk ratio 1.7 (95% confidence interval 1.6-1.8). The risks were similar after exposure for first- and second-generation antipsychotics. The exposed infants had increased risks for drug withdrawal symptoms, symptoms from the nervous system and breathing disorders including persistent pulmonary hypertension, a rare but potentially severe complication.

Breastfeeding has traditionally been advised against during on-going lithium therapy. However, our clinical experience together with a handful of smaller studies have indicated that it can be safe if the infants are followed up by a paediatrician. This has not been studied in any larger studies, which is why we in study IV thoroughly studied the medical records of 30 infants exposed to lithium through breastmilk, forming the largest group of infants studied to date. We found that the lithium levels in the infants' blood were generally low after one month of age, $\leq$ 0.2mmol/l, equalling to around 10% of the maternal levels. In the first month of life, the infants' lithium levels varied with two infants presenting with levels in the therapeutic range for the mothers. A third of the infants had a slow weight gain in the first month of life, but regained it thereafter, and two infants were described as tired. All

other infants were healthy and seemingly unaffected by the lithium exposure, including the ones with higher levels of lithium in blood.

In summary, treatment with the included psychiatric drugs during pregnancy and while breastfeeding can be associated with negative outcomes for the mother and the infant that need to be acknowledged by health care practitioners. However, none of the studies found reasons to advise against treatment with these drugs. A thorough risk-benefit – analysis is always important when considering drug treatment during pregnancy or while breastfeeding.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Psykiatriska tillstånd som depression, ångest, bipolär sjukdom och psykostillstånd drabbar unga vuxna i hög grad och kan bli livshotande om de inte behandlas. Under graviditet och amningsperiod ställs behandlingen på sin spets, dels då detta är en speciellt skör period för kvinnan, dels då eventuell påverkan på fostrets och barnets mående också måste tas i beaktande vid en läkemedelsbehandling. Denna avhandling fokuserar på att beskriva effekterna av antidepressiv och antipsykotisk medicinering under graviditeten hos den gravida kvinnan och hos barnet i nyföddhetsperioden, samt effekten på barnet av litiumbehandling under pågående amning.

Studie I var en randomiserad studie om behandling av måttlig depression med det antidepressiva läkemedlet sertralin under graviditet. På grund av rekryteringssvårigheter gick det inte att besvara studiens huvudsakliga frågeställning, att bedöma den psykomotoriska utvecklingen i två-årsåldern hos barnen till dessa mödrar. Däremot publicerade vi en studie om sertralinhalterna i blodet under och efter graviditeten hos de nio mödrar som behandlats med sertralin och sju av deras barn, vilket blev en av de större studierna i detta fält. Sertralinhalterna i blodet varierade tiofaldigt mellan kvinnorna, men medianhalten bland kvinnorna var 25-40% lägre under graviditeten än en månad efter förlossningen. Sertralinhalterna hos de nyfödda barnen låg kring 25-33% av moderns halt och sjönk undan raskt. Symtom som kortvarig andningsstörning, lågt blodsocker och skakighet observerades hos både barnen som var utsatta för sertralin och de som var utsatta för placebo under graviditeten utan någon tydlig skillnad mellan grupperna.

I studie II och III studerade vi komplikationer kopplade till antipsykotikabehandling under graviditet för mor (studie II) och barn (studie III), genom att med avancerade statistiska metoder analysera data om 1.3 miljoner graviditeter uthämtade från de svenska befolkningsbaserade registren. Under 2677 (0.2%) av graviditeterna hade kvinnorna behandlats med antipsykotika: 728 med första generationens antipsykotika, 1710 med andra generationens antipsykotika med hög risk för biverkningar relaterade till vikt och blodsockerreglering (olanzapin, klozapin och kvetiapin), och 541 med resterande andra generationens antipsykotika (främst aripiprazol och risperidon). En kontrollgrupp utgjordes av 34 492 kvinnor som inte behandlats med antipsykotika under graviditeten men däremot innan och/eller efter den. 2.9% av kvinnorna som behandlats med olanzapin, klozapin eller kvetiapin under graviditeten fick diagnosen graviditetsdiabetes jämfört med 1.2% av de obehandlade kvinnorna, justerad riskkvot 1.8 (95% konfidensintervall 1.3-2.4) talandes för en måttlig riskökning för graviditetsdiabetes. Dessa kvinnor hade också en ökad risk att föda barn som var för tunga för graviditetstiden. Vi fann också att alla kvinnor som behandlades med antipsykotika under graviditeten hade en måttligt ökad risk att föda med kejsarsnitt samt att föda barn lätt till måttligt för tidigt, dvs i graviditetsvecka 32-36. Studien III visade att 19% av barnen som var utsatta för antipsykotika under fosterlivet behövde vård på en neonatalavdelning jämfört med 8% av barnen till obehandlade kvinnor, justerad riskkvot 1.7 (95% konfidensintervall 1.6-1.8). Risken var lika för barn till kvinnor behandlade med första som med andra generationens antipsykotika. Barnen som var exponerade för antipsykotika under fosterlivet hade ökad risk att drabbas av utsättningssymptom, symptom från nervsystemet samt andningsstörningar inklusive persisterande pulmonell hypertension, en ovanlig men potentiellt allvarlig komplikation i nyföddhetsperioden.

Medicinering med litium under pågående amning har länge avrått. De senaste årtiondena har både ett fåtal mindre studier och vår kliniska erfarenhet indikerat att amning under pågående litiumbehandling kan ske säkert, förutsatt att barnet följs upp av barnläkare. Detta har dock inte visats i någon större klinisk studie. För studie IV granskade vi journalerna på 30 mödra-barn-par där mödrarna behandlats med litium under amningsperioden, vilket är den största gruppen mödra-barn par studerade hittills. Vi fann att litiumhalten i blodet hos barnen efter en månads ålder var låg, ≤0.2 mmol/l, med en medianhalt kring 10% av moderns. Under den första levnadsmånaden varierade barnens litiumhalt dock mer

och hos två barn var den inom målvärdet för moderns pågående behandling. En tredjedel av barnen växte långsamt under den första månaden men tillväxten återhämtade sig efter detta, och två barn beskrevs som trötta. I övrigt var alla barn, även de två med högre litiumhalter i blodet, välmående utan tecken till påverkan av litiumbehandlingen.

Sammanfattningsvis kan behandling med psykiatriska läkemedel under graviditet och amningsperioden vara förenat med negativa effekter för mor och barn som vårdgivare behöver vara medvetna om, men ingen av studierna i denna avhandling har funnit någon anledning att avråda från behandling med de inkluderade läkemedlen under graviditet respektive amning. Däremot är en noggrann risk-nytto - analys av stor betydelse vid läkemedelsbehandling under graviditet och amning.

ABSTRACT

The common major depressive disorder and anxiety disorders are often treated with antidepressants. Treatment with mood-stabilizers and antipsychotics are important for pregnant women with bipolar and psychotic disorders, as these women are at risk of postpartum psychosis and even suicide if not treated. The aim of this thesis was to elucidate the risks of psychotropic drug treatment in the perinatal period. Study I aimed at studying sertraline plasma concentrations in pregnant women and their infants and the clinical effects on the infants. Studies II and III focused on antipsychotic treatment during pregnancy and complications for the mother and the infant, respectively. In study IV, we studied infant health and serum lithium concentrations after exposure to lithium through breastmilk.

Study I was a part of a randomized controlled trial where women with moderately severe depression in early pregnancy were randomized to treatment with sertraline or placebo together with internet-based cognitive behaviour therapy. Plasma sertraline concentrations were measured in 9 women during and after pregnancy and in 7 of their infants. In study II we extracted data on 1.3 million pregnancies from the Medical Birth Register and the Prescribed Drug Register to study the effects of antipsychotic treatment on pregnancy complications. For study III, these registers were combined with two neonatal quality registers to study the neonatal morbidity in the exposed infants. For study IV, data was extracted retrospectively from the medical records of 30 infant-mother pairs where the infant was exposed to lithium through breastmilk.

In study I, the inter-individual variation between the maternal plasma sertraline concentrations measured during pregnancy was tenfold, but the median sertraline concentration was 25-40% lower during pregnancy than postpartum. The medians of the sertraline concentrations measured in cord blood and infant serum at 48 hours of age were 33 and 25% of the median of the maternal concentrations at delivery, and the effects on the infants were mild and transient. In study II, the risk for gestational diabetes was increased after use of olanzapine, quetiapine and clozapine, adjusted risk ratio [RR] 1.8 (95% confidence interval [CI]1.3-2.4). In study III, the 2677 infants exposed to antipsychotics had an increased risk of being admitted to neonatal care, adjusted RR 1.7, (95% CI 1.6-1.8). In study IV, the lithium concentrations in infant serum were low, ≤0.2mmol/l, after one month of age, with the median concentration around 10% of the mothers. In the first month of life, serum lithium concentrations varied more, and two infants had therapeutic lithium concentrations, the highest being 1.2 mmol/l. A third of the infants had poor weight gain in the first month and two were described tired, but no other effects on the infants were found.

Psychotropic drug treatment in the peripartal period is associated with some adverse outcomes, but none of the studies in this thesis found any reason to advise against treatment with the included drugs during pregnancy or while breastfeeding. A thorough risk-benefit analysis is required when drug therapy is considered in the peripartal period, as well as increased monitoring of the exposed pregnant women and their infants.

LIST OF SCIENTIFIC PAPERS

I. Heinonen E, Blennow M, Blomdahl-Wetterholm M, Hovstadius M, Nasiell J, Pohanka A, Gustafsson LL, Wide K. Sertraline concentrations in pregnant women are steady and the drug transfer to their infants is low. *European Journal of Clinical Pharmacology* 2021;77(9):1323-31. doi: 10.1007/s00228-021-03122-z

II. Heinonen E, Forsberg L, Nörby U, Wide K, Källén K. Antipsychotic use during pregnancy and risk for gestational diabetes: a national register-based cohort study in Sweden. *CNS Drugs* 2022 doi: 10.1007/s40263-022-00908-2

III. Heinonen E, Forsberg L, Nörby U, Wide K, Källén K. Neonatal morbidity after foetal exposure to antipsychotics – a national register-based study. *Manuscript submitted Jan 2022*.

IV. Heinonen E, Tötterman K, Bäck K, Sarman I, Svedenkrans J, Forsberg L. Lithium and breastfeeding – drug concentrations and morbidity in exposed infants. *Manuscript submitted March 2022*.

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Heinonen E, Szymanska-von Schultz B, Kaldo V, Nasiell J, Andersson E, Bergmark M, Blomdahl-Wetterholm M, Forsberg L, Forsell E, Forsgren A, Fröödj S, Goldman A, Nordenadler E, Sklivanioti M, Blennow M, Wide K, Gustafsson LL. MAGDALENA: study protocol of a randomized, placebo-controlled trial on cognitive development at 2 years of age in children exposed to SSRI in utero. BMJ Open 2018;8:e023281. doi:10.1136/ bmjopen-2018-023281

LIST OF ABBREVIATIONS

AAP	α_1-acid glycoprotein
AR	Alteration ratio
aRR	Adjusted Risk Ratio
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
BCRP	Breast Cancer Resistance Protein
BSID	Bayley Scales of Infant Development
C/D	Concentration by Dose
CB	Cord Blood
CI	Confidence Interval
CPAP	Continuous Positive Airway Pressure
CYP	Cytochrome P450
DMS	N-Desmethylsertraline
ECT	Electroconvulsive Therapy
EEG	Electroencephalogram
EPDS	Edinburgh Postnatal Depression Scale
F-GA	First-Generation Antipsychotics
GDM	Gestational Diabetes
GFR	Glomerular Filtration Rate
HR S-GA	High Metabolic Risk Second-Generation Antipsychotics
I-CBT	Internet-based Cognitive Behaviour Therapy
IADPSG	International Association of the Diabetes and Pregnancy Study Groups
ICD	International Classification of Diseases
I/M-ratio	Infant/Mother-ratio
IP	Infant plasma
IQ	Intelligence Quotient
IQ-range	Interquartal Range
IUGR	Intra-uterine Growth Restriction
LGA	Large for Gestational Age
MADRS	Montgomery-Åsberg Depression Rating Scale
MBR	Medical Birth Register
MDD	Major Depressive Disorder
MP	Maternal Plasma

M/P-ratio	Milk/Plasma Ratio
NAS	Neonatal Abstinence Score
NICU	Neonatal Intensive Care Unit
P-gp	P-glycoprotein
PDR	Prescribed Drug Register
PPHN	Persistent Pulmonary Hypertension of the Newborn
PRS	Perinatal Revision South
RDS	Respiratory Distress Syndrome
RID	Relative Infant Dose
RR	Relative Risk
S-GA	Second-Generation Antipsychotics
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard Deviation
SGA	Small for Gestational Age
SNRI	Serotonin and Noradrenaline Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
SNQ	Swedish Neonatal Quality Register
T2DM	Type 2 Diabetes Mellitus
TCA	Tricyclic antidepressants
TDM	Therapeutic Drug Monitoring
TIS	Teratology Information Services
TTN	Transient Tachypnoea of the Newborn
UGT	Uridine 5’-diphospho-glucuronosyltransferase
WHO	World Health Organization

CONTENTS

1 INTRODUCTION

I stumbled across this field of research in 2015 when I was a new resident in paediatrics at Karolinska University Hospital and looking for a research project to engage in, with a special interest in the neurology of the newborn. I had also a clear thought that I wanted to do research within a field that was meaningful to me and to many others, and I wanted the importance of the research to be easily explainable to others. Then one day, out of nowhere, my now main supervisor Katarina Wide approached me with a project that was about to start that was going to follow depressed pregnant women with or without antidepressant treatment and evaluate the effects in their infants and children. Straight away, I felt that this was the ideal field for me to engage in. The significance for the pregnant women was clear: no-one wants to hurt their unborn baby, but how do you know which hurts the baby more, the medication or the feeling of being depressed and not taking care of yourself and getting help for most of your pregnancy? I felt that with interests in both neonatology and paediatric neurology, I was the right candidate to follow up these babies and to work towards finding an answer to this dilemma.

The MAGDALENA-study (acronym in Swedish: Maternell Affektiv Sjukdom under Graviditet – Depression och Antidepressiva Läkemedels Effekter på Neurologisk utveckling och Adaptation) was finished early in 2019 due to recruitment difficulties. Due to this, we never found the answer to its main endpoint, the effects of maternal depression and the antidepressant drug sertraline on the psychomotor development of the children at two years of age. However, we published an article about the variability in the plasma sertraline concentrations in mothers and children exposed to sertraline (Study 1). Only recently, a Dutch research group with similar interests as ours, published an observational study on antidepressant exposure and the psychomotor development in the children, since they had also experienced problems recruiting women with untreated depressive mood during pregnancy. Their findings are in line with our hypothesis, that no clinically significant difference is found in the psychomotor development between the children exposed to antidepressants and children exposed to maternal mood disorder only.[1] The findings are reassuring, even though we wish that we could have confirmed them in a randomized setting, like we and another Dutch study tried.[2] The study protocol article that I wrote for the MAGDALENA-study is attached to this thesis, as working with the study is a significant part of my doctoral education, that is not fully reflected in the four included studies. It has taught me a lot about both multiprofessional randomized trials and prenatal depression.

After finishing the MAGDALENA-study early, the scope of this thesis changed, widening towards more classes of psychotropic drugs. This gave me the chance to learn to perform pharmacoepidemiological register-based studies. I am grateful to Katarina Wide and my other supervisors and collaborators to have given me this opportunity to explore this field of research, widening my perspective. I would have not wanted this thesis to be built in any other way, as the variety of the included studies has given me a firm ground to stand on as an independent researcher.

2 LITERATURE REVIEW

2.1 PSYCHIATRIC ILLNESS DURING THE PERINATAL PERIOD

2.1.1 Depression, anxiety disorders and antidepressants

The child-bearing years are the most common time for onset of major depressive disorder (MDD) in women. Peripartal depression affects around 10% of pregnant women, and depressive/anxiety disorders are present in as many as 18% of pregnancies.[3-7] Untreated depression during pregnancy is linked to an increased risk of pregnancy complications such as pre-eclampsia, preterm birth and fetal growth restriction.[8,9] The affected infants also seem to have an increased risk of admission to neonatal care and difficulties in neonatal adaptation and attachment.[10-13] Some have also suggested an association between maternal perinatal mood disorder and an increased risk of emotional problems as well as depression in the offspring. These risks seem proportionate to the severity and duration of the maternal disorder and seem decreased by maternal treatment and preventive efforts.[14-16] It is however not clear based on current evidence whether these associations are a causal effect of the maternal depression or due to genetic factors.[17-20]

Women experiencing postpartum depression have often experienced depressive symptoms already before and/or during the pregnancy. The most common underlying diagnoses are unipolar depression and anxiety disorders. Postnatal screening of maternal mood with Edinburgh Postnatal Depression Scale (EPDS) performed at child health care centres is a way to find the women experiencing postpartum depression.[21 22] However, a study showed that around a fifth of the women screening positive on EPDS might in fact be affected by bipolar disorder.[16] There is no consensus regarding prophylactic antidepressant drug treatment during pregnancy in women with a stable mood and history of postpartum depression.[23]

When medical treatment for depression during pregnancy is considered, the potential risks of the treatment for both mother and fetus should be contrasted to the risk of the untreated condition. First-line treatment of moderate to severe depression during pregnancy is selective serotonin reuptake inhibitors (SSRIs) including sertraline and citalopram, either alone or together with psychotherapy. If treatment with SSRIs is not sufficient, serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine or the tricyclic antidepressant (TCA) nortriptyline can be used. Electroconvulsive therapy (ECT) can be indicated for postpartum psychosis or during pregnancy for severe depression with melancholia or psychosis, catatonic symptoms or if the risk of suicide is high.[24] Pregnancy is not protective against depression and women with ongoing antidepressant treatment are five times more prone to relapse if the treatment is discontinued, compared with the women continuing their treatment during pregnancy.[25] The fact that only 2-5% of pregnant women are treated with antidepressants, together with the falling prescription rates of antidepressants during pregnancy, indicates that depression during pregnancy might be undertreated.[3 6 26-29]

Antidepressant treatment during pregnancy is generally not associated with an increased risk of birth defects, but the use of paroxetine and perhaps also fluoxetine should, if possible, be avoided during pregnancy due to their potential association with an increased risk for cardiac malformations.[30-34] Antidepressant treatment is associated to increased risks for preterm birth and lower birth weight and APGAR-scores. Up to 30% of newborns exposed to SSRIs in the third trimester show signs of poor adaptation including irritability, jitteriness, hypoglycaemia, respiratory disorders, and even seizures. The symptoms are mostly mild and transient, but these infants have an increased risk of needing care at the neonatal intensive care unit (NICU).[26 35-39] The risk increases for these outcomes are markedly lower when controlled for variables that reflect the severity of the maternal illness.[26] The risk for persistent pulmonary hypertension is slightly increased after exposure to SSRIs, but the absolute

risk is still very low, with PPHN seen in around 0,3-0,5% of the infants exposed to SSRIs compared to 0,1-0,3% in non-exposed infants.[26 40] It is not known to date, whether the neonatal symptoms are caused by a reaction on drug withdrawal, serotonergic overstimulation or early neurological effects on the infant, and to what extent the symptoms are explained by the underlying maternal mental disorder. There seems to be an increased risk for both preterm birth and low birth weight connected to increasing severity of the underlying antenatal depression, and it is hard to disentangle the effects of the treatment from the ones of the underlying condition as well as lifestyle-related confounders such as smoking.[9 15 26 41 42]

A potential association between intrauterine exposure to SSRIs and long-term cognitive developmental and behavioural effects has been suggested by some,[1 17-19 43] but recent larger register-based studies have not been able to verify these findings, as this association disappeared after adjustment for maternal, paternal and pregnancy-related traits.[44 45] Also, no difference in the infants' long-term neurodevelopment was found when comparing maternal and paternal use of antidepressants during the first trimester.[45] This highlights the potential role of genetics on the long-term neurodevelopment, and shows that the possible effects connected to SSRIs may at least to some extent be explained by familial confounding rather than a direct causal effect of the drug exposure.

2.1.2 Bipolar disorder, postpartum psychosis, and mood stabilizers

Bipolar disorders are characterized by manic or hypomanic and depressive episodes separated by periods of normal mood, affecting 1-2% of the general population.[46] Women with bipolar disorder have a high risk for relapse both during the pregnancy and in the postpartum period with up to 20% of women with bipolar disorder experiencing a relapse postpartum.[47 48] Prophylactic medication is shown to decrease the risk of relapse by a third, but even with adequate treatment the risk is imminent and needs to be considered.[49-51] Women with bipolar disorder seem to have an increased risk for pregnancy- and neonatal complications whether they are treated with mood stabilizers or not, possibly due to lifestyle-related risk factors like obesity and smoking being overrepresented amongst these women.[52]

Postpartum psychosis is defined as a sudden onset of severe mental illness shortly after the delivery. It can present as a mania, severe psychotic depression, or mixed episodes with periods of both elevated and depressed moods, and it can be the first presentation of a bipolar disorder. Women with bipolar disorder or previous postpartum psychosis have an increased risk of being affected.[48 49]

Bipolar disorder can be treated with lithium or the anticonvulsants lamotrigine, valproic acid and carbamazepine. However, the latter two are known human teratogens and should not be used during pregnancy, and lamotrigine treatment might not be effective enough to ensure mood stability.[53-55] Treatment with lithium during the peripartal period is proven effective, but reports on its teratogenicity, especially the increased risk for the cardiac malformation Ebstein's anomaly, and the increased neonatal morbidity connected to the exposure, have led to it often being discontinued before pregnancy. However, the absolute risk for Ebstein's anomaly is still very low and the neonatal effects mild and transient, why lithium is today considered safe to use throughout the pregnancy, if monitored closely. As the renal clearance of lithium increases during pregnancy, the lithium serum concentrations need to be monitored closely, and towards the end of the pregnancy the dose needs to be increased guided by the serum lithium concentrations. The dose needs to be decreased again immediately after the delivery to the preconceptional dose, to avoid intoxication postpartum.[53 56-61] Neonatal symptoms caused by fetal lithium exposure include drowsiness, sloppiness, poor weight gain and risk for thyroid and renal disorders. The symptoms are most likely linked to the passage of lithium over the placenta causing infant lithium serum concentrations at level with the maternal concentrations at birth, but the symptoms have also been seen at lower infant lithium serum concentrations.[59 61 62] The symptoms are transient and do not necessitate discontinuation of the maternal treatment, which would increase the

risk for relapse markedly.[50 51] Instead, to minimize the neonatal symptoms, women are recommended to make a brief suspension in the lithium treatment around the delivery.[59]

During the last decade, the use of second-generation antipsychotics (S-GAs) such as olanzapine and quetiapine as mood stabilizers has increased rapidly, amongst both the general population and pregnant women.[47 63 64]

2.1.3 Psychotic disorders and antipsychotics

Psychotic disorders affect around one percent of the population.[65] Generally, men have a higher risk for psychotic disorders than women, but the risk for affective psychosis is as high for women as it is for men.[66] Two thirds of women with psychotic disorders have given birth to a child.[67] These women have an increased risk for both pregnancy complications, such as pre-eclampsia, fetal distress, induction of labour, ceasarean section, intrauterine growth restriction (IUGR) and preterm delivery, and neonatal complications such as low Apgar scores, poor neonatal adaptation and hypoglycaemia, regardless of whether they receive antipsychotic treatment or not.[68-71]

Antipsychotics are traditionally divided into first-generation antipsychotics (F-GAs), also called typical antipsychotics, such as haloperidol and flupentixol, and S-GAs, also called atypical antipsychotics, such as risperidone, olanzapine, quetiapine and aripiprazole. Women with psychotic disorders are often recommended continuation of the antipsychotic treatment throughout pregnancy, due to the high risk of relapse at discontinuation of treatment.[72] However, a recent study showed that over half of the women treated with antipsychotics discontinued their treatment before or early in the pregnancy.[73]

The use of F-GAs seems stable at around 0.1% of pregnancies during the last two decades, whereas the use of S-GAs has increased rapidly, due to their increasing use as mood stabilizers as well as off-label treatment of other psychiatric disorders such as depression and obsessive compulsive disorders.[47 63 64 73 74] Studies on antipsychotic exposure during pregnancy are complicated by high rates of polypharmacy, with up to 65% co-medication with antidepressants, and around 20-25% with other mood stabilizers and benzodiazepines.[73 75 76]

The risk for malformations after antipsychotic treatment in the first trimester seems slightly increased, but not for any specific malformation or any specific drug, with the potential exception of risperidone being linked to a slightly increased risk for malformations when studied alone.[75 77-79] Olanzapine, aripiprazole and quetiapine, the antipsychotics used the most during pregnancy, are probably not linked to any consistent, congenital harm for the infant.[77 79 80] The neonatal effects after fetal exposure to antipsychotics seem comparable with the effects after fetal exposure to antidepressants, but with the neurological symptoms of increased muscle tone, jitteriness and feeding difficulties being more common in infants exposed to antipsychotics.[39 74 79-81] There also seems to be an increased risk for preterm birth after intrauterine exposure to antipsychotics, but this risk is difficult to study due to confounding by the underlying disorder.[71 76 82 83] The neonatal morbidity seems similar after exposure to first- and second-generation antipsychotics, and seems increased with polypharmacy.[42 75 84]

The S-GAs are known to have less extrapyramidal side-effects than the F-GAs, but concern is raised about their metabolic side-effects.[85] The drugs with the most prominent metabolic side-effects are clozapine, olanzapine, and quetiapine, whereas aripiprazole seems to have weight loss as a side effect. Gestational diabetes is a potential metabolic side-effect of antipsychotics. It affects both the pregnant mother's health and the placental permeability and fetal growth.[75 78 81 86-89] A systematic review showed a ten-fold variability in the prevalence of gestational diabetes in both the women exposed to antipsychotics during pregnancy (2-20%) and the unexposed women (1-10%). After adjustment for the underlying disease, they did not find any increased risk for gestational diabetes connected to antipsychotic treatment.[90]

2.2 PSYCHOTROPIC DRUG TREATMENT DURING LACTATION

2.2.1 Antidepressants

SSRIs and SNRIs are generally safe to use during lactation with fluoxetine being the exception. The infant plasma concentrations of fluoxetine after exposure through breastmilk can be as high as the mother's and adverse effects like excessive crying, decreased sleep, vomiting and diarrhoea have been shown in the exposed infants. Sertraline is the most studied of all SSRIs with generally low concentrations in breastmilk and non-detectable concentrations in infant plasma and is therefore often recommended as the SSRI of choice during lactation.[91 92]

Of the SNRI:s, the use of venlafaxine during lactation is the most studied, and therefore it is preferred over other SNRI:s.[92] The TCAs pass over to the infant through breastmilk in such a low degree, that at least nortriptyline and imipramine are considered safe to use during lactation. Doxepin however is a very sedative TCA and is considered contraindicated during lactation due to its sedative effects on the infant.[93] Amongst other antidepressants bupropion is also sometimes advised against especially if combined with SSRIs, due to case reports of seizures and potential toxic bupropion concentrations in exposed infants.[94]

2.2.2 Mood stabilizers

Lithium passes over to breastmilk and can accumulate in the breastmilk with concentrations higher than the ones in maternal plasma reported previously. Negative events such as acute toxic reactions and shift in the levels of thyroid hormones have been described in breastfed infants, and breastfeeding has traditionally been contraindicated during ongoing lithium medication.[56 95 96] A few smaller case series have however found low lithium serum concentrations in both breastmilk and the serum of breastfed infants, with lithium concentrations around half of the maternal serum concentration in breastmilk, and around a quarter of the maternal serum concentration in infant serum.[97-99]

Lamotrigine, levetiracetam and carbamazepine are all known to pass over to breastmilk.[100 101] Breastfeeding is considered safe for most anticonvulsants, but infants exposed to lamotrigine through breastmilk have increased risks for toxic reactions such as a toxic rash and lethargy and increased liver enzymes and thrombocytopenia, why these infants should be monitored while breastfed.[101]

2.2.3 Antipsychotics

The use of S-GAs is increasing rapidly.[63 64] The effect of these drugs on breastfed infants are however studied very scarcely and the recommendations are often based on single case reports. However, at least the two most common S-GA:s, olanzapine and quetiapine, are considered safe to use during lactation.[102]

2.3 PHARMACODYNAMICS OF SELECTED PSYCHOTROPIC DRUGS

2.3.1 Antidepressants

The underlying mechanism of depression is unclear, why also the definite mechanism of action of antidepressants is not confirmed. Imbalances in the neurotransmitters of the central nervous system such as serotonin and noradrenaline, are believed to play a role in the development of depression. Simply explained, the SSRIs act through increasing the level of serotonin in the synapses of the brain by blocking the reuptake of sertraline back into the pre-synaptic neuron, leading to increased signalling over the synapses. Other antidepressants work in similar ways to SSRIs, inhibiting the reuptake of other neurotransmitters such as noradrenaline (the SNRIs), or blocking the adrenergic, muscarinic, and/or histaminergic receptors (the TCAs).[103]

The clinical effect of antidepressants normally takes a few weeks to show. Around 30-40% of depressed patients fail to show improvement with antidepressant treatment, and those that do may only show partial improvement.[103] More research is needed to both understand the pathomechanism of depression and to find more efficient treatments for it.

2.3.2 Mood stabilizers

Lithium is an inorganic monovalent cation taken orally as lithium sulphate (Lithionit®) or lithium carbonate.[104 105] It is clinically effective at a plasma concentration of 0.5-1.0 mmol/ml, and produces a variety of toxic effects at concentrations over 1.5mmol/ml. Lithium is known to produce many detectable biochemical changes in the brain, but it is still unclear how these changes are related to its therapeutic effect. One theory is that its main effect is to inhibit the hydrolysis of inositol phosphate, causing decreased production of phosphatidylinositides, which at high levels may promote uncontrolled cell signalling.[103 106] The anticonvulsants used as mood stabilizers act through a blockade of sodium channels in the brain (carbamazepine, lamotrigine) or through a more non-specific blockade of sodium and calcium channels as well as an increase of the content of GABA in the brain (valproate).[103]

2.3.3 Antipsychotics

Somewhat simplified, the F-GAs are known to have their action through antagonism of the dopaminergic D_2-receptors in the brain. They are efficient, but burdened with extrapyramidal, hyperprolactinaemic, hypotensive, and sedative side-effects. The S-GAs are a heterogeneous group of compounds with different mechanisms of action, but they are all weaker antagonists of the D_2-receptors than the F-GAs, and instead affect a wide range of other receptors such as α-adrenergic receptors, histaminergic H_2-receptors, muscarinic acetylcholine receptors and serotonergic receptors. Some S-GAs, such as sertrindole, antagonize dopaminergic D_2-receptors, but appear to be more selective to the receptors in the mesolimbic system responsible for the antipsychotic effect, rather than the nigrostriatal system causing the unwanted motor effects.[103 106] The three antipsychotics classed as high-risk metabolic S-GAs in this thesis, olanzapine, clozapine and quetiapine, are all known to cause increased Body Mass Index (BMI) as their side-effect, potentially through their affinity to the histaminergic H_1-receptors, whereas aripiprazole, not working through histaminergic but instead serotonergic and dopaminergic receptors is in studies potentially connected with a decreased BMI instead.[103 107]

2.4 CHANGES IN PHARMACOKINETICS DURING PREGNANCY

There are many reasons for the plasma concentrations of drugs during pregnancy differing from the non-pregnant state. The changes in plasma-concentration during pregnancy can vary between individuals, as do the drug concentrations in the non-pregnant state. Factors that affect the inter-individual variability in the plasma concentrations are genetic factors, compliance to treatment, and drug-drug interactions, to name a few.[108]

The plasma concentrations of drugs may be affected by the physiological changes caused by the pregnancy (Figure 1). Slower gastric emptying and decreased bowel movements caused by increased progesterone levels may decrease the percentage of oral drugs taken up by the body, increasing the time to reach the peak concentration, but not necessary decreasing the extent of drug absorption.[108] Decreased secretion of gastric acids in pregnant women might also reduce absorption of weakly basic drugs, but the clinical implication of this is questioned by some.[108-110] Increased levels of extracellular water and fat affect the drug distribution depending on the level of hydrophilicity of the drug.[108 111-113] Both the glomerular filtration rate (GFR) and the renal blood flow are increased during pregnancy, increasing the clearance of drugs excreted by the kidneys, such as lithium.[108]

In plasma, most drugs are bound to albumin and α_1-acid glycoprotein (AAP), also called orosomucoid. The levels of these proteins are decreased during pregnancy, leading to decreased total drug concentrations and increased unbound fractions of highly protein bound drugs such as sertraline.[108 112 114 115]

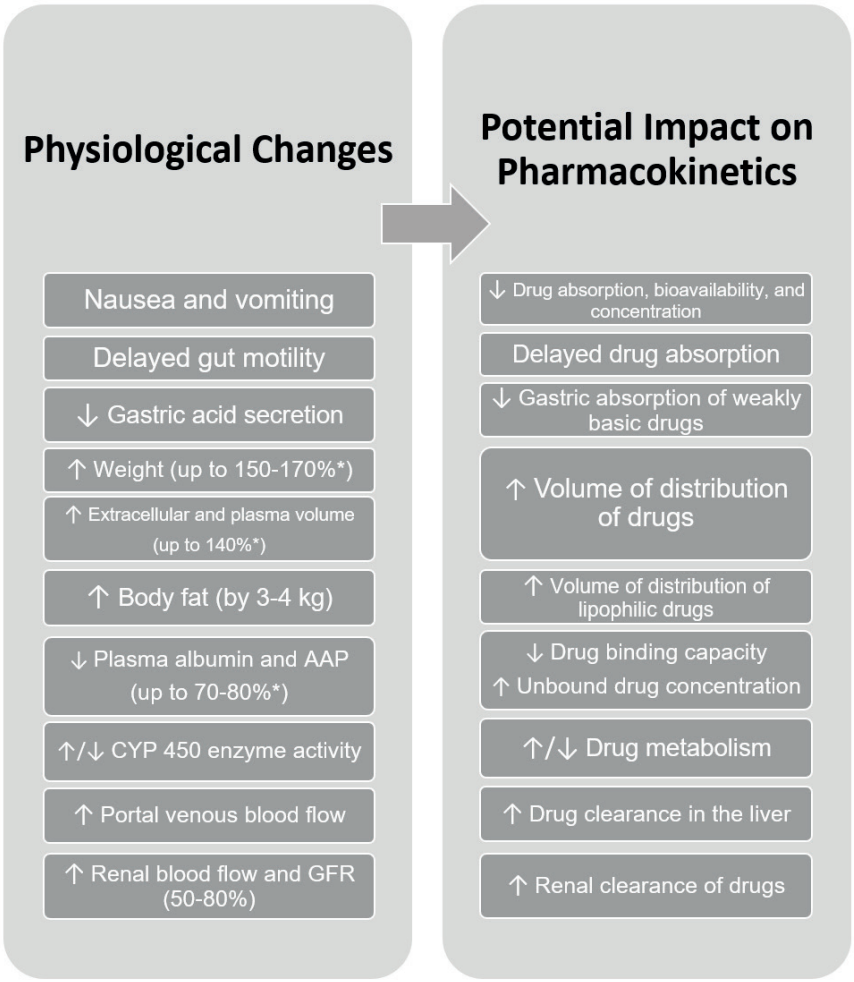

Figure 1. Physiological changes during pregnancy and their effects on pharmacokinetics adapted from Table by Zhao 2014.[108 111 112] AAP= α_1-acid glycoprotein, GFR = Glomerular filtration rate, * of pre-pregnant state

2.4.1 Drug-metabolizing changes during pregnancy

Hydrophobic drugs such as antidepressants, antipsychotics and anticonvulsants are converted in the liver by a two-step metabolism into more hydrophilic metabolites in order to be excreted by the kidneys and/or the bile. The various Cytochrome P450-enzymes (CYP) are, together with several other enzymes like monoamine oxidases and xanthine oxidases, responsible for the oxidative, reductive, and hydrolysing reactions that are traditionally classed as phase I metabolism. In the phase II metabolism, the drug or the metabolite that has undergone a phase I reaction is further conjugated by enzymes like glucuronosyltransferases, N-acetyltransferases and sulfotransferases.[116]

The speed at what the drugs are metabolized in the liver may be affected by the pregnancy-induced increase in hepatic blood flow. The increased levels of oestrogen, and progesterone during pregnancy are believed to play a role in the altered activities of the drug metabolizing enzymes.[108 58 114] Table 1 describes the pregnancy-related changes seen in enzyme activities for the main CYP-enzymes involved in the metabolism of antidepressants and antipsychotics as well as the affected drugs.

Table 1. Pregnancy-induced changes in activity of the enzymes of the CYP 450-family important for metabolism of psychotropic drugs with the antidepressant and antipsychotic drugs metabolized by these enzymes listed [58 108 112 116-120]

ENZYME	CHANGE IN ACTIVITY DURING PREGNANCY	DRUGS METABOLIZED BY THE ENZYME			
		Antidepressants		Antipsychotics	
		SSRI	SNRI	F-GA	S-GA
CYP 1A2	↓	Fluvoxamine	Duloxetine	Haloperidol	Olanzapine Clozapine
CYP 2C9	↑	Fluoxetine Sertraline			
CYP 2C19	-/ ↓*	Citalopram Escitalopram Fluoxetine Sertraline	Venlafaxine		
CYP 2D6	↓/↑*	Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline	Duloxetine Venlafaxine	Chlorpromazine Haloperidol Perphenazine Zuclopenthixol	Aripiprazole Risperidone
CYP 3A4	↑	Citalopram Escitalopram Fluoxetine Sertraline	Venlafaxine	Haloperidol Levomepromazine	Aripiprazole Risperidone Quetiapine Ziprasidone

↑ = increase, ↓ = decrease, - = unchanged, * depending on genetic phenotype, SSRI = Selective serotonin reuptake inhibitors, SNRI = serotonin and noradrenaline reuptake inhibitors, F-GA = First-generation antipsychotics, S-GA = Second-generation antipsychotics

2.4.1.1 CYP 1A2

The enzyme activity of CYP 1A2 has been studied through the elimination clearance of caffeine, and is shown to decrease by a factor of two by mid-gestation and a factor of three by the third trimester, compared to the non-pregnant state.[108]

2.4.1.2 CYP 2C9

Although not as well studied as the other CYP-enzymes, the activity of CYP 2C9 seems to increase during pregnancy. This is indicated by the decreased plasma concentrations of phenytoin and indomethacin, two drugs mainly metabolized by CYP 2C9, in pregnant women. In a study on indomethacin, the plasma concentration after a single oral dose was 37% lower in pregnant women compared to non-pregnant age- and weight- matched controls.[108 121]

2.4.1.3 CYP 2C19

It is not yet fully confirmed, but some studies indicate that the activity of CYP 2C19 seems to decrease during pregnancy.[108 111 118] Sertraline is metabolized in the liver partly by CYP 2C19, as well as CYP 3A4 and CYP 2D6.[118] There is a great genetically coded inter-individual variability in the metabolic capacity of CYP 2C19, with individuals ranging from ultra-rapid to poor metabolizers. This could be the cause of the inter-individual variability in sertraline plasma concentrations.[122 123] The activity of CYP 2C19 decreases with around 50% during pregnancy, but the pregnancy-related changes in enzyme activity also vary between the different phenotypes of the enzyme.[120] A study on the metabolism of the anti-malaria drug proguanil showed that the metabolism of proguanil decreased by 60% during the third trimester in extensive metabolizers, whereas it was unchanged in poor metabolizers.[124]

2.4.1.4 CYP 2D6

The activity of CYP 2D6 has been shown to both increase and decrease during pregnancy, depending on the phenotype of the enzyme. Pregnancy seems to induce the enzyme activity to a varying degree in all but poor metabolizer phenotypes. A four- to five-fold increased apparent oral clearance of the CYP 2D6 substrate metoprolol is reported and the increased activity of CYP 2D6 has been shown to switch the metabolism of catapressan from mainly renal to mainly hepatic.[58 108] Further, a study on paroxetine showed increased metabolism of paroxetine during pregnancy in extensive and ultra-rapid CYP 2D6 metabolizers, while the drug was accumulated in poor and intermediate metabolizers. This study also found that the decreased plasma concentrations in extensive and ultra-rapid metabolizers were connected to increased levels of clinical symptoms.[125]

2.4.1.5 CYP 3A4

The activity of CYP 3A4, responsible for the metabolism of a wide range of antidepressants and antipsychotics, increases with up to 100% during pregnancy, leading to increased metabolism and a risk for decreased plasma concentrations of these drugs.[111 113 114 117] Co-medication with other drugs such as antiepileptic drugs can further increase the effect of CYP 3A4.[117] There is no consensus on whether women treated with drugs mainly metabolized by CYP 3A4 would be in need of increased dosage during pregnancy secondary to this increased drug metabolism.[126] A study on the S-GA aripiprazole showed, that even the lower plasma concentrations during pregnancy were safe and effective and there was no need for dose increase.[127] It is speculated, that pregnant women might actually need lower plasma levels compared to their non-pregnant state, and that dose-adjustments should only be made if this pharmacokinetic change also causes a change in the pharmacodynamics of the drug, expressed as a decreased clinical effect.[112 127]

2.4.1.6 UGT 1A4

The hormonal changes are also known to increase the activity of several phase II glucuronidation enzymes such as Uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A1 and 1A4. For example, the metabolism of the antiepileptic drug lamotrigine that is mainly metabolized by UGT 1A4 in the phase II reaction, is shown to increase by up to 300% in most women in the third trimester, but only up to 21% in some. No genetic reason is yet found behind these differing changes in enzyme activity.[108 128] Therefore, serial dose increases might be needed during pregnancy to maintain adequate plasma concentrations of lamotrigine and a sufficient clinical effect of the treatment.[129]

2.4.2 Therapeutic Drug Monitoring

Due to the major physiological and drug metabolic changes during pregnancy, therapeutic drug monitoring (TDM) during pregnancy is recommended for anticonvulsants, antipsychotics, and antidepressants. Sometimes, measurement of the unbound (free) drug concentration would be more adequate than the total drug concentration, due to pregnancy induced changes in protein binding affecting the unbound fraction of the drug.[111 112 130-132] TDM also aids in monitoring the compliance to the treatment. For lithium, a drug with a narrow therapeutic window, TDM is a necessity to avoid severe toxicity in both mother and child.[53 56] Even though TDM is shown to increase the safety of both antidepressant and antipsychotic treatment during pregnancy, it is not a clinical routine in Sweden.[133-136]

2.4.3 The placental barrier

The placenta was long thought to function as a barrier between the maternal and fetal blood circulations, protecting the fetus from chemicals administered to the mother. However, after the thalidomide tragedy, we learned that drug passage over the placenta can cause great harm in the fetus.[137 138] On the other hand, the knowledge of transplacental passage can also be used in treating fetal conditions like arrhythmias.[139 140]

In the first trimester, the maternal-fetal exchange of both nutrients and xenobiotics passes mainly through the fluid in the exocoelomic cavity surrounding the fetus. By 12 weeks of gestation, this cavity disappears and the maternal blood flow to the placenta increases. The placental barrier consists of layers of cytotrophoblasts and syncytiotrophoblasts, but as the pregnancy proceeds, the thickness of this barrier decreases leading to an increased permeability for small molecules, such as the unbound form of drugs, that can cross the barrier through passive diffusion following a concentration gradient.[108] There is a risk of weakly basic drugs accumulating in the fetus due to the pH in infant plasma being 0.1 units lower than in maternal plasma. Larger particles like immunoglobulins or drugs with higher molecular weights need active transfer to cross the placenta, either through carrier-mediated transfer or receptor-mediated endocytosis. Factors affecting the level of drug transfer over the placenta are the molecular weight, lipophilicity, degree of ionization and protein binding of the drug, with uncharged and lipophilic compounds passing the barrier more readily.[108 141] Figure 2 shows a schematic drawing of the different transport methods across the placenta.

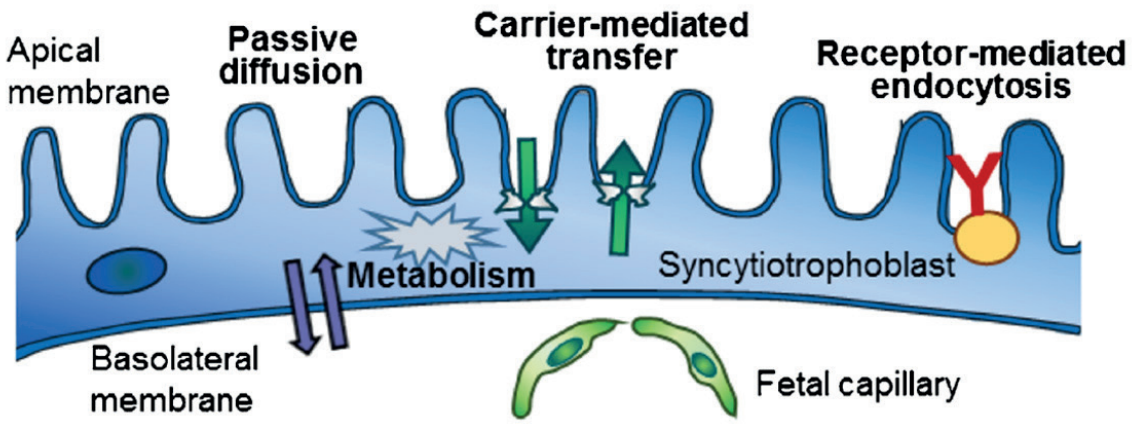

Figure 2. A schematic drawing of the placental barrier showing the major mechanisms for passage of drugs into and across the syncytiotrophoblast. Drugs and their metabolites can cross the placenta by passive diffusion, carrier-mediate transfer (facilitated diffusion or active transport), or transcytosis. Within the syncytium, drugs can undergo metabolism. The Figure is originally published by Tetro et al., Pharm Res. 2018 (with permission).[141]

2.4.4 The role of the placenta

The placenta itself can affect the drugs (placental pharmacokinetics), and the drugs can affect the placenta (placental pharmacodynamics). The placenta expresses its own drug metabolizing enzymes similar to the ones in the liver including several CYP-enzymes, that vary in activity throughout the pregnancy.[112 141] The placenta also expresses its own drug transporters, p-glycoprotein (p-gp) and breast cancer resistance protein (BCRP).[112] These are located on the maternal facing side of the syncytiotrophoblast, actively transferring drugs and other xenobiotics back to the maternal circulation and away from the fetus. The expression of these placental drug transporters is regulated by progesterone, oestrogen and corticosteroids. The expression of p-gp is halved between the end of the first trimester and term, potentially causing increased exposure to drugs transported by it, whereas the levels of BCRP are seen to increase with the proceeding pregnancy. [108 112 142 143] Pregnancy pathologies such as pre-eclampsia reduce the expression of these transporters, and the efflux of drugs by the transporters can also be decreased by polypharmacy with other substrates and/or inhibitors of the same transporter. In both cases, there is a risk for increased drug exposure and adverse effects for the fetus. [142 144 145]

2.4.5 Placental passage of psychotropic drugs

Sertraline and its main weakly active metabolite N-desmethylsertraline (DMS), the transfer of which are studied in Study I, are weak basic compounds that are up to 98% protein-bound in human plasma. Most likely, they bind mainly to AAP like other basic drugs, although this is not verified.[115 146 147] During the course of the pregnancy the infant-mother ratios of plasma albumin and AAP increase, and at birth the level of albumin in the infant is just above the maternal level, but the level of AAP is still only around a third of the maternal level.[148] This could be the reason to why the median umbilical cord to maternal plasma ratio of sertraline is only around 0.3-0.4 found in our first study, and shown by others.[134 149] Citalopram, an other common antidepressant, seems to be passing over to the infant to a higher extent, with a median umbilical cord to maternal plasma ratio around 0.8, possibly explained by it being protein bound to lesser extent, 80%.[136]

Serum concentrations of lithium seem equilibriated between mother and fetus during pregnancy, with an umbilical cord to maternal plasma ratio of 1.05 measured.[59] The placental transfer of antipsychotics varies largely, with umbilical cord to maternal plasma ratios around 20% for quetiapine, 50% for risperidone and aripiprazole, 62% for haloperidol and 72% for olanzapine.[87 127 135] Most antipsychotics

are highly protein bound, and their placental transport is likely to be affected by their grade of protein binding and affinity for the placental transport proteins.[150] Cases of intoxication in the mother may cause toxic concentrations in the fetus, which is seen for quetiapine.[150 151] Also, even a small decrease in the level of protein binding of drugs could cause a significant increase in the amount of free drug passing over to the fetus.[108]

2.5 DRUG METABOLISM IN THE FETUS AND THE INFANT

The fetus and the amniotic fluid form additional compartments for drug distribution. The fetal liver metabolizes drugs slower than an adult liver. The fetal first-pass metabolism is limited by around 30-70% of the blood coming in from the umbilical vein bypassing the liver through the ductus venosus. The fetal-specific CYP 3A7, activity of which corresponds to the activity of CYP 3A4 in the adult liver, accounts for one third of fetal hepatic cytochrome P450. CYP 2D6 and CYP 2C19, two of the cytochrome P450-enzymes most active in the metabolism of antipsychotics and antidepressants, are apparently absent in the fetal liver.[152] The drug metabolism in the fetus is not only protective, as the metabolites caused by fetal drug metabolism might contribute to adverse effects in the fetus. The renal drug elimination is limited in the fetus, as the fetal kidney is not fully developed and the fetal urine passing into the amniotic fluid is swallowed by the fetus.[108 112]

At birth, the total hepatic CYP concentration is around a third of the adult concentration, and the function and the quantity of the CYP-enzymes increase at varying rates. The level of CYP 3A4 is around 10% of the adult concentration at birth, and the shift from CYP 3A7 to 3A4 is gradual over the first year of life. The levels of CYP 2C19 increase rapidly after birth, reaching adult levels at six months of age. The infant kidney function is low, with a mean GFR of 20 ml/min/1.73m^2 at birth and 40 ml/min/1.73m^2 measured at one week of age, equalling approximately 20 vs 40% of the normal adult GFR, respectively. In term infants, the GFR increases over the first weeks of life, reaching close to the adult levels already at a few months of age. In preterm infants, the GFR is lower at birth and increasing at a slower rate after birth.[152-154]

The transition from fetal to extrauterine life and the first days of life are connected to a shift in body fluids and a weight loss of 5-10% of the body weight in healthy infants. The point of lowest weight for breastfed infants is normally around day three in life, coinciding with the lactogenesis in the mother. The weight loss in the first days of life is due to loss of mainly extracellular body water. The urine production is also low in the first days of life, with the infant being oliguric in the first 24-48 hours of life. Therefore, newborn infants are at risk of dehydration, and if exposed to drugs depending on renal clearance, intoxication, especially if the start of breastfeeding is delayed of any reason.[155 156]

2.6 DRUG TREATMENT DURING LACTATION

Generally, drugs considered safe for use during pregnancy are usually also safe to use during lactation, and potential adverse events in nursing infants are more common within the first two months in life. LactMed is a reliable, accessible source of peer-reviewed information on drug safety during pregnancy.[157] There is only a handful of medications contraindicated for use during lactation, including chemotherapy, radioactive drugs, and drugs of abuse. The use of codeine during lactation is recommended against due to its variable conversion to morphine in the different phenotypes of CYP 2D6, with a risk of high morphine doses passing over to breastmilk in ultra-rapid metabolizers. Clinical monitoring is recommended for infants exposed to amiodarone, lithium and cyclosporine through breastmilk.[108 158] All anticonvulsants, apart from phenobarbital, can be used during lactation in healthy full-terms, but these exposed infants should also be monitored clinically due to the risk of lethargy, apnoea's and poor weight gain, especially in infants exposed to lamotrigine.[159 160]

Transmission of drugs between the maternal bloodstream and breastmilk is bidirectional, where unbound drugs can diffuse back and forth along a concentration gradient (Figure 3).[108 161] Factors that affect the drug passage over to breastmilk are the degree of protein binding of the drug in maternal plasma vs in the breastmilk, the lipophilicity and other biochemical properties of the drug, and the lipid content of the milk. For most drugs, the infant plasma concentrations after exposure through breastmilk are lower than the therapeutic concentrations in the mother.[108]

There are three ways of measuring infant drug exposure through breastmilk: the milk/plasma (M/P) ratio, the infant/mother (I/M) ratio, and the relative infant dose (RID). The M/P ratio is calculated by dividing the drug concentration in breastmilk with the one in maternal plasma. This ratio depends on when in relation to the given dose the concentrations are measured, and a single sample cannot fully describe the infant exposure. Traditionally however, an M/P ratio of less than one is considered safe for the infant.

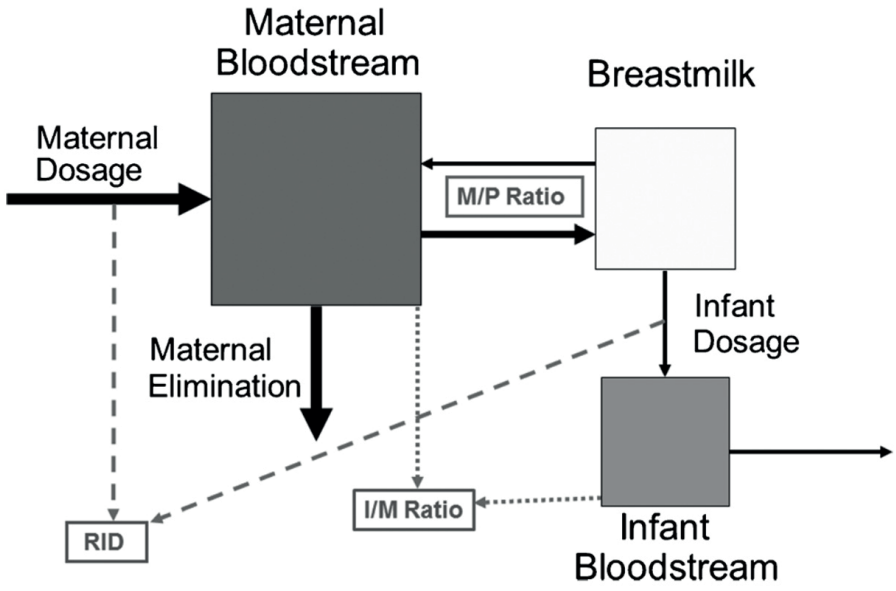

Figure 3. A Schematic drawing of drug passage into the nursing infant and the ways to assess it. The Figure is originally published by Anderson, Pharm Res. 2018 (with permission)[161] M/P Ratio = Milk/plasma Ratio, I/M Ratio = Infant/Mother Ratio, RID = Relative Infant Dose

The I/M ratio describes the ratio between the drug concentration in infant vs maternal plasma and is considered a safe estimate of infant drug exposure when applied at steady state for drugs with long half-lives, when the plasma concentrations in both the mother and the infant can be considered steady. The RID is calculated by multiplying the drug concentration in breastmilk with the daily milk volume ingested by the infant, approximated to 150ml/kg if exclusively breastfed, and dividing this estimated infant dose with the maternal dose per kg maternal body weight. A World health organization (WHO) work group has defined empirical thresholds for the I/M ratio and the RID, where <10% is considered safe, and >25% potentially toxic. The caveat to RID is that it can give false security, as an increased maternal dosage is not reflected in a changed RID. The value of all these measurements is also limited if the toxicity of the specific drug is unknown. Instead, if a therapeutic interval is known for the drug, the measuring of the drug concentration in infant plasma is likely to be a better way to explore infant exposure than calculation of the ratios.[161]

2.7 PREGNANCY COMPLICATIONS

2.7.1 Gestational Diabetes

Obesity predisposes for gestational diabetes mellitus (GDM).162 163 Nearly half of pregnant women in Sweden are overweight with a BMI >25 and 16% are obese with BMI >30 at admission to antenatal care.[164]

The frequency of GDM in Sweden in our second study on pregnant women in Sweden 2006-2017 is just over one percent. During this time period in Sweden, GDM was likely to be underdiagnosed, due to differing screening methods and diagnosis thresholds across Sweden, as well as low compliance to the risk factor based screening for gestational diabetes at the antenatal clinics.[165 166] At this time, only 30% of the women with risk factors for GDM underwent oral glucose tolerance test (OGTT) as recommended.[165] National thresholds for blood glucose levels after OGTT were published by the Swedish National Board of Health and Welfare in 2015 (Figure 4).[167] These are the same levels that were decided on by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) in 2010, being the first criteria based on adverse pregnancy outcomes, and endorsed by the WHO in 2013.[167-169] These criteria were spread in Sweden in 2018 with the national study on gestational diabetes, CDC4G, which has resulted in much higher incidences of GDM being reported. In 2020, the nationwide prevalence of GDM was 5.1%, with frequencies up to 10-15% reported by the regions.[164 170] A similar pattern of increased prevalence of GDM has been shown in other countries after implementation of these criteria.[169] However, the percentage of pregnant women tested with OGTT is still low in many Swedish regions, with Stockholm and Gävleborg performing OGTT in only 12% of pregnant women, whereas Skåne and Blekinge offer it to all pregnant women. There are different risk factor based screening policies in the regions, where the decision on performing OGTT is based on random blood glucose tests and risk factors such as obesity, GDM at a previous pregnancy, a first degree relative with diabetes mellitus or history of having given birth to a child large for gestational age (LGA).[164 167 171 172] The lack of consensus on diagnostic criteria for GDM is also a problem worldwide. This has led to highly varying frequencies of GDM, even between populations with similar demographics and health care systems. For example, the frequency of GDM in the UK and Norway was 15 and 22% in 2016, whereas it was only around 1-2% in Ireland and Sweden.[173]

The initial treatment for GDM is dietary changes. If this is not efficient, medical treatment with metformin is initiated. Insulin treatment is the third and last treatment option.[174] GDM imposes risks for both mother and child, which can be minimized with early diagnosis and efficient treatment.[175] Mothers with GDM have an increased risk of developing Type 2 Diabetes Mellitus (T2DM) and cardiovascular disease later in life compared to mothers without GDM, with relative risks ranging between 3 and 47, due to both differing study methods, but potentially also differing underlying genetic risks.[173 176 177] The fetus exposed to high plasma glucose concentrations is at a direct risk for increased fetal growth and macrosomia, leading to increased risks for late preterm births, birth injuries, asphyxia, respiratory disorders and hypoglycaemia due to fetal hyperinsulinism.[178-180] There are also studies showing that the infants exposed to maternal GDM also have an increased risk for impaired glucose tolerance later in life, as well as T2DM, obesity, neurodevelopmental adversities and ophthalmic disease.[177]

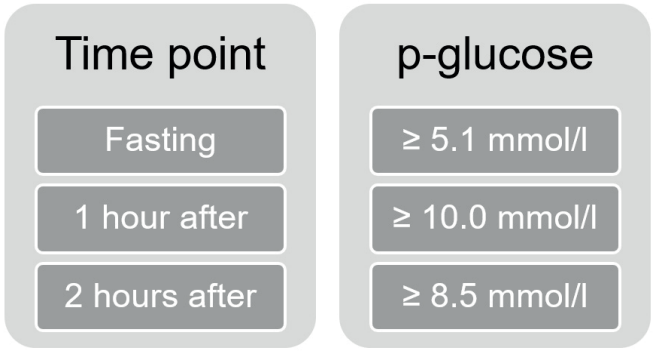

Figure 4. Recommended reference values for p-glucose thresholds in venous blood for oral glucose tolerance test (OGTT) with 75g glucose in Sweden since 2015.[167]

2.7.2 Pre-eclampsia and HELLP

Pre-eclampsia is a multiorgan hypertensive disorders in pregnancy and is a cause for both maternal and perinatal morbidity and mortality, including preterm birth. Pre-eclampsia affects 2-8% of pregnancies, presenting after 20 weeks of gestation, with hypertension combined with proteinuria and/or acute kidney injury, liver dysfunction, neurological symptoms, haemolysis, thrombocytopenia, or fetal growth restriction. The HELLP-syndrome is a serious manifestation of pre-eclampsia, a pregnancy-associated liver disease presenting with haemolysis (H), elevated liver transaminases (EL), and low platelets (LP). In some cases, pre-eclampsia may develop or be detected for the first time intrapartum or early postpartum.[181 182]

The underlying aetiology of pre-eclampsia is still not fully understood. An accepted etiologic theory behind pre-eclampsia is abnormal formation and structuring of the placenta, insufficient remodelling of spiral arteries, endothelial dysfunction, vasoconstriction, placental ischemia and oxidative stress and dysregulation leading to maternal and fetal physiologic dysfunction.[183 184]

The symptoms of pre-eclampsia range from head-ache, visual disturbances, altered mental status and epigastric pain to clonus and a sudden increase of oedema. Complications to pre-eclampsia are placental abruption, disseminated intravascular coagulation (DIC), bleeding, liver capsule rupture or hematoma and fetal growth restriction, and it can also have long-term effects for the mother such as cardiovascular disease and neurological disorders. Low-dose aspirin is recommended as prophylaxis for women at risk of pre-eclampsia, as well as treatment of an elevated blood pressure, but regardless of vast research in the field, delivery of the fetus is still the only treatment of pre-eclampsia.[181 182 185]

2.7.3 Disturbances in fetal growth

Environmental influences that may impact the fetal growth. Swedish normal reference values are used when fetal growth is assessed, and infants with a birth weight < -2 standard deviations (SD) are classed as small for gestational age (SGA), and infants heavier than +2 SD are defined as LGA.[186]

The infant being SGA can be constitutional and not being connected to any increased pathology. However, SGA can also be caused by intrauterine growth restriction (IUGR) due to chronic maternal conditions (diabetes mellitus, hypertension, or liver disease), infections (cytomegalovirus, toxoplasmosis, rubella, HIV), low nutritional status or maternal substance use (smoking, alcohol, illicit drugs, medication). Placental factors such as placental insufficiency, single umbilical artery, placental haemangiomas and chronic placental abruption can also cause IUGR. A third of the cases of IUGR are caused by chromosomal abnormalities such as trisomies or genetic syndromes like achondroplasia.[187]

[188] Growth restricted infants are at risk for being asphyxiated, for acquiring neurological disorders and for intrauterine and postnatal death, but antenatal knowledge of the growth restriction can prevent or decrease these risks.[189-191] IUGR is diagnosed by repeated ultrasound scans and measurements of the blood flow in the umbilical and the cerebral arteries in the fetus and the uterine artery in the mother. The cerebroplacental ratio between the doppler pulsatility indexes in the fetal cerebral artery and the umbilical artery is measured to assess redistribution of the fetal blood flow to the cerebral circulation secondary to placental insufficiency. Redistribution has been associated with fetal distress at delivery, NICU admissions and poorer neurological outcomes.[192 193]

Macrosomia is a term for increased birth weight, with several definitions, such as birth weight >4000g or >4500g.[194] There is a positive linear relationship between maternal hyperglycaemia and infant birth weight, with elevated maternal blood sugar levels even below the threshold for diabetes causing increased infant growth.[195] Maternal glucose diffuses freely over the placenta and can lead to fetal hyperglycaemia leading to increased release of insulin, insulin-like growth factor and growth hormone in the fetus. This can result in increased fetal fat deposition and macrosomia.[194 195] In women with gestational diabetes, the risk of macrosomia increases two- to threefold, even with treatment.[196 197] Infants with macrosomia are at risk for birth complications such as shoulder dystocia and brachial plexus injury and neonatal complications such as respiratory disorders, polycythaemia and hypoglycaemia due to the infant's sustained increase in insulin production. Affected infants also have an increased risk for obesity later in life, when compared to normal-weight newborns.[194]

2.7.4 Preterm delivery

Around 50% of all preterm deliveries are caused by a spontaneous start of delivery, either due to cervical insufficiency, preterm start of contractions or premature rupture of membranes. Other reasons for preterm delivery are multiple birth, intrauterine fetal demise, and iatrogenic delivery with induction of labour or caesarean section due to maternal or fetal prenatal complications. The most significant risk factor for preterm delivery is the history of a previous preterm delivery, increasing the risk by 2-6 times, and the genetic contribution to preterm delivery is as high as 25-30%. The main hypothesis regarding the cause of spontaneous preterm delivery is that of an ascending infection from the vagina to the uterus and the inflammation caused by it resulting in contractions, rupture of membranes and delivery. Pre-eclampsia and the placental insufficiency followed by it affecting the fetus are common reasons for iatrogenic preterm birth.[198-200]

Up to every fourth expecting mother is experiencing stress during pregnancy, and there are several pathways through which maternal stress may increase the fetal stress. Increased maternal cortisol levels can cause increased levels of placental corticotropin releasing hormone, increased dopamine levels may lead to vasoconstriction in the fetus and increased maternal proinflammatory cytokines and prostaglandins may cause inflammation and an increased sensitivity for infections. Maternal chronic stress is therefore connected to an increased risk of preterm delivery and might also lead to long-term neurological consequences for the infant.[201-203]

Vaginal progesterone is shown to be the only intervention with a consistent effect to prevent preterm delivery.[204] If preterm delivery is imminent before 34 completed weeks of gestation, the mother is given two injections of betamethasone to improve the infant's lung maturation, and before 32 completed weeks of gestation the mother also receives an infusion of antenatal magnesium sulphate for neuroprotection of the infant. Prepartal magnesium sulphate administration has been shown to decrease the risk of cerebral palsy in the infant by up to 30%.[205 206]

2.8 NEONATAL DISORDERS

2.8.1 Preterm birth

Preterm birth is defined by the WHO as birth before 37 completed weeks of gestation and is divided based on gestational weeks into; late preterm 34-37 weeks of gestation, moderately preterm 32-34 weeks of gestation, very preterm 28-32 weeks of gestation and extremely preterm <28 weeks of gestation, 22+0 weeks of gestation being the limit of viability in Sweden today. Globally, around 10% of newborns are born preterm, and 5.7% in Sweden.[198] Preterm birth is the most common cause of neonatal death, elevates the risk for morbidity during the perinatal period and can lead to lifelong disability.[207-209] The complications of preterm birth include respiratory disorders like respiratory distress syndrome (RDS) and bronchopulmonary dysplasia, bacterial infections, necrotizing enterocolitis, intraventricular haemorrhage, periventricular leukomalacia and retinopathy of prematurity.[209 210] Late to moderate preterm birth is associated with use of several psychotropic drugs during pregnancy, although a causal effect is not clear.[26 38]

2.8.2 Respiratory disorders

Respiratory distress is common in newborns, and a chest x-ray is often diagnostic to the cause. RDS is the disorder of the very and extremely preterm infants, caused by surfactant deficiency. RDS is treated with intratracheal surfactant administration together with invasive ventilation or continuous positive airway pressure (CPAP) and can cause the long-term respiratory complication bronchopulmonary dysplasia. The respiratory disorders in full-term infants are instead caused by infections, meconium aspiration or transient tachypnoea of the newborn (TTN), caused by a delay in reabsorption of the lung fluid. The risk for TTN is increased after caesarean section and late and moderately preterm birth. Persistent pulmonary hypertension of the newborn (PPHN) is caused by a failure of the pressure in the pulmonary vasculature to drop and adapt to the new ex-utero environment after birth, often connected to an underlying pathology such as lung parenchymal disease, infection or perinatal asphyxia. PPHN is a severe complication that affects approximately one in 1000 infants.[211] Both TTN and PPHN have been associated with use of psychotropic drugs, especially SSRIs, but the pathogenesis for this is not clarified.[26 36 211 212]

2.8.3 Neonatal hypoglycaemia

Hypoglycaemia is common in the neonatal period and at-risk infants are screened for it in the first hours to days in life.[213] The definition of neonatal hypoglycaemia and the acceptable cut-off for plasma glucose levels are debated. The clinical threshold for hypoglycaemia is often defined as the plasma glucose below 2.6 mmol/L.[214] Maternal risk factors for neonatal hypoglycaemia are maternal hyperglycaemia and diabetes, pre-eclampsia, treatment with antidepressants, tocolytics or betablockers and drug abuse. Neonatal risk factors are preterm birth, IUGR or SGA, LGA, perinatal asphyxia, hypothermia, other neonatal disorders like respiratory disorders or sepsis, and delayed start of breastfeeding.[214 215] Both SGA and LGA infants suffer from hyperinsulinism, secondary to high intrauterine levels of catecholamines and glucose, respectively. The hyperinsulinism in especially SGA infants can be persistent, and infants with syndromes like Beckwith-Wiedemann syndrome are known for their prolonged hyperinsulinism.[213 214]

As it normally takes 2-5 days for the maternal breastmilk to be present in sufficient amounts, infants with risk factors for developing hypoglycaemia are given prophylactic oral feeding with expressed breastmilk or infant formula.[214 216] Mild neonatal hypoglycaemia is treated, according to the Swedish Guidelines, with increased enteral feeds and dextrose gel. If the hypoglycaemia persists after one to two doses of dextrose gel, combined with supplementary feeding, or if the plasma glucose falls

below 1.5mmol/L, intravenous glucose infusion with a preceding intravenous bolus dose of glucose. Severe hypoglycaemia can lead to cerebral symptoms such as seizures or impaired consciousness and might have long-term neurodevelopmental consequences for the affected infants.[214] However, most hypoglycaemias seen in full-term infants with appropriate weight for gestational age , including infants exposed to antidepressants during pregnancy, are mild and transient.[36 214]

2.8.4 Neurological disorders

Newborns may experience a wide variety of neurological disorders, including seizures, abnormal muscle tone (increased or decreased), lethargy, irritability or feeding disorders. These symptoms can be caused by birth asphyxia, a stroke, hypoglycaemia, systemic infections, metabolic or genetic disorders, or drug exposure during pregnancy. Preterm infants are at risk of both intraventricular and parenchymal brain haemorrhages, as well as periventricular leukomalacia, i.e. loss of tissue due to necrosis in the sensitive periventricular white matter due to hypoxia and inflammation.[217 218] The neurological symptoms seen in infants exposed to psychotropic drugs are normally mild and transient including feeding difficulties, jitteriness and tiredness, but also seizures are described after exposure to antidepressants, especially SSRIs.[26 36 219] However, the causality of the connection is not confirmed, as three comparative studies show no risk increase for neonatal seizures when the exposed infants are compared to infants to depressed mothers without an antidepressant treatment.[219-222] Suspected withdrawal symptoms in infants exposed to psychotropic drugs can be monitored with the neonatal abstinence score developed by Finnegan presented in Figure 6 the Methods-section.[223 224]

3 RESEARCH AIMS

3.1 GENERAL AIMS OF THE THESIS

The studies included in this thesis aimed at describing how psychotropic drugs and maternal psychiatric illness during the perinatal period influence the health of the mother and the infants, with emphasis on the safety of the drug use.

3.1.1 Study I

We aimed to investigate the plasma sertraline and DMS concentrations and the potential changes in them in pregnant women during and one month after pregnancy, as well as the plasma sertraline concentrations and clinical outcomes in their infants. We also studied the relation between plasma concentrations in mother and infant.

3.1.2 Study II

Study II aimed to describe the pregnancy complications after treatment with antipsychotics during pregnancy in a nationwide register-based cohort, with emphasis on gestational diabetes after treatment with olanzapine, quetiapine, or clozapine. The studied outcomes were gestational diabetes, fetal growth disturbances (small for gestational age and large for gestational age), pre-eclampsia, caesarean section, preterm birth, and perinatal death.

3.1.3 Study III

The aim of the study was to describe the severity and panorama of neonatal complications after fetal exposure to antipsychotic drugs in a nationwide, register-based cohort. The studied outcomes were admission to neonatal care, malformations, neonatal diagnoses, the need of respiratory support and length of stay at neonatal care.

3.1.4 Study IV

We aimed at describing infant health and lithium concentrations in infant serum after lithium exposure through breastmilk and relating the lithium serum concentrations in the infants to the serum concentrations in their mothers'.

4 MATERIALS AND METHODS

A summary of the materials and methods of the four included studies, two clinical (papers I and IV) and two epidemiological (papers II and III), is presented in Table 2.

4.1 THE CLINICAL COHORT STUDIES

Studies I and IV were clinical cohort studies. Drug exposure was studied in mother-infant pairs during pregnancy (study I) and lactation (study IV), studying both maternal (study I) and neonatal (studies I and IV) effects.

4.1.1 Study I

This study was a part of a randomized controlled trial on sertraline treatment for major depressive disorder (MDD) during pregnancy aiming at including 200 women and their infants. The study design is fully described in the study protocol publication.[225] The article that is included in this thesis focuses on the plasma sertraline concentrations during and after pregnancy in the mothers and in cord blood and in plasma at two days of age in their infants, as well as the clinical outcomes in the infants.

4.1.1.1 Patients

The patients were recruited through maternity clinics, advertisements, and social media in week 9-21 of pregnancy. All included women had a moderate MDD at inclusion, and women with comorbidities or chronical drug treatments were excluded. All women who screened positive for depression in the initial screening, the Edinburgh Postnatal Depression Scale (EPDS), were assessed by a psychiatrist who performed a Structured Clinical Interview for DSM-IV Axis I disorders (SCID).[21 226 227] The included women were offered a twelve-week program of internet-based cognitive behaviour therapy (I-CBT) with pregnancy-adapted treatment modules.[228] Additionally, the women were randomized to sertraline or placebo with the daily dose starting at one capsule á 25mg, doubled after two weeks. The treatment effect was followed up by the Montgomery Åsberg Depression Rating Scale (MADRS) at follow-up visits to the study midwife.[229] The severity thresholds of MADRS are presented in Figure 5. The dose of the study drug was increased in steps of one capsule when lacking treatment response, up to a dose of four capsules equalling to 100 mg of sertraline (or placebo). If the patients in the placebo arm did not improve despite the I-CBT treatment, they were unblinded and switched to treatment with sertraline. This pharmacology part of the study describes the sixteen included mother-infant-pairs, focusing on the nine mothers who in the end received treatment with sertraline.

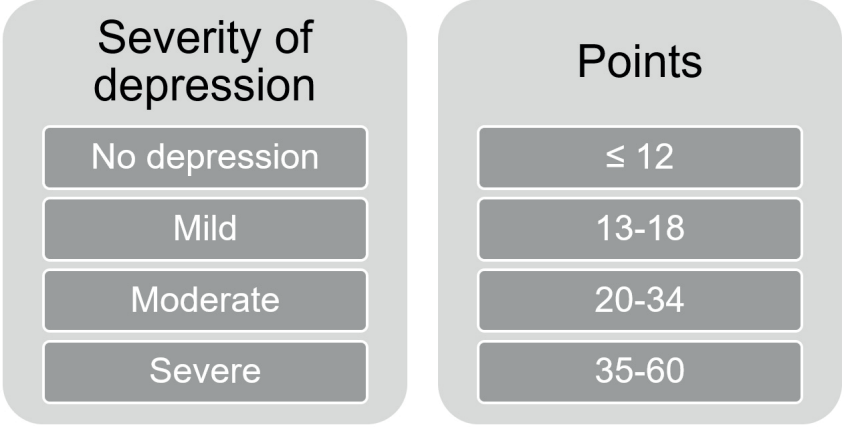

Figure 5. MADRS thresholds for the severity of depression. (MADRS = The Montgomery Åsberg Depression Rating Scale)[230]

Table 2. Overview in the four included studies in the thesis.

	PAPER I	PAPER II	PAPER III	PAPER IV
TYPE OF STUDY	Prospective cohort (RCT)	Nationwide register study	Nationwide register study	Retrospective cohort
DATA COLLECTION	Prospective	MBR, PDR	MBR, PDR, SNQ, PRS	Medical records
SUBJECTS (N)	16 (9 exposed)	1 307 487 (2677 exposed)	1 307 487 (2677 exposed)	30 (all exposed)
EXPOSURE	Sertraline treatment during pregnancy	Antipsychotic treatment during pregnancy	Antipsychotic treatment during pregnancy	Treatment with lithium during lactation
OUTCOMES	Sertraline plasma concentrations in: *women during and after pregnancy *exposed infants Neonatal symptoms after exposure	GDM, LGA, SGA, pre-eclampsia, preterm birth, caesarean section, perinatal death	NICU admissions, neonatal morbidities and treatments, length of stay at NICU, malformations	Lithium serum concentrations in: *exposed infants *breastfeeding mothers Infant growth, clinical health and kidney and thyroid levels
COVARIATES	—	Maternal age, parity, BMI, smoking	Maternal age, parity, BMI, smoking, caesarean section, other neurotropic drugs	—
TIME POINTS	**Mother:** 2nd trimester, 3rd trimester, delivery, 1 month after delivery **Infant:** umbilical cord, infant plasma	—	—	1-2 weeks of age 2-4 weeks of age 1-2 months of age >2 months of age
STATISTICS	Descriptive statistics, Pearson correlation, Spearman correlation, Wilcoxon Signed Rank test	Descriptive statistics, chi^2 test, modified Poisson regression	Descriptive statistics, chi^2 test modified Poisson regression, univariate ANOVA	Descriptive statistics, Wilcoxon Signed Rank test
PUBLICATION STATUS	Published in European Journal of Clinical Pharmacology 2021	Published in CNS Drugs 2022	Submitted	Submitted

RCT = Randomized controlled trial, MBR = Medical birth register, PDR = Prescribed drug register, SNQ = Swedish neonatal quality register, PRS = Perinatal revision syd, GDM = Gestational diabetes mellitus, LGA = Large for gestational age, SGA = Small for gestational age, NICU = Neonatal intensive care unit, BMI = Body mass index

4.1.1.2 Data collection

Total concentrations of sertraline and its main metabolite N-desmethylsertraline (DMS) were measured in maternal plasma once in the second and once in the third trimester, the morning after the delivery and one month postpartum. The infant plasma sertraline and DMS concentrations were measured in cord blood and at 48 hours of age together with the routine neonatal screening. The samples were frozen for later analysis and a joint analysis by liquid chromatography coupled to tandem mass spectrometry was performed at the end of the study period. A detailed description of the laboratory method is found in the online supplement of study I.[149] Plasma glucose concentrations were measured in the infants at 6 and 48 hours of age

The infants included in the study were observed at the maternity ward for at least 48 hours and the modified Finnegan neonatal abstinence score (NAS) was used every 8 hours to detect neonatal withdrawal symptoms.[223 231] NAS was originally developed to detect drug withdrawal symptoms in infants exposed to opioids but has also been used to assess neonatal symptoms after fetal exposure to SSRIs. It's accuracy for this use is however not validated.[36 232] The assessment includes four categories of symptoms: central nervous system, respiratory, gastrointestinal and 'other', with a maximum score of 41 points and cut-offs for mild and severe abstinence at 4 and 8 points respectively, at two consecutive assessments.[223] An English version of the modified score chart that was used is presented in Figure 6.[224]

	Time →									
CNS		Score								
Cry	High-pitched, possible to soothe	2								
	High-pitched, 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	No retractions	1								
(>60/min)	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 6. Neonatal Abstinence Score, modified from Finnegan Score to Swedish and thereafter translated to English. CNS = Central Nervous System.[223 224]

4.1.1.3 Statistical methods

The plasma sertraline and DMS concentrations originally measured in molar units (nmol/L) were converted to mass units (ng/mL) and divided by the daily dose to achieve comparable concentration-by-dose (C/D) units for both sertraline and DMS. Alteration ratios (AR) for the plasma sertraline and DMS concentrations between the pregnant and the non-pregnant state were calculated by dividing the concentrations measured during pregnancy with the non-pregnant reference, and analysed by Wilcoxon's Signed Rank Test for Related Samples with a significance level of 0.05. Pearson's correlation test was used to calculate the correlation between sertraline concentrations in maternal plasma (MP) versus in cord blood (CB) and infant plasma (IP). Penetration ratios to the infant were calculated by dividing the sertraline concentration measured in CB and IP, respectively, with the concentration in MP. Spearman's correlation test was used to study the correlation between the sertraline concentration and treatment effect.

4.1.2 Study IV

This study was a retrospective cohort study on data collected from electronic patient files, investigating the health and serum drug concentrations in infants exposed to lithium through breastmilk. The main outcomes were the infant lithium serum concentrations and the ratio between infant and maternal lithium serum concentrations. Secondary outcomes were infant growth and clinical well-being, recommendations to reduce breastfeeding, and infant kidney and thyroid function.

4.1.2.1 Patients

The included infants were identified through diagnostic codes in the medical records of infants followed up at the Neonatal and Liljeholmen Paediatric Outpatient Clinics at Karolinska University Hospital, Stockholm, between January 2018 and June 2021 and at the Neonatal Outpatient Clinic at Sachs' Children's and Adolescents' Hospital at Southern Hospital, Stockholm, between January 2006 and June 2020. Signed informed consents from the parents were required for study participation.

The infants had been followed as per the clinical follow-up routine at the time of their inclusion. According to the routine established at Karolinska University Hospital, Stockholm in 2018, the maternal lithium dose was titrated by the psychiatrist. The mother-to-be was, if breastfeeding was found feasible by both her and her psychiatrist, referred to an experienced paediatrician for antenatal information about potential risks and the follow-up routine. The clinical recommendations stated that the infant lithium concentration was to be measured in the umbilical cord and in infant serum at 48 hours of age, together with tests for thyroid and kidney function. Thereafter, the lithium serum concentrations, thyroid and kidney functions and the infant clinical health were monitored at two, four and eight weeks of age, with a continued follow-up thereafter if needed. The mothers were instructed to switch to formula feeding and contact health care in case of dehydration or signs of lithium intoxication in the infant. At Sachs' Children's and Adolescents' Hospital, the clinical examinations and were similar, but at less structured time intervals in the earlier years of follow-up.

4.1.2.2 Data collection

All data were collected from medical records. Information on maternal illness, smoking alcohol, social factors and pharmacotherapy during pregnancy and breastfeeding were collected from the mothers' health care records. The infants' serum lithium concentrations, growth, diagnoses, level of breastfeeding, clinical follow-up, and interventions as well as serum concentrations of thyroid stimulating hormone (TSH) and free thyroid hormone (fT4), and plasma concentrations of sodium, potassium and creatinine were collected from the infants' health care records.

Two different colorimetric measuring instruments from Roche® were used for the analyzes of lithium serum concentrations, Modular P between 2006-2016 and Cobas 8000 since 2016. The uncertainty of the measurement is 10% for serum lithium concentrations around 0.5mmol/l and 5% for concentrations around 1.4mmol/l for both instruments. An internal analysis made at the Karolinska University Laboratory showed a good concordance between the methods, as well as between the analyses made in the different laboratories in Stockholm, allowing us to compare the lithium serum concentrations over the time period of 2006-2021.

To calculate the infant-mother ratios, the maternal serum lithium concentrations closest in time to the infants' were used, these concentrations were through concentrations, but could be measured up to two weeks before or after the infant's concentration. The follow-up visits were divided into four groups: within 2 weeks of age, 2-4 weeks of age, between 1-2 months of age and after 2 months of age. Inadequate infant growth was defined as a less than 15 gram daily weight gain since the last visit, equalling a loss of approximately half a standard deviation on the weight curve of the Swedish growth charts 233. For visits before two weeks of age, growth was considered inadequate if the infant had not regained their birthweight.

4.1.2.3 Statistical methods

Descriptive data of the serum lithium concentrations in the included infant-mother dyads are presented. Infant/mother ratios are calculated by dividing the infant serum concentration with the paired maternal serum concentration. Wilcoxon Signed Rank Test for Related Samples was used for comparison of concentrations measured before and after one month of age with a significance level of 0.05

4.2 THE REGISTER-BASED TRIALS

In studies II and III we have combined information from Swedish national health care and quality registers to answer our research questions. The included registers and study methods are described below.

4.2.1 The Registers

Sweden has a long tradition of collecting information about the health of its citizens, stored in population-based registers held by The National Board of Health and Welfare ('Socialstyrelsen').[234] These registers can be used for research purposes after ethics approval form either the Regional Board of Ethics (before 2020) or the Swedish Ethical Review Authority (since January 1st, 2020) and the register holder. Linkage between the different registers can be made using the Swedish personal identification number, a unique ten digit number that all inhabitants receive at birth or at immigration.[235] The health care registers can also be linked to the Swedish national quality registers, developed by an organization of health care professionals and patient representatives, to provide the Swedish health care system with an opportunity to monitor the quality of the care.[236]

4.2.1.1 The Medical Birth Register

The Medical Birth Register (MBR) was founded in 1973 and contains data on antenatal care, delivery, and examination of the newborn for >97% of all births.[237] The information in the register is extracted from patient records from antenatal clinics as well as delivery and neonatal units in the hospitals. The MBR contains information on maternal health and social situation during pregnancy and includes maternal factors like medications, smoking habits, BMI, mode of delivery, and infant factors like the APGAR-score, anthropometric data and gestational age as well as diagnostic codes according to the International Classification of Disease (ICD) 10 for both mother and infant.[237]

4.2.1.2 The Prescribed Drug Register

The Prescribed Drug Register (PDR) covers over 99% of the drug prescriptions dispensed in Swedish pharmacies since July 2005.[238] The register holds information on the dose, substance and brand of the drug, as well as the personal identification number, age and sex of the patient and information about the prescriber. Therefore, since 2005, researchers in Sweden have been able to extract information on drug use during pregnancy from both the MBR and the PDR.[239] The agreement between the registers is better for drugs used in chronic illnesses compared to short term treatments. In a study on the comparability of the two registers, the agreement between the registers was 60% for antidepressants and 48% for antipsychotics.[240] In our study II and III, we extracted data on antipsychotic exposure from both registers.

4.2.1.3 The Swedish Neonatal Quality Register

The Swedish Neonatal Quality Register (SNQ) was started in 2000 to provide detailed information on neonatal care in order to improve the quality of the care and to facilitate research. The NICUs in Sweden have gradually joined the register, and since 2012, it contains data on admissions of infants up to 28 days of age to all 37 NICUs in Sweden.[241] The SNQ includes data on diagnoses according to ICD-10, the given treatments and procedures, duration of the hospitalization and many other variables.[242] Before SNQ, there was several similar local registers, of which the Perinatal Revision South (PRS), a database from the southern Swedish region, holding obstetric and neonatal data from 1995 and forward was included in the register linkage as well.[241 243]

4.2.2 Patients and data collection

The data sources, exposures, and co-variates of the two register-based studies are summarized in Table 1. Studies II and III were register-based studies combining data from the MBR,[237] the PDR,[239] and for study III also SNQ 244 and PRS 243. Swedish personal identification numbers were used for register linkages. The study populations consisted of all singleton births in Sweden registered in the MBR between July 1, 2006, and December 31, 2017. Women with a diagnosis of pre-pregnancy diabetes or with valproate treatment (N03A G01) were excluded from the analyses.

Information on drug exposure and maternal and fetal background characteristics were collected from the MBR and the PDR, where the drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Antipsychotic exposure was defined as a filled prescription of drugs belonging to ATC-class N05A, antipsychotics. Exposures to the antipsychotics dixyrazine (N05AB01), prochlorperazine (N05AB04), melperone (N05AD03) and lithium (N05A N01) were excluded from the exposed group and considered as covariates, due to the use of these drugs as antiemetics (dixyrazine, prochlorperazine, melperone) and as a mood stabilizer (lithium). The other antipsychotics were divided into F-GAs and S-GAs according to Figure 7.[106] For study II, the three antipsychotics with a high metabolic risk, olanzapine, quetiapine, and clozapine were extracted from the group of S-GAs and called high-risk S-GAs (HR S-GAs).

Antipsychotics exposure was allocated into any exposure (drugs dispensed at any time during or one month before the pregnancy), late exposure (drugs dispensed during the last 90 days of the pregnancy with or without earlier dispenses), and early exposure only (drugs dispensed one month before and during pregnancy but not during the last 90 days of the pregnancy). We also created a reference group with women exposed to antipsychotics any time during the study period, before or after the pregnancy, but not during or one month before the pregnancy. Exposure data was also collected on neurotropic drugs known to or suspected to cause similar neonatal morbidities as antipsychotics: antidepressants (ATC-code N06A), antiepileptics (N03A), opioids (N02A), centrally acting sympathomimetics (N06BA), sedatives (N05B, N05C) and milder sedatives (alimemazine, promethazine and the excluded antiemetic antipsychotics from N05A).

1st generation AP	
Levomepromazine	251
Flupentixol	165
Haloperidol	162
Perphenazine	93
Zuclopenthixol	75
Chlorprothixene	45
Chlorpromazine	4
Pimozide	4
Fluphenazine	3
Thioridazine	1
TOTAL	803

2nd generation AP	
Quetiapine	1026
Olanzapine	771
Aripiprazole	334
Risperidone	191
Ziprasidone	34
Clozapine	29
Paliperidone	9
Sertrindole	2
TOTAL	2396

Figure 7. The division of antipsychotics into first- and second-generation antipsychotics and the individual prescriptions of them in pregnant women 2006-2017.[106] AP = antipsychotics

4.2.2.1 Outcomes study II

For study II, the maternal and pregnancy outcomes were extracted from the MBR. The main outcome gestational diabetes was defined as the ICD-10 code O24.4 recorded. The secondary outcomes were the infant being LGA (Z-score >2SD) or SGA (Z-score <-2SD) measured with Z-scores based on infant weight for gestational age (GA) and sex,245 pre-eclampsia, caesarean section, very preterm birth (<32 weeks of gestation), late to moderate preterm birth (32-36 weeks of gestation) and perinatal death.

4.2.2.2 Outcomes study III

Data on admissions to NICU and the neonatal morbidities were extracted from SNQ and PRS, where they were registered as ICD-10-codes and/or checkboxes. The NICU admission was the main outcome of study III, whereas the secondary outcomes were TTN, PPHN, RDS, hyperbilirubinemia, hypoglycaemia, feeding difficulties, neurological disorders (a composite outcome including seizures, congenital hyper-/hypotonia, hypoxic ischemic encephalopathy and other disturbances of cerebral status), withdrawal symptoms, any malformations, heart malformations and need for treatment with CPAP or a ventilator.

4.2.3 Statistical methods

Exposures were defined as any antipsychotic use versus no use, use of the different antipsychotic groups versus no use, use of antipsychotics in early and late pregnancy, respectively, versus no use, and use during versus use before or after pregnancy. Risk ratios (RRs) for dichotomous outcomes were obtained by using modified Poisson regression in multivariable regression models. In the final analyses, adjustments were made for maternal age, primiparity, smoking, and BMI, and for study III also maternal use of other neurotropic drugs and caesarean section. As a sensitivity analysis for study III, the risks were also adjusted for gestational age and Z-score. Missing data regarding maternal smoking and BMI were replaced by the overall means. For descriptive data, chi-square tests were used to detect heterogeneity between exposure groups.

In study II, the role of BMI was further explored through sensitivity analyses with BMI-strata-specific risk estimate and a separate model without adjustment for BMI. In study III, the difference in length of stay at NICU between the exposure groups was evaluated with univariate ANOVA of the logarithmic variable for length of stay that followed the normal distribution. Number needed to harm (NNH) was calculated from the adjusted risk difference between exposed and non-exposed infants.

4.3 ETHICAL CONSIDERATIONS

With psychotropic drugs, there is often an ethical dilemma between the mothers wish to become pregnant and breastfeed, her right to achieve adequate treatment and the safety of this treatment for the fetus and infant. Unfortunately, drug treatment during the peripartum period, especially during lactation, is not enough studied for these risks to be clarified.

As important as this field is to study, it is also ethically challenging. We attempted an RCT where we thought it was feasible, in studying treatment of depressed pregnant women where a non-pharmacological treatment option is available but failed due to slow recruitment. With psychotic or bipolar disorder, for which non-pharmacological treatment is not available, randomization to treatment would not be ethical. Because of these challenges, research in this field is often conducted on unsatisfyingly small or selected cohorts. Our hope is that improving register-based studies worldwide will help us fill the gaps of knowledge in this important field of research, where experimental trials are not ethical or feasible.

4.3.1 Study I – the MAGDALENA-study

Ref.no: 2014/952-31

When starting the study, the ethical dilemma was whether it was ethical to treat pregnant women with ICBT and randomize them to add-on treatment with either sertraline or placebo. As treatment with ICBT has been shown to be evidence-based in both the non-pregnant and pregnant populations, this approach was considered ethically justified.[228] The treatment of choice today for antenatal moderate depression is pharmacological treatment with SSRIs.[24] However, data on long-term effects on the exposed children at the time were limited and contradictory,[246] and we wished for this study to increase the knowledge on the effects on the cognitive development in children exposed to SSRIs and/or maternal antenatal depression. Therefore, it was also considered that the gains of the study did heavily outweigh any ethical or medical risks for these women and their infants. Our strict inclusion criteria of only including moderately depressed mothers ensured that no mildly depressed women received SSRI without having an indication for the treatment, and no women with a severe depression were insufficiently treated due to randomization to placebo. Furthermore, the women were closely monitored during the study period and received extensive support by research midwives, psychologists and a psychiatry nurse connected to the study. The children were only observed except for atraumatic buccal swabs and two blood samples in the neonatal period, of which one was coordinated with the neonatal screening test at 48 hours of age and the other could be well motivated by the increased risk for hypoglycaemia reported previously infants exposed to SSRIs.[36]

4.3.2 Studies II & III – antipsychotic treatment during pregnancy

Ref.no: 2013/342-31/5 (2019-02066)

Women needing antipsychotic treatment are often affected by a serious psychiatric disorder and in need of social and medical support. Almost two-thirds of the women with psychotic disorders are mothers.[247] Therefore, as there is a substantial amount of pregnant women being in need for treatment with antipsychotics, the ethical question to answer is: which treatment gives the greatest efficacy for the mother and the least side-effects for the infant? Another aspect is also that from the child's point of view, the best for the child is a healthy parent, and the health care system and research society need to support the families in achieving that, with medication if necessary. To ensure a safe pregnancy for both mother and fetus, more research is needed on the effects of maternal antipsychotic treatment. It is important to quantify the effects of the antipsychotic exposure and try to separate them from the

effects of the underlying disorder, as well as to study the effects of the different antipsychotic drugs when possible. Even though register-based studies have limitations and caution needs to be taken when interpreting the results, hopefully these studies can bring the research society a step closer to creating clinical guidelines and treatment recommendations for this long-disregarded group of patients.

4.3.3 Study IV – effects of exposure to lithium through breastmilk

Ref.no: 2020-05558

Is it ethically questionable to allow mothers to breastfeed while using drugs that we know may impose a risk for the infant? Probably so. However, in the end, this is not a matter where the caregivers hold the answers, but rather a personal decision of the mothers. Women base the decision of breastfeeding on several factors, and some women may choose to breastfeed while continuing the potentially harmful treatment even though this would be strongly advised against. Some women also quit their medication to be able to breastfeed, risking their own health instead.

Breastfeeding has several important health benefits for both mother and infant. To advise against breastfeeding "to be on the safe side" might mean deriving the mother-infant pair of something highly beneficial. Lithium is one of the drugs traditionally advised against, as it is known to pass over via breastmilk, with cases of lithium intoxications described in breastfed infants. However, the long clinical experience of monitoring the exposed infants at Sach's Children's and Adolescents' hospital, has indicated, that the exposed infants are healthy, their serum lithium concentrations are generally low, and that the attendance rate to the follow-up is good. In this setting, the most ethical course is to provide the women who wish to breastfeed with on-going lithium treatment, a way to do so in a controlled way with clinical and laboratory follow-up of the infant. When we already have this clinical experience, the most ethical way forward is to properly evaluate this through a retrospective journal study and share the knowledge.

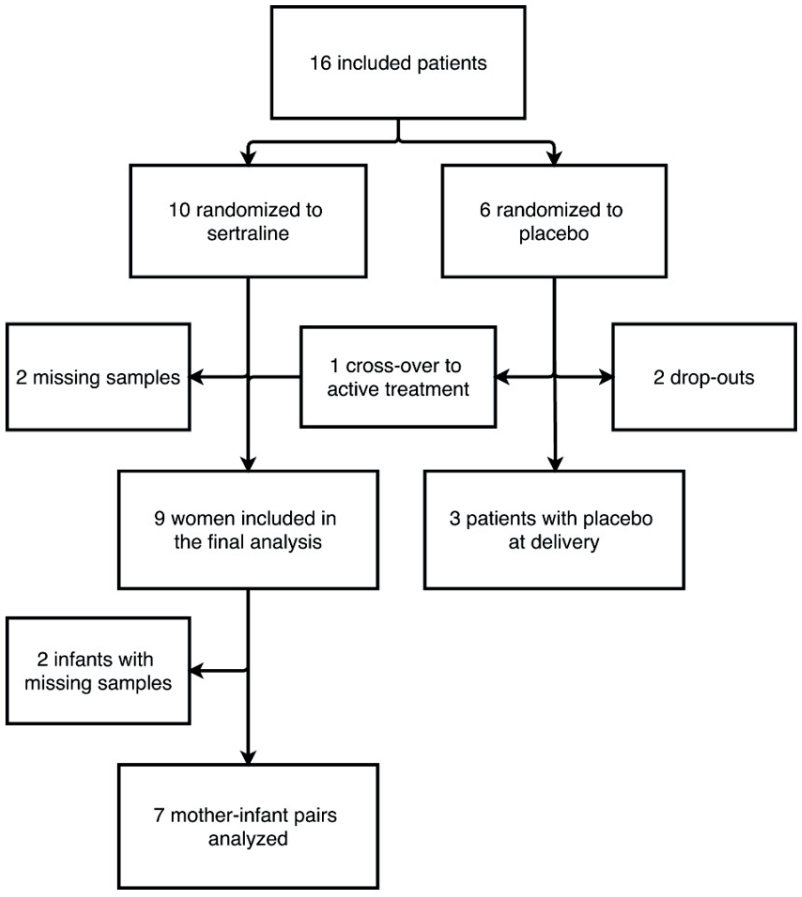

Figure 8. Flow-chart of the participants in study I. Nine women with two or more available plasma sertraline concentrations were included in the maternal analysis, and seven mother-infant-pairs had sufficient data for analysis of placental cross-over. Three patients in the placebo group fulfilled the study but they were not analysed in this pharmacological part of the study. Figure from the online supplement of Heinonen et al EJCP 2021.[149] Published with permission.

5 RESULTS

A summary of the main results is presented here. Detailed results are found in the individual papers included in the thesis.

5.1 SERTRALINE CONCENTRATIONS IN PREGNANCY AND IN THE INFANT

In total, 16 women were included in the randomized MAGDALENA study that ran between May 2016 and March 2019. Ten women were randomized to sertraline and six to placebo treatment. In the end, nine women were treated with sertraline and were, together with seven of their infants, included in the analysis of plasma sertraline concentrations (Figure 8). Two infants were not included, due to lacking samples and lacking informed consent from the father, respectively. The median doses of sertraline in the second and third trimesters were 50mg a day (range 50-75mg a day) and at delivery and postpartum 75mg a day (range 50-100mg a day).

5.1.1 Drug concentrations over time during pregnancy

Plasma sertraline and DMS concentrations were measured in the included women in the second trimester, around pregnancy week 21 (range 16-25), in the third trimester, around pregnancy week 30 (range 25-36), the morning after the delivery and one month postpartum. All measured concentrations were through concentrations, apart from one taken at the delivery, taken 7 hours after the dose and four that lacked information on last dose. The concentration measures of sertraline and DMS during pregnancy show an up to tenfold inter-individual variation, but the intra-individual dose-adjusted sertraline concentrations seem relatively steady during pregnancy with an increase postpartum (Table 3, Figure 9). The median dose-adjusted sertraline concentrations were 40% and 24% lower in the second and third trimester than the non-pregnant reference measured postpartum, 0.15 and 0.19 vs 0.25 (ng/mL)/(mg/day), but the difference was not statistically significant (p=0.345). The median alteration ratio between the pregnant and the non-pregnant state was 0.8 for both sertraline and DMS, with an almost 10-fold inter-individual variation.

Table 3. Measured and dose-adjusted plasma concentrations of sertraline and desmethylsertraline measured during and after pregnancy in the mother and in umbilical cord and at 48 hours of age in the infant.

		SERTRALINE CONCENTRATION				DESMETHYLSERTRALINE CONCENTRATION			
		Measured (ng/mL)		Dose-adjusted (ng/mL)/(mg/day)		Measured (ng/mL)		Dose-adjusted (ng/mL)/(mg/day)	
	N	Median	Range	Median	Range	Median	Range	Median	Range
2ND TRIMESTER	7	7.65	3.98-17.14	0.15	0.08-0.34	24.25	15.78-10.52	0.49	0.32-0.88
3RD TRIMESTER	9	9.49	1.53-20.81	0.19	0.03-0.38	35.06	10.52-61.36	0.70	0.21-1.11
MOTHER AT DELIVERY	8	14.38	3.64-24.17	0.19	0.07-0.32	33.60	7.01-61.36	0.46	0.14-0.82
MOTHER 1M POSTPARTUM	8	17.90	6.12-52.02	0.25	0.12-0.69	45.29	16.95-87.66	0.69	0.34-1.17
UMBILICAL CORD	5	4.28	1.22-6.12	0.08	0.02-0.09	9.93	4.97-17.24	0.18	0.10-0.23
INFANT 48 HOURS	5	4.59	1.25-7.04	0.06	0.02-0.09	17.53	9.93-20.45	0.23	0.13-0.27

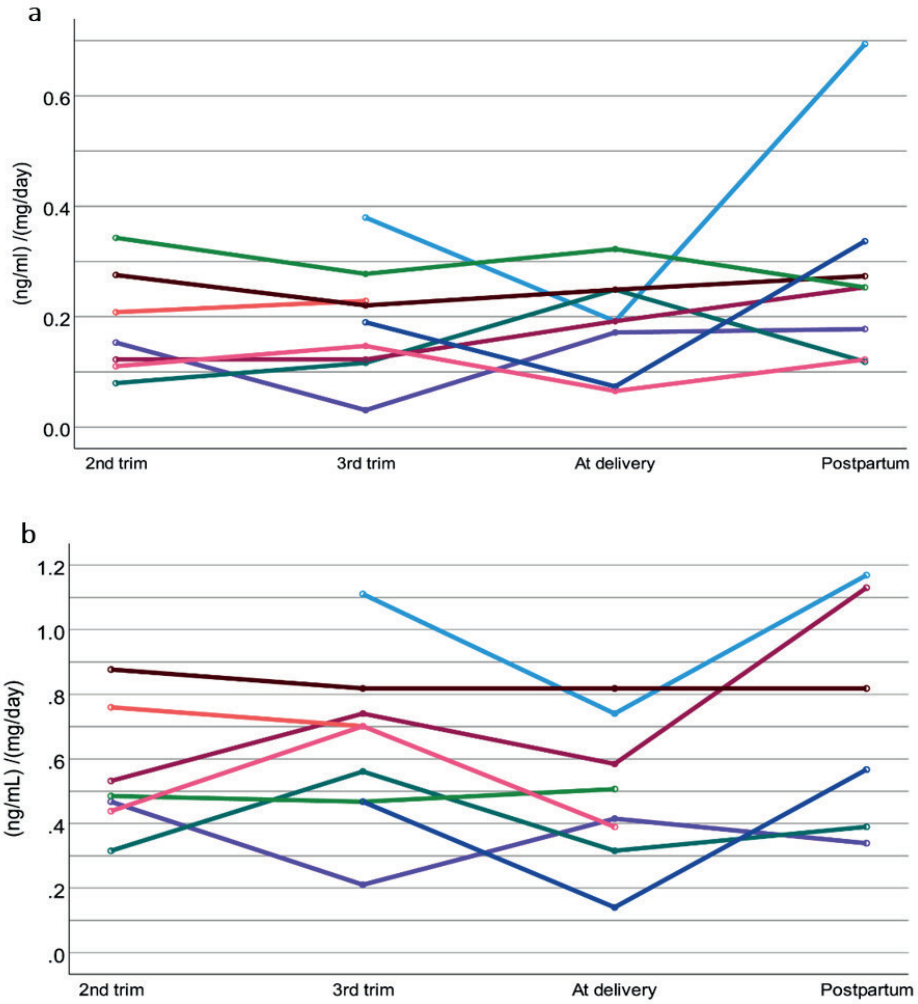

Figure 9. Dose-adjusted plasma sertraline (a) and desmethylsertraline (b) concentrations during pregnancy. Each line represents a study participant. The concentrations were measured at visits in the second trimester, in the third trimester, at delivery and one month postpartum. Figure from the online supplement of Heinonen et al EJCP 2021.[149] Published with permission.

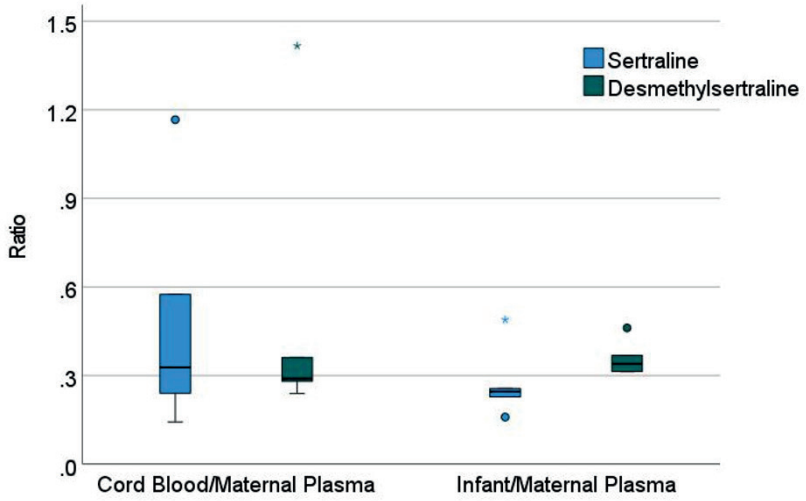

Figure 10. Placental penetration ratio of sertraline and its metabolite N-desmethylsertraline to the infant measured at birth in cord blood and infant plasma at 48 hours, divided with the respective concentration measured in maternal plasma at delivery.

5.1.2 Infant drug concentrations

Infant concentrations of sertraline and DMS were measured in cord blood and in infant plasma at 48 hours of age, presented in Table 3. All but one infant had lower plasma concentrations of sertraline and DMS at birth than their mothers (Figure 10).

The infant plasma concentrations of sertraline and DMS were correlated with the maternal plasma concentrations measured at delivery (Figure 11). The Pearson correlation coefficients for the correlations ranged between 0.64 and 0.83, without any of them being statistically significant. (p=0.08-0.24)[149]

5.1.3 Neonatal outcomes

All infants were healthy at birth, with all 5' APGAR-scores ≥ 9. Two infants were born with caesarean sections and the others with vaginal birth, of which one with instrumental assistance. One infant exposed to sertraline had a single low glucose of 2.5mmol/L which was resolved after supplemental feeding. One exposed infant was born in pregnancy week 33 and was treated at NICU without complications. One infant in the placebo group was SGA, all others were appropriate weight for gestational age. Two infants exposed to sertraline and one to placebo received treatment with CPAP in the delivery room, all less than 20 minutes. One infant exposed to sertraline sought the hospital at one week of age due to jitteriness so intense that seizures could not be outruled, but all examinations including EEG were normal

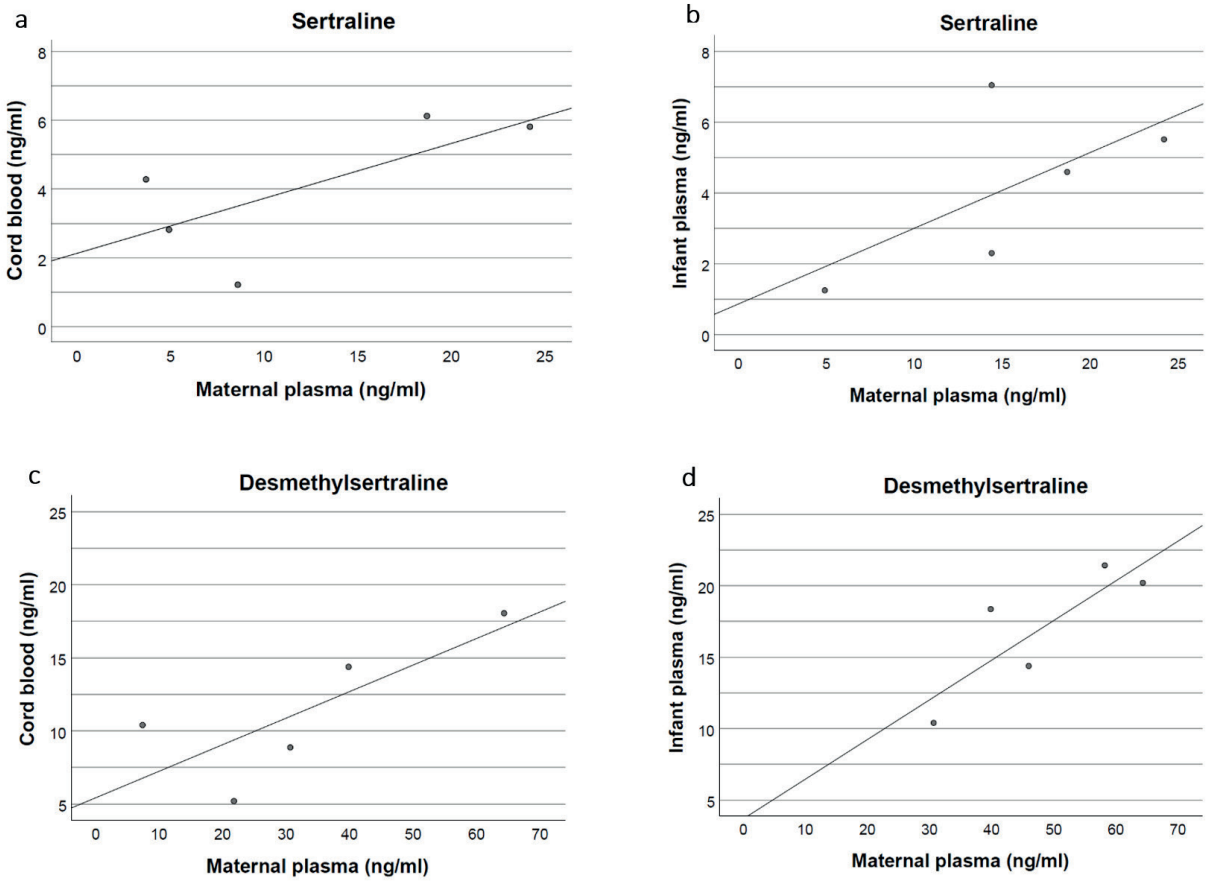

Figure 11. Scatterplots of the sertraline (a,b) and desmethylsertraline (c,d) plasma concentrations in the mother and the infant. Sertraline plasma concentrations in a) maternal plasma vs cord blood (r^2 linear =0,49) and b) maternal vs infant plasma (r^2 linear =0,41). Desmethylsertraline plasma concentrations in c) maternal plasma and cord blood (r^2 linear =0,61) and d) maternal and infant plasma (r^2 linear =0,70). Figure from the online supplement of Heinonen et al EJCP 2021.[149] Published with permission.

5.1.3.1 Neonatal Abstinence Score

One infant in the placebo group had a NAS score of 7 indicating moderate abstinence according to the score, without any ongoing maternal drug treatment registered. Two infants in the sertraline group showed signs of mild adaptation difficulties with NAS scores of 4, neither requiring any treatment for this.

5.2 ANTIPSYCHOTIC USE IN PREGNANCY AND RISKS FOR MOTHER AND INFANT

In studies II and III, the mothers exposed to antipsychotics during pregnancy and their infants were compared to women not treated during pregnancy and their infants, as well as women treated before or after but not during pregnancy and their infants. Out of the 1 307 487 singleton births in Sweden between July 2006 and December 2017 in Sweden, 1 299 216 births were included after exclusion of women with pre-pregnancy- diabetes and valproate treatment (Figure 12). In 2677 of the pregnancies, the women were treated with an antipsychotic drug, and in 302 of these, the women were treated with more than one category of antipsychotics. 34 492 women were treated with antipsychotics before and/or after but not during the current pregnancy. The background characteristics of the included women are presented in Table 4.

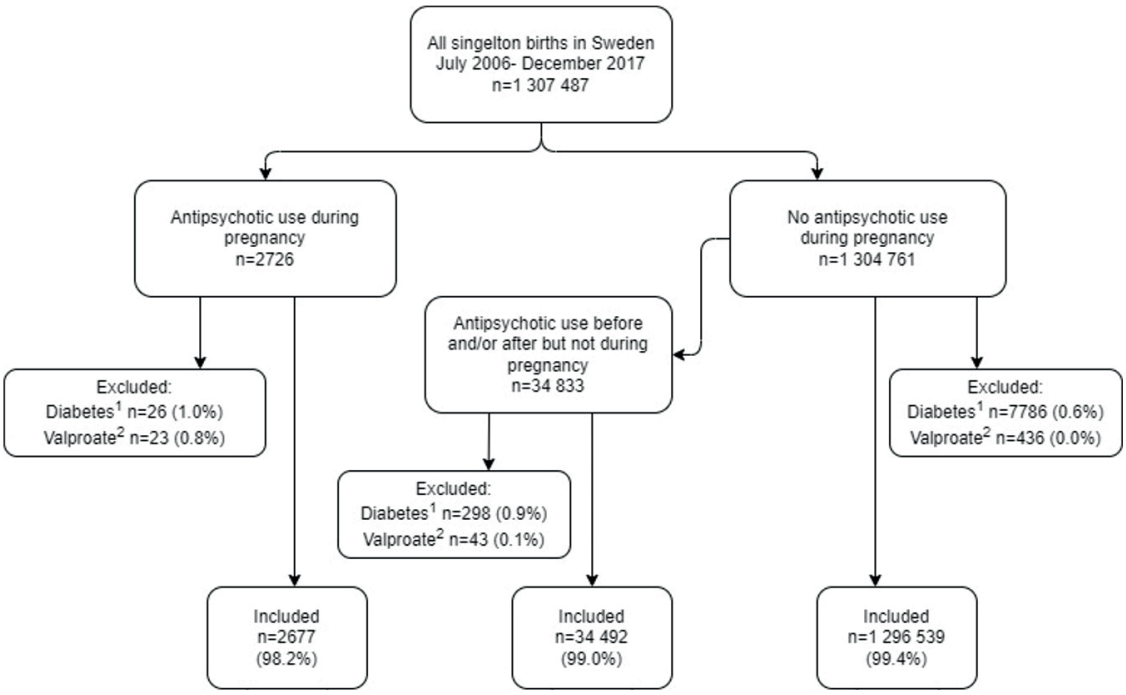

Figure 12. Flow-chart for inclusions for studies II and III. Modified from Heinonen et al. CNS Drugs 2022.[248] Published with permission.

Table 4. Background Characteristics of the Study Population. Modified from Table 1 from Heinonen et al. CNS Drugs 2022.[248] Published with permission.

	Antipsychotic use during pregnancy n = 2677 n (%)	Antipsychotics before or after but not during pregnancy n = 34 492 n (%)	No antipsychotic use during pregnancy [a] n=1 296 539 n (%)
Maternal age, years			
<20	70 (2.6)	1059 (3.1)	26 613 (2.1)
20–35	1883 (70.3)	26 638 (77.2)	991 018 (76.4)
35+	724 (27.0)	6795 (19.7)	278 908 (21.5)
Parity			
Primipara	1891 (70.6)	20 727 (60.1)	818 330 (63.1)
Multipara	786 (29.4)	13 764 (39.9)	470 320 (36.3)
BMI in early pregnancy			
<18,5	51 (1.9)	928 (2.7)	29 242 (2.3)
18.5–24.9	1015 (37.9)	16 356 (47.4)	705 995 (54.5)
25–29.9	772 (28.8)	8516 (24.7)	306 678 (23.7)
>=30	618 (23.1)	5723 (16.6)	153 350 (11.8)
Unknown	221 (8.3)	2969 (8.6)	101 271 (7.8)
Smoking in early pregnancy			
No	1818 (67.9)	26 774 (77.6)	1 154 817 (89.1)
Yes	733 (27.4)	5939 (17.2)	73 287 (5.7)
Missing information	126 (4.7)	1779 (5.2)	68 435 (5.3)
Maternal cohabitation			
Not living with the father	657 (24.5)	4824 (14.0)	80 275 (6.2)
Other neurotropic drugs			
Lithium	124 (4.6)	292 (0.8)	294 (0.0)
Opioids	44 (1.6)	604 (1.8)	5 352 (0.4)
Antiepileptics	215 (8.0)	725 (2.1)	3714 (0.3)
Antidepressants	755 (28.2)	4409 (12.8)	28 335 (2.2)
Psychostimulants	88 (3.3)	328 (1.0)	1118 (0.1)
Anxiolytics, sedatives	436 (16.3)	1429 (4.1)	6 049 (0.5)
Mild anxiolytics, sedatives[b]	366 (13.7)	2516 (7.3)	26 938 (2.1)

[a] includes all pregnancies without antipsychotics during pregnancy, including the control group.

[b] Including promethazine, alimemazine, dixyrazine, prochlorperazine and melperone. BMI = Body mass index.

5.2.1 Antipsychotic prescriptions to pregnant women

In the 11 years between 2006-2017, a total of 803 women were prescribed F-GAs and 2396 S-GAs during pregnancy. In this period, the yearly prescriptions of S-GAs for pregnant women increased with 300%, from 91 in 2006 to 367 in 2017. The three most prescribed antipsychotics were quetiapine, olanzapine, and aripiprazole (Figure 13).

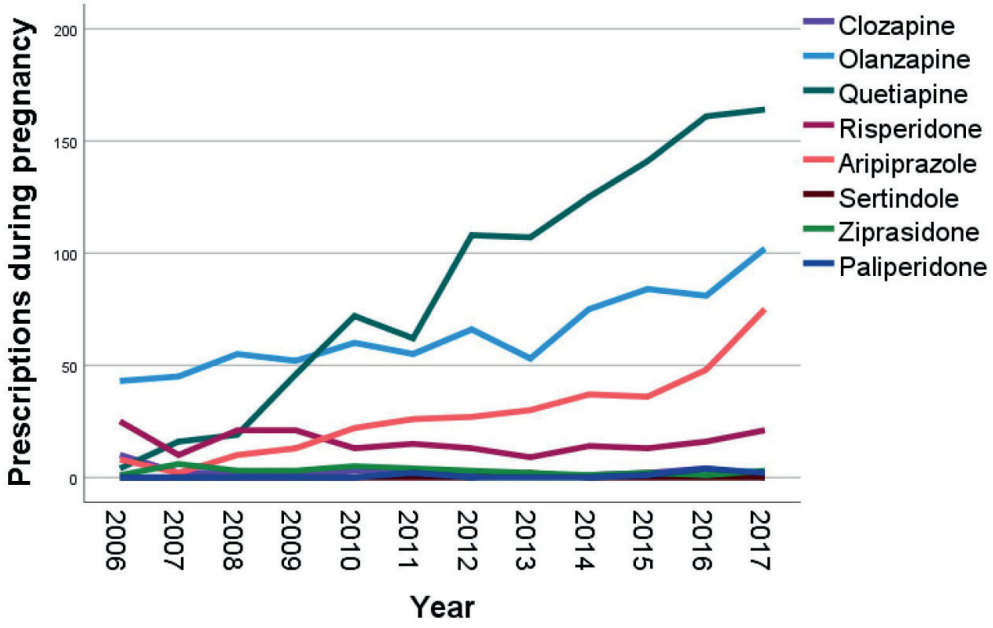

Figure 13. Time trend in the percentage of pregnant women in Sweden receiving a prescription of second-generation antipsychotics. From Heinonen et al. CNS Drugs 2022.[248] Published with permission.

5.2.2 Gestational diabetes and fetal growth

Of the women treated with the HR S-GAs olanzapine, quetiapine and clozapine and the women treated with F-GAs, 2.9% were diagnosed with GDM, compared to 2.6% of women treated with other S-GAs, 1.2% of the unexposed population and 1.4% of the control group. Compared to the unexposed population, the adjusted risks for GDM and the infant being LGA were increased after exposure to the HR S-GAs but not to the other groups of antipsychotics. (Table 5, Figure 14). The crude risk for the infant being SGA was increased after exposure to both HR S-GAs and F-GAs, but this increase also stopped being significant after adjustments. All risks were similar but slightly lower, when the exposed women were compared to women treated with antipsychotics before or after but not during the current pregnancy (Table 5).

Table 5. Crude and adjusted Risk Ratios for gestational diabetes and the infant being small or large for gestational age, after use of antipsychotics during pregnancy compared with no use during pregnancy and use before or after but not during pregnancy. From Heinonen et al. CNS Drugs 2022.[248] Published with permission.

	Use vs no use during pregnancy		Use during vs before/after pregnancy	
	Crude RR (95% CI)	**Adj.* RR (95% CI)**	**Crude RR (95% CI)**	**Adj.* RR (95% CI)**
F-GAs				
Gestational Diabetes	1.9 (1.2-2.9)	1.3 (0.9-2.1)	1.7 (1.1-2.6)	1.2 (0.8-1.9)
Small for Gestational Age	1.6 (1.1-2.3)	1.3 (0.9-1.8)	1.4 (1.0-2.0)ǂ	1.2 (0.8-1.7)
Large for Gestational Age	0.8 (0.5-1.3)	0.8 (0.5-1.2)	0.7 (0.5-1.1)	0.7 (0.5-1.1)
High metabolic risk S-GAs				
Gestational Diabetes	2.2 (1.6-2.9)	1.8 (1.3-2.4)	1.8 (1.4-2.5)	1.6 (1.2-2.1)
Small for Gestational Age	1.6 (1.2-2.0)	1.2 (1.0-1.6)ǂ	1.4 (1.1-1.8)	1.2 (0.9-1.5)
Large for Gestational Age	1.5 (1.2-1.9)	1.6 (1.3-2.0)	1.3 (1.0-1.6)	1.3 (1.1-1.6)
Other S-GAs				
Gestational Diabetes	1.5 (0.9-2.7)	1.1 (0.7-1.9)	1.4 (0.8-2.4)	1.0 (0.6-1.7)
Small for Gestational Age	1.1 (0.7-1.8)	0.9 (0.6-1.5)	1.0 (0.6-1.7)	0.9 (0.6-1.5)
Large for Gestational Age	1.4 (0.9-2.0)	1.3 (0.9-2.0)	1.2 (0.8-1.8)	1.2 (0.8-1.7)

* = adjusted for maternal age, parity, smoking and BMI. ǂ = not statistically significant. RR = Risk Ratio, CI = Confidence Interval.

5.2.2.1 The role of confounders

Increased BMI was strongly associated with GDM, and without adjustment for BMI, the adjusted risk ratios (aRR) for GDM were higher for all exposure groups, 1.6 (95% CI 1.0-2.5) for F-GAs, 2.0 (95% CI 1.5-2.7) for HR S-GAs and 1.5 (95% CI 0.9-2.5) for other S-GAs when compared to the unexposed population. To study the effect of BMI further, the risk for GDM after exposure to HR S-GAs was stratified on BMI. The aRR for GDM was only increased for women exposed to HR S-GAs in the strata of overweight women (BMI 25-30) with an adjusted RR of 2.4 (95% CI 1.4-3.9), and not in normal weight (BMI <25) or obese (BMI >30) women, with aRRs of 1.3 (95% CI 0.5-3.6) and 1.4 (95% CI 0.9-2.2) respectively. However, no statistically significant difference in the risk for GDM was found between the strata (p=0.298).

Smoking was negatively associated with GDM, but instead associated with the infant being SGA. A sensitivity analysis showed that adjustments for concomitant medication with other psychotropic drugs listed in Table 4 did not significantly affect the risks for GDM, SGA and LGA.

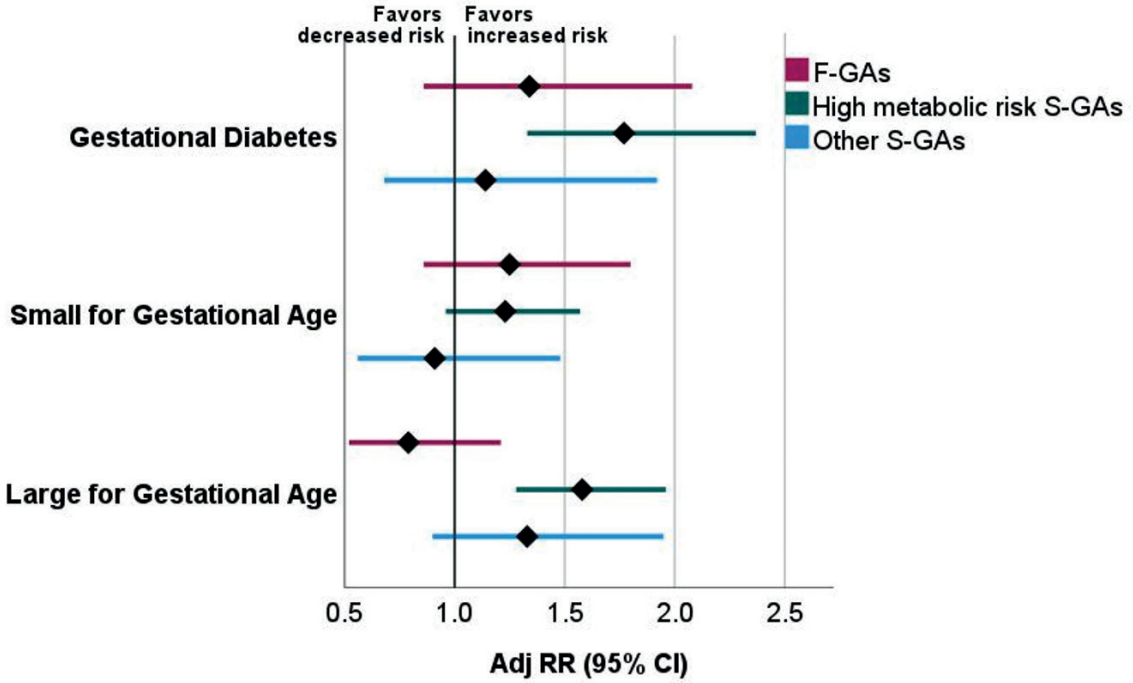

Figure 14. Risk ratios (RR) with 95% confidence intervals (CI) for gestational diabetes and the infant being small for gestational age or large for gestational age after exposure to antipsychotics compared to the unexposed population, after adjustment for maternal age, parity, smoking and BMI. The risks are presented separately for the first-generation antipsychotics (F-GAs), the high metabolic risk second-generation antipsychotics (S-GAs) olanzapine, quetiapine and clozapine and other S-GAs (mainly aripiprazole and risperidone).

5.2.3 Preterm labour and other pregnancy outcomes

Risks for the other pregnancy outcomes apart from GDM, SGA and LGA were analysed for all antipsychotics as a group and are presented in Figure 16. The risk for moderate to late preterm labour (pregnancy weeks 32+0 to 36+6) was increased for women treated with antipsychotics, when compared to both the untreated population and the control group. The risk for caesarean section was increased, but only marginally when compared to the control group. Use of antipsychotics during pregnancy was not associated to an increased risk for very preterm labour, pre-eclampsia or perinatal death. (Figure 15).

5.2.4 NICU admissions

Around every fifth infant exposed to antipsychotics in utero was admitted to NICU (Figure 16). The risk for being admitted to NICU was moderately increased for exposed infants, both when compared to the unexposed population and infants to mothers using antipsychotics before or after but not during pregnancy (Figure 16), and the NNH for NICU admission compared to the population adjusted for maternal factors was 18. The risk was similar for infants exposed to F-GAs and S-GAs, with RRs after exposure in late pregnancy of 2.1 (95% CI 1.7-2.5) and 1.8 (95% CI 1.6-2.0) respectively after adjustments for maternal age, parity, smoking, BMI, caesarean section, and concurrent psychotropic medications. The risk for admission to NICU was increased both for infants exposed in early pregnancy only and in late pregnancy, compared to non-exposed peers, aRRs 1.5 (95% CI 1.3-1.7) and 1.8 (95% CI 1.6-2.0), respectively. A sensitivity analysis with additional adjustments for gestational age and Z-score for infant weight did not markedly reduce the risk for being admitted to NICU for any group of infants.

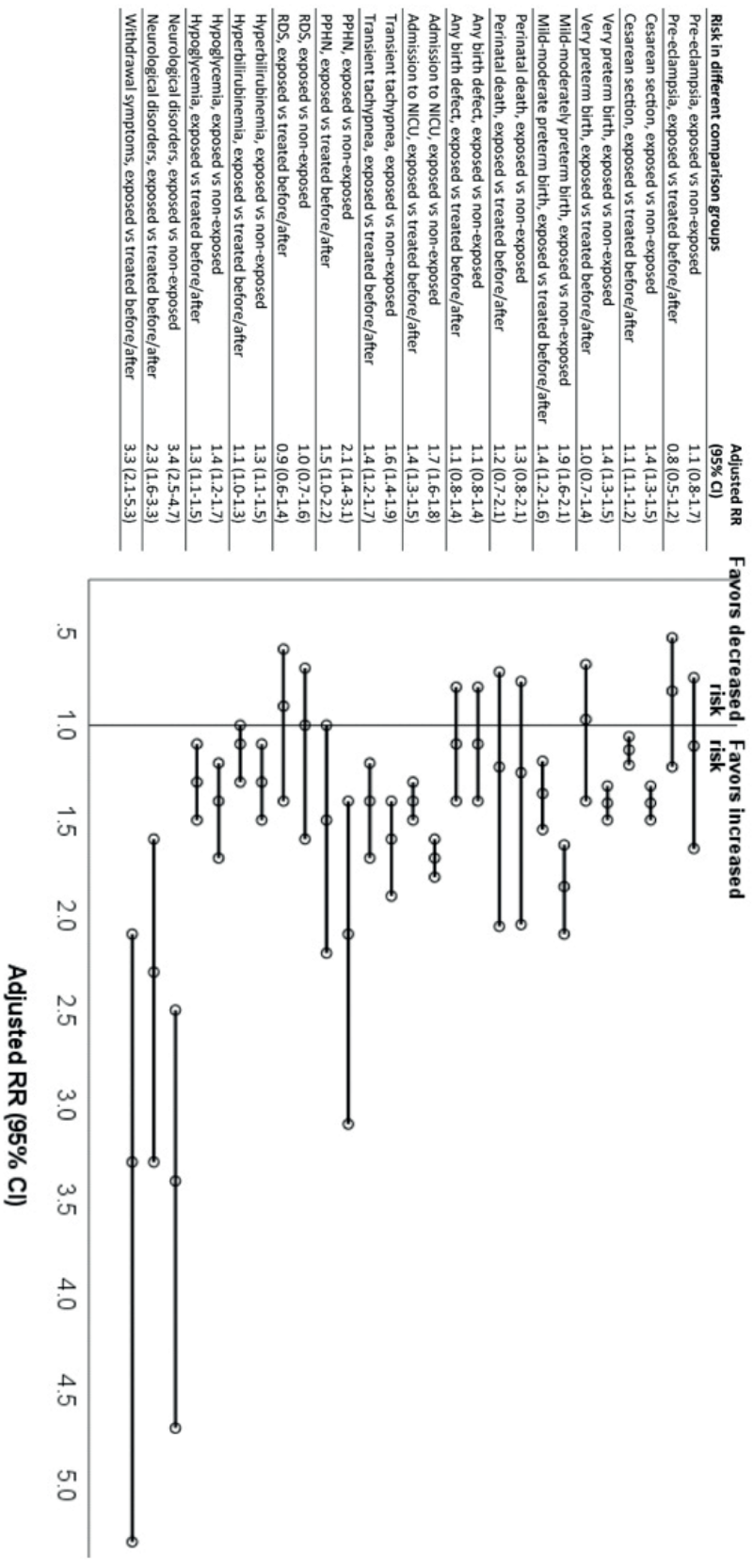

Figure 15. Risk Ratio (RR) for pregnancy and neonatal outcomes after antipsychotic exposure during pregnancy. Adjusted for maternal age, parity, BMI, and smoking, as well as for caesarean section and concurrent use of neurotropic drugs for the neonatal outcomes.

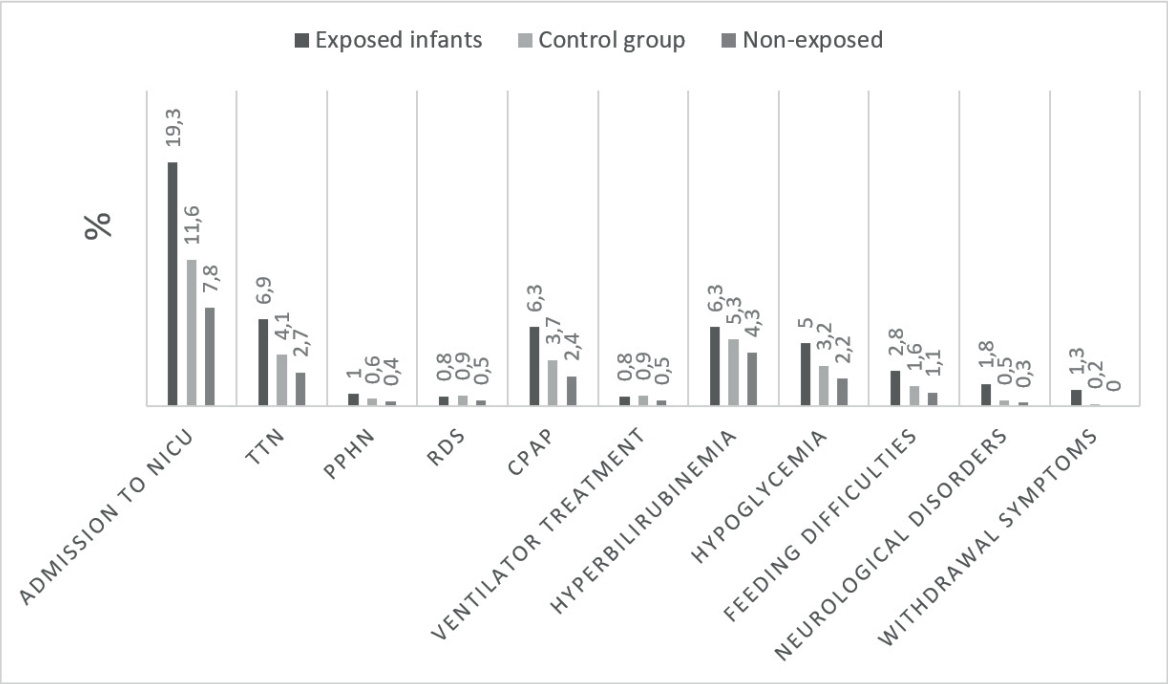

Figure 16. The percentage of NICU admissions, need of respiratory support and neonatal morbidity amongst exposed infants, the non-exposed population, and the control group of infants whose mothers had been treated with antipsychotics before or after pregnancy. NICU = neonatal intensive care unit, TTN = transient tachypnoea of the newborn, PPHN = persistent pulmonary hypertension of the newborn, RDS = respiratory distress syndrome. Adjusted for: Primipara, Age, Body Mass Index (BMI), Smoking, Caesarean section, Concurrent neurotropic drugs

5.2.4.1 Length of stay at NICU

The median length of stay at NICU was 5 days for both exposed and non-exposed full-terms, but there was a statistically significant difference with the exposed infants having slightly longer stays than the non-exposed. However, when looking at full-term infants with PPHN and neurological disorders, the exposed infants had a shorter median length of stay than the non-exposed. The median length of stay amongst exposed full-terms with PPHN was 8 days (IQ-range 3-9 days) vs 9 days (IQ-range 5-17 days) in non-exposed full-terms with PPHN. Exposed infants with neurological disorders had a median length of stay at NICU of 9 days (IQ-range 6-11 days), compared to 11 days (IQ-range 7-18 days) in their non-exposed peers.

5.2.5 Neonatal diagnoses

The most frequent outcomes affecting 5-7% of the exposed infants were TTN, hyperbilirubinemia, and hypoglycaemia. However, the relative risks for these conditions were only moderately increased for exposed infants, with aRRs 1.3-1.6 when compared to the unexposed population, and 1.1.-1.4 when compared to the control group (Figure 15). Additional adjustment for gestational age and Z-score for weight did not markedly change these risks. No statistically significant differences between the exposure groups were found for respiratory distress syndrome, ventilator treatment, any malformations or heart malformations (Figure 15).

The neonatal disorders with the highest risk increases associated with antipsychotics exposure were withdrawal symptoms from therapeutic drugs, aRR 17.7 (95% CI 9.6-32.6), neurological disorders, aRR 3.4 (95% CI 2.5-4.7) and PPHN, aRR 2.1 (95% CI 1.4-3.1), when compared to the population (Figure 15). However, the absolute frequency of these diagnoses in exposed infants was only 1-2 percent (Figure 16).

5.2.5.1 Neurological disorders

The neurological disorders included seizures, congenital hyper-/hypotonia, hypoxic ischemic encephalopathy and other disturbances of cerebral status including both lethargy and agitation/irritability. The frequency of these outcomes was only 1.8% amongst exposed infants, but when compared to the non-exposed infants with a frequency of 0.3% of neurological disorders, the crude RR for neurological outcomes was 5.8 (95% CI 4.4-7.7) when compared to the non-exposed infants and 3.3 (95% CI 3.6-8.0) when compared to the control group. The aRRs were 3.4 (95% CI 2.5-4.7) and 2.3 (95% CI 1.6-3.3), respectively. The NNH for neurological disorders was 139.

5.2.5.2 Persistent pulmonary hypertension

The risk of PPHN for infants exposed to antipsychotics compared to non-exposed infants was clearly increased, with a crude RR of 2.8 (95% CI 1.9-4.1), and adjusted for parity, maternal age, BMI, smoking, caesarean section, and concurrent use of other neurotropic drugs 2.1 (95% CI 1.4-3.1). When the exposed infants were compared to infants to mothers with antipsychotic treatment before and/or after the pregnancy, the crude and adjusted RRs for PPHN were 1.7 (1.1-2.5) and 1.5 (1.0-2.2). In a sensitivity analysis only including term infants, the risk estimates for PPHN were unchanged. In another sensitivity analysis including all infants, the risk estimates were adjusted gestational age and Z-score for infant weight as well as the other cofactors, the adjusted risk ratios for PPHN were no longer statistically significant, with aRRs 1.5 (95%CI 0.9-2.6) and 1.2 (95% CI 0.7-2.2) compared to the unexposed population and infants to mothers treated with antipsychotics before/after pregnancy, respectively. The absolute risks for PPHN were 1.0, 0.6 and 0.4% for exposed infants, the control group, and the unexposed population, respectively, and the NNH for PPHN was 227.

5.3 INFANT MORBIDITY AFTER EXPOSURE TO LITHIUM THROUGH BREASTMILK

In study IV, we performed a retrospective study on serum lithium concentrations and clinical and laboratory findings in 30 infants exposed to lithium through breastmilk, followed up at Neonatal and Liljeholmen Paediatric Outpatient Clinics at Karolinska University Hospital (9 infants) and at the Neonatal Outpatient Clinic at Sachs' Children's and Adolescents' Hospital at Southern Hospital (21 infants). A total of 66 serum lithium concentrations were measured in the included infants and 47 in their mothers. Throughout the visits, around 50% of the infants were exclusively breastfed, and the other half were partly breastfed with varying levels of complementary bottle feeds with infant formula.

5.3.1 Serum lithium concentrations in mother and child

The lithium serum concentrations in the included infants are presented in Figure 17. Only two infants had therapeutic lithium serum concentrations, 0.7 and 1.2mmol/l respectively. These were both measured within the first month in life, and all concentrations measured after the first month were at or below 0.2mmol/l. The mean lithium concentrations in maternal serum were stable around 0.6-0.7 (SD 0.1-0.2), resulting in mean infant-mother ratios of 0.37 at 1-2 weeks postnatal age, 0.18 at 2-4 weeks, and 0.1 after one and two months of age (Figure 18).

5.3.2 Infant growth, laboratory follow-up and clinical symptoms

Around 25% of the infants had a poor weight gain at the visits 1-2 weeks and 2-4 weeks after birth, whereas the rate was 4% and 13% at 1-2 and 2-4 months of age, respectively. Three women were advised to reduce breastfeeding due to either a high plasma lithium concentration or poor weight gain in the infant, and one due to polypharmacy. The infants' thyroid- and kidney levels were measured at all visits, with no clinically significant adversities found. Two infants were described as tired before one month of age, but apart from this and the slower weight gain, no suspect adverse effects were found. None of the included infants presented with deviations in muscle tone or irritability examined at the visits.

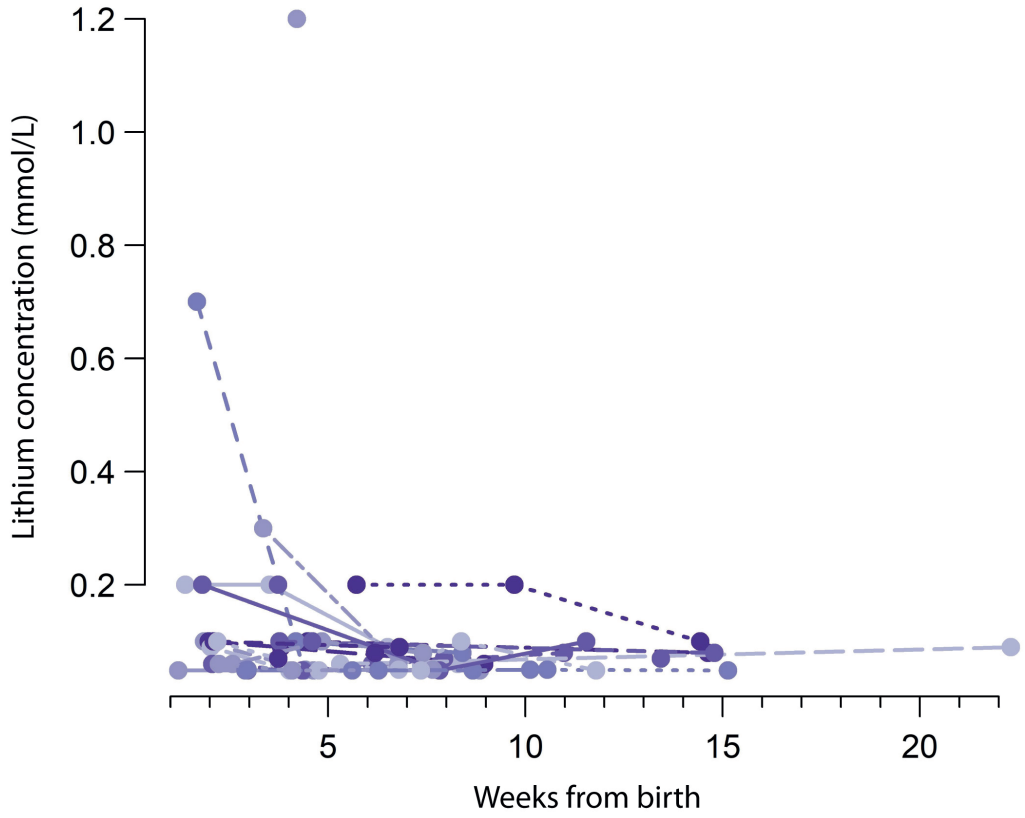

Figure 17. Lithium serum concentrations in the 30 infants in study IV exposed to lithium through breastmilk presented on a logarithmic scale. Created by Ida Hed Myrberg, statistician, Biostatistics Core Facility, KI

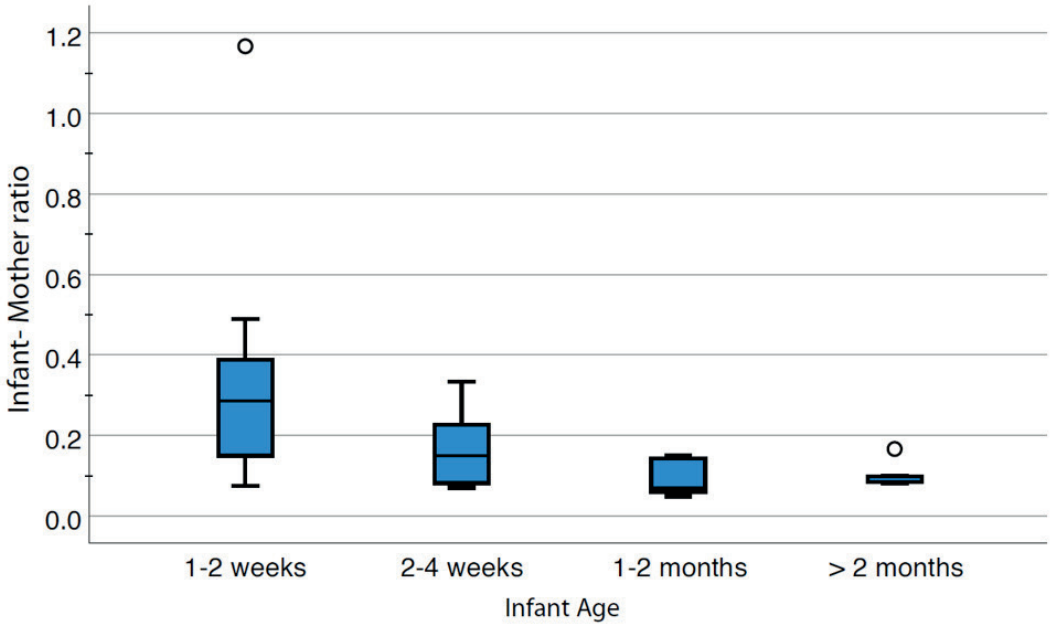

Figure 18. Infant/mother ratios of lithium serum concentrations measured at the clinical follow-up of the infant. Submitted for publication.

5.4 MATERNAL HEALTH AND RISK FACTORS

Maternal health and risk factors connected to infant health were addressed in all the included studies.

5.4.1 Risk factors amongst participating mothers

In study I, all included women had a moderately severe depression at inclusion in the first trimester. In study IV, all but four women were diagnosed with bipolar disorder but had generally a good disease control and stable mood, most likely thanks to their lithium therapy. The relevant background factors for the mothers in study IV are presented in Figure 19. In studies II and III, we did not study other maternal diagnoses than the pregnancy complications, but instead we studied and adjusted for factors connected to the maternal mental disorder (Table 4, Figure 20).

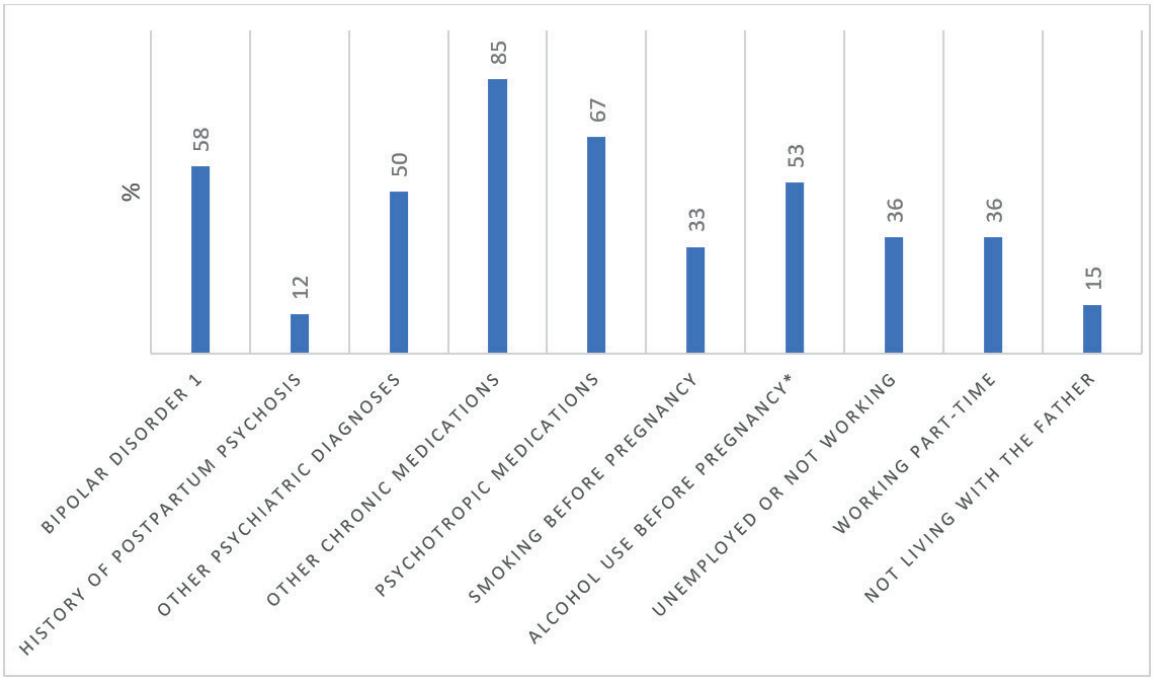

Figure 19. Selected background characteristics of the mothers in study IV. *Any use of alcohol

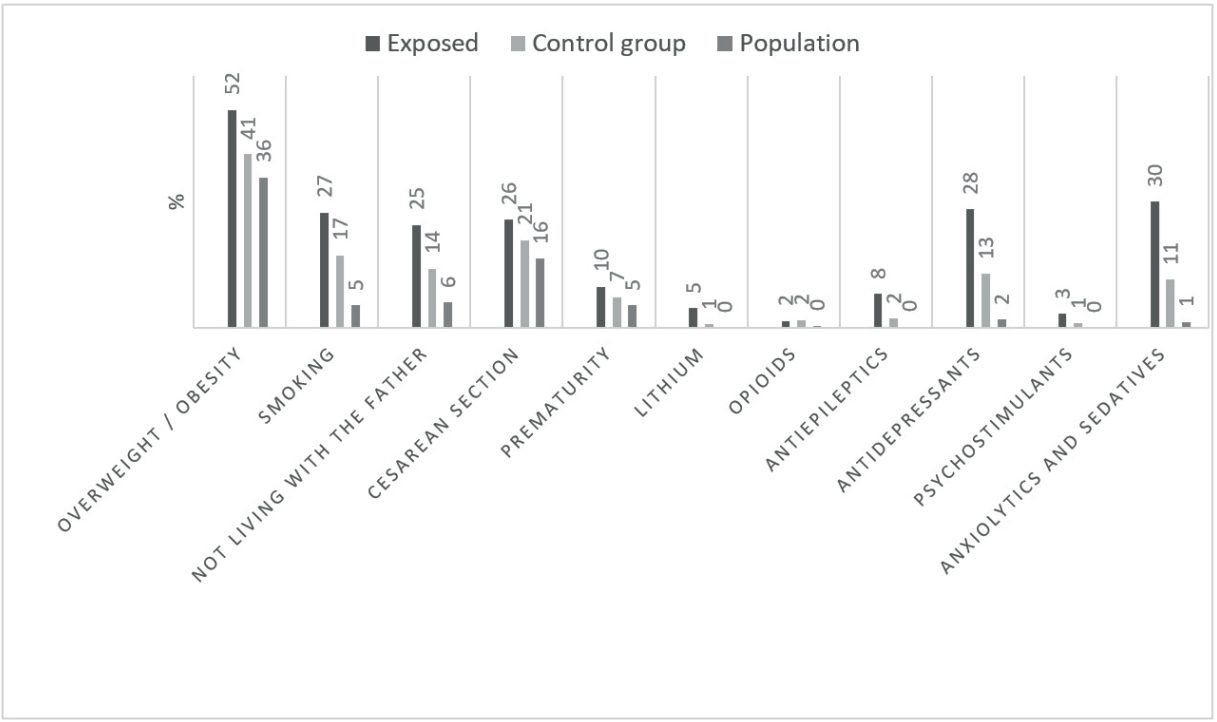

Figure 20. Percentage of women with relevant comorbidities and psychiatric co-medications in the different treatment groups. Exposed = women treated with antipsychotics during pregnancy, control group = women treated with antipsychotics before or after but not during pregnancy, population = all women not exposed to antipsychotics during pregnancy.

5.4.1.1 Polypharmacy

As study I was randomized in nature, no chronic psychotropic drug treatment apart from the study drug was allowed for. Some concomitant medications like thyroid hormone substitution and asthma medication were allowed. The only concomitant psychotropic drug was promethazine, an antihistamine used temporarily by three women in the study. Temporary use of this drug is common for pregnancy-related nausea and anxiety.

In the three other studies, polypharmacy was a relevant factor to consider when interpreting the outcomes. In study II and III, 30% of the exposed women had also used anxiolytics and sedatives and 28% antidepressants during pregnancy. The usage of these drugs was also markedly more common in the women treated with antipsychotics before or after but not during pregnancy than in the non-exposed population (Table 4, Figure 19). The concomitant neurotropic drugs were adjusted for in all analyses of infant outcomes in study III.

Polypharmacy was also common in the women included in study IV and not adjusted for due to the observational nature of the study. Out of the 30 included women, 60% were treated with at least one other psychotropic drug: 23% with antipsychotics (quetiapine, olanzapine, and aripiprazole), 20% with antidepressants (fluoxetine, sertraline, citalopram), 33% with sedatives and anxiolytics (zopiclone, oxazepam, zolpidem, promethazine and hydroxyzine), and 13% with psychostimulants (methylphenidate and dexamphetamine) (Figure 19). Some of these drugs, especially the anxiolytics, were prescribed to only be taken as needed, others on regular basis. One woman was recommended to not breastfeed exclusively due to several co-medications, even though the infant was well.

5.4.2 Changes in maternal mood during treatment

The participants included in the MAGDALENA study all had a MDD of moderate grade, with MADRS points ranging between 20 and 30 at inclusion. The MADRS points were followed at the two follow-up visits during pregnancy and one month postpartum, with the results presented in Figure 21. Generally, the MADRS scores decreased during the course of the treatment, but at the end of the study one month postpartum, four women had MADRS scores >20 and based on that and the clinical interview needed referral to further care. Three of these women, one from the sertraline group and two from the placebo group had initially had a decrease in their MADRS points, with points around 13-14 in the second and third trimester.

We studied the correlation between the sertraline plasma concentration and the change in MADRS scores, without any correlations found or even suspected, with p-values ranging between 0.38 and 0.81 for the different time points.

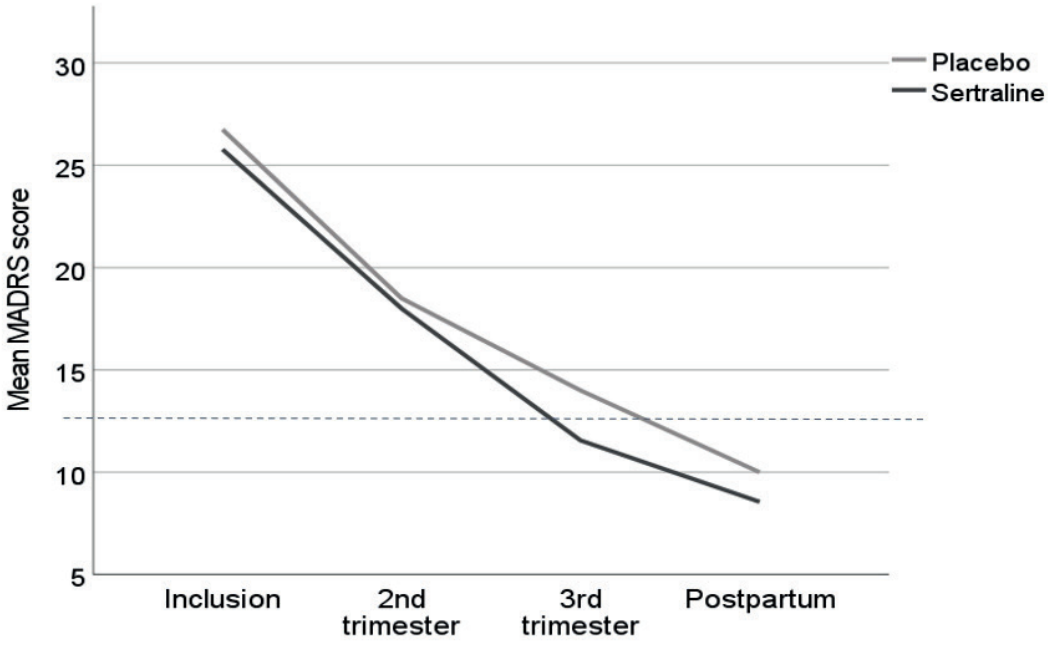

Figure 21. Mean MADRS scores at the study visits in study I, the MAGDALENA study, divided by the given treatment into sertraline (n=9) and placebo (n=7) treatment groups, with the dotted line representing the threshold of depressive disorder, 12 points.

6 DISCUSSION

6.1 GENERAL DISCUSSION

Pregnant women in need of psychotropic drug treatment have been called "the last therapeutic orphans", and rightly so. Even though treatment of perinatal psychiatric disorders results in better outcomes for both the pregnant mother and her infant, the evidence-based treatment options for these women are still limited.[249 250] The teratogenicity of most psychotropic drugs is relatively well studied, but there are still huge gaps in knowledge of their pharmacokinetics, pharmacodynamics and side-effects on the pregnant women, as well as their short- and long-term effects on the exposed infants. Also, the ways of communicating the existing research to the pregnant women and their care-givers are insufficient. Today still, pregnant women are often reluctant towards psychotropic drug treatment during pregnancy, which we got to experience in our RCT, and health care professionals are often restrictive and following the approach "better safe than sorry" when advising on medication during pregnancy. This is of course motivated if the disorder is mild or the drug is insufficiently studied, or in fact, connected to increased teratogenic risks, but can be detrimental for women with severe disorders like bipolar and psychotic disorders studied in this thesis.[51] The balance of how to best treat the maternal condition while minimizing the risk for the fetus is therefore delicate, and clinicians not handling these questions on a daily basis will need guidance. The studies in this field are mostly observational with varying methodological drawbacks, which makes it difficult to draw clinical conclusions from their results.

To improve the safety and quality of drug treatment during pregnancy and lactation, several countries have established Teratology Information Services (TIS), centres for expertise on the safety of drug use during pregnancy and lactation. These centres provide health care professionals, and in some cases also the pregnant and breastfeeding women, with information and individual risk assessments.[251 252] Unfortunately, Sweden does not have a TIS-centre for the women and caregivers to contact. Instead, the websites Janusmed graviditet (regarding drug safety during pregnancy) and Janusmed amning (regarding drug safety during lactation) are held to guide clinicians with safety classifications for drugs.[253]

6.2 DISCUSSION ON MATERNAL EFFECTS

The maternal effects and pregnancy complications were studied in study I and II. In study I, the focus was on TDM of the pregnant women treated with sertraline, whereas study II focused on the risk of developing GDM after exposure to S-GAs with high metabolic risks.

6.2.1 Pharmacokinetics of drugs during pregnancy

TDM and close clinical monitoring of women treated with psychotropic drugs during pregnancy is recommended due to the pharmacokinetic changes known to be caused by pregnancy, but not always practiced.[120] For some drugs, such as lithium, there are clear guidelines with up-titration of the dose during pregnancy due to its increased renal elimination, whereas for other drugs like sertraline, it is still debated whether a dose increase is needed even with decreased plasma concentrations..[120 254 255]

Sertraline is metabolized in the liver by several CYP-enzymes, of which CYP 2C19 might play a crucial role in its Phase I -metabolism. The activity of CYP 2C19 decreases with around 50% during pregnancy, meaning that sertraline plasma concentrations might in fact increase during pregnancy, as has been shown by some.[120 131] Instead, in our first study, we found that the median dose-adjusted sertraline plasma concentrations in the second trimester were around 60% of the non-pregnant reference measured postpartum. Although this difference was not statistically significant, others have

found similar decreases in sertraline plasma concentrations during pregnancy, indicating that perhaps also other factors than the decreased activity of CYP 2C19 affect the sertraline plasma concentrations. Due to 98% of sertraline being protein bound, other thinkable explanations for the decreased sertraline plasma concentrations during pregnancy are the increased plasma volume and decreased levels of plasma proteins, affecting both the total sertraline plasma concentration and possibly also the partition of the free (unbound) form of sertraline. The increased activity of other relevant drug metabolizing enzymes such as CYP 3A4 and CYP 2D6 might also compensate for the decreased activity of CYP 2C19.[256]

In our study there was one woman with a very high sertraline plasma concentration (Figure 9), and a limitation of our study is that we could not perform further genetic analyses of the women's genotypes of CYP 2C19. We speculate however, that this patient might have had a poor metabolizer genotype of CYP 2C19. The genetic variants of CYP 2C19 range from poor to ultra-rapid metabolizing capacity, and the genotypes seem to react differently to the hormonal changes during pregnancy. TDM analyses of sertraline should be considered during pregnancy to reduce the risk of unwanted side-effects in poor metabolizers as well as to examine reasons for a poor clinical effect in ultra-rapid metabolizers. In pregnant women with deviating plasma sertraline concentrations, pharmacogenetic testing for the genotype of CYP 2C19 to localize the ultra-rapid metabolizers needing higher doses of sertraline seems indicated, especially if the low plasma concentration is accompanied by an insufficient clinical effect.[122] A problem with TDM for sertraline however is, that there is a tenfold inter-individual variation in its plasma concentrations, and its therapeutic range is wide, from 10 up to 150ng/ml. Also, no association is found between the measured concentration and the clinical effect.[118 132 257 258] Therefore, for TDM during pregnancy, the best reference value is supposedly the woman's own pre-pregnant concentration.[131]

6.2.2 Changes in maternal mood

As all women in Study I had a moderate MDD at inclusion, one of the aims of the study was to treat this disorder, with I-CBT and sertraline or placebo. The women's mood was followed up with regular visits to the study midwife and the psychiatry nurse, and the women were also provided phone contact with these between the visits if needed. Generally, all measured plasma concentrations were below or in the lower range of the therapeutic range of sertraline, and similar to previous studies, we found no statistical significance between the sertraline dose or plasma concentration and the decrease in MADRS-scores.[257] All mothers showed, regardless of treatment regime, decreased MADRS-scores along the course of the pregnancy (Figure 10). The general improvement in maternal mood amongst the included women might instead have been due to the sick leave that was offered if needed or the natural course of the pregnancy with the second trimester bringing relief to the tiredness and nausea characterizing the first trimester. The I-CBT probably contributed somewhat to the improved maternal moods as well, but as the women only completed around half of the ten treatment modules, it is not likely that this is the sole explanation. Instead, we believe, that the regular contact with the study midwife and specialist nurse in psychiatry was a great contributing factor to the improved maternal moods. This differs markedly from the standard care of moderate depression during pregnancy today, that is normally treated by the primary health care centres with limited resources. Therefore we conclude that the effect of continuous and highly available care should not be neglected.

6.2.3 Gestational diabetes after antipsychotic exposure

In study II we studied the risk of pregnancy complications after treatment with antipsychotics during pregnancy, through a large nationwide dataset with 1.3 million pregnancies, derived from the Swedish national registries. We found that the rate of GDM was 2.6-2.9% in women who had used antipsycho-

tics during pregnancy, compared to 1.2% in the population. The risk increase was statistically significant for the HR S-GAs but not the other antipsychotics. However, as described in the background to this thesis, the incidence of GDM in Sweden has increased rapidly in the last five years after introduction of the national guidelines for glucose thresholds for OGTT.167 In 2020, the national frequency of GDM was 5.1% with regional variations between 1.4 and 14.6%.164 With this in mind, it is relevant to question the clinical significance of the 1.6% difference found between the exposure groups in our study. Could it have been that the women treated with antipsychotics were already considered a risk group for GDM and therefore more often offered OGTT, introducing a differential information bias? As the risk of giving birth to an LGA infant was also increased amongst women treated with HR S-GAs, and as LGA is strongly connected to GDM and maternal hyperglycaemia in general, we conclude that we have reason to believe that the risk-increase for GDM after exposure to HR S-GAs is true.[180]

6.3 DISCUSSION ON THE EFFECTS ON THE INFANT

In studies I and III, we studied the effects on the infants after fetal exposure to sertraline (Study I) and antipsychotics (study III). Study I was a prospective clinical study with a small, but within the field significant cohort size, with detailed information on drug passage to the infant. Study III was a nationwide register-based study including 1.3 million pregnancies, with results presented on group level, being to our knowledge the first of its kind to specify the neonatal outcomes to this extent.

6.3.1 Infant outcomes and concentrations after exposure to sertraline

The seven infants exposed to sertraline in study I were all healthy, with no signs of hypoglycaemia or drug withdrawal. One of the infants was born preterm. The cohort size was too limited to draw any conclusions regarding the previously described PNAS from the study.

The median plasma sertraline concentration in the infants was around a third of the mothers', which is in line with the findings of a handful of previous studies.[134 259-261] We speculate, that the low infant levels of sertraline might be explained by sertraline mostly being bound to AAP, present in the infant at levels around a third of the mother's. This is supported by sertraline and DMS being weak basic compounds, being more likely to bind to the more acidic AAP, rather than albumin.[115 146 147 262] To clarify this further, it would have also been interesting to measure the free form of sertraline in both mothers and infants, to see whether this is increased as a result of the decreased opportunities for protein bidning. Not being able to do so, is one of the draw-backs of study I.

The median plasma sertraline concentration in the infants decreased and the median concentration of its metabolite DMS increased between the samples measured in the umbilical cord and in infant plasma at 48 hours of age, indicating metabolism of sertraline in the infant. Sertraline elimination half-life is known to be around 32 hours in adults, and even though the half-life is not possible to calculate from our data, it seems reasonable to believe that the infant liver does have the ability to eliminate sertraline.[263] This is also in line with clinical data from a previous study, showing that the symptoms in the exposed infants peak around 37 hours of age, but can last for several days.[36]

6.3.2 Infant outcomes after fetal antipsychotic exposure

Study III showed that 19% of the infants exposed to antipsychotics during fetal life were admitted to NICU. The most common morbidities amongst the exposed infants were, similar to in their non-exposed peers, TTN, hyperbilirubinemia and hypoglycaemia. The relative risks for these outcomes were however not as strongly increased as they were for the rarer withdrawal symptoms, neurological disorders and PPHN. All these risks were also increased when the exposed infants were compared to

infants to the mothers treated with antipsychotics before and/or after pregnancy, but not as markedly. This is in line with our hypothesis and indicates that a part of the risk increase for neonatal morbidity is explained by underlying unmeasurable factors connected to the indication for the treatment, but a moderate risk-increase connected to the drug exposure cannot be excluded. As all the antipsychotics bind to serotonergic receptors in the brain to a varying degree, these drugs could also have yet unstudied direct effects on the fetal brain. Some residual confounding by indication and misclassification caused by longer periods of time between filing the prescription and actually using the drug are likely to be present in the comparison of the two groups treated with antipsychotics. Even with this in mind, we believe that this comparison adds to understanding the risks for these women and infants.

6.3.2.1 Neurological disorders

The composite outcome of neurological disorders in study III includes a variety of neurological effects, including morbidities from asphyxia and seizures to congenital disturbances in muscle tone, lethargy, and irritability. The diagnoses were studied on group level due to the low number of exposed infants with neurological disorders (47 infants), and on this level, the risk for neurological outcomes was markedly increased after fetal exposure to antipsychotics, both when compared to the non-exposed population and to the control group. It would of course be relevant to study the specific neurological outcomes individually in relation to the antipsychotic exposure, but as both the exposure and the outcomes are rare, a much larger cohort than ours with 1.3 million infants would be needed. The neurological disorders in the exposed infants seem less severe than other neurological reasons for being admitted to NICU, as the median length of stay at NICU was two days shorter in the exposed infants with neurological disorders than in their non-exposed peers, 9 vs 11 days. There is also a possibility that some exposed infants were more closely monitored regarding neurological symptoms due to the knowledge of their drug exposure, and therefore more likely to acquire a neurological diagnosis in SNQ.

6.3.2.2 Persistent pulmonary hypertension

In the analyses, we paid special attention to PPHN, as the risk for this has not to our knowledge been studied before in infants exposed to antipsychotics but has been shown to be increased after fetal exposure to SSRIs.[26 40 212 264 265] The adjusted RR for PPHN found after antipsychotic exposure was 2.1 (95% CI 1.4-3.1), similar to the risk for PPHN found after SSRI exposure. The absolute risk of PPHN amongst infants exposed to antipsychotics, one percent, was however twice as high as in infants exposed to SSRIs.[26] The length of stay at NICU was one day shorter for full-term infants with PPHN exposed to antipsychotics compared to their non-exposed peers, 8 vs 9 days, suggesting that the severity of PPHN connected to antipsychotic exposure could be milder than for full-terms suffering from PPHN from other causes.

The correlation between fetal antipsychotic exposure and PPHN did not sustain after adjustments for preterm birth and Z-score for birth weight, indicating that at least a part of the risk increase is depending on these factors. Both preterm birth and fetal growth disturbances (infants being LGA or SGA) are connected to increased risk of TTN, being a risk factor for PPHN. Both preterm birth and LGA are also associated to fetal exposure to antipsychotics. Therefore, these factors could be seen as mediators for the association between fetal antipsychotic exposure and PPHN and should therefore not be adjusted for.

The causality of this association is to date unknown, but we speculate that due to both antipsychotics and antidepressants affecting the serotonergic pathways, the increased risk for PPHN could be caused by an effect on the serotonergic pathways in the lung vessels. Another more clinical explanation model is, that both antidepressants and antipsychotics are associated with an increased risk for poor neonatal adaptation and TTN, causing poor ventilation and impaired pulmonary vasodilation leading to the development of PPHN.[266] Overall, it should be noted, that the absolute risk for PPHN is very low amongst the exposed infants and this finding should not indicate any changes in treatment recommendations for pregnant women.

6.3.2.3 Drug withdrawal symptoms

The risk of drug withdrawal symptoms is hard to evaluate based on register data due to the differential information bias in acquiring this diagnosis, i.e., an infant not exposed to any drugs will not require this diagnosis. As a consequence of this, the frequency of drug withdrawal symptoms amongst the non-exposed infants was zero percent, leading to very high risk estimates for withdrawal symptoms after intrauterine exposure to antipsychotics. The diagnosis of drug withdrawal symptoms is also very unspecific in the registers, why the composite of neurological symptoms was a more reliable outcome to interpret in our study.

6.4 DISCUSSION ON PSYCHOTROPIC DRUG TREATMENT DURING LACTATION

The prevalence of breastfeeding is high in Sweden. At two months of age, over 85% of infants are breastfed.[267] Many new mothers with psychiatric disorders but with currently stable mood because of adequate medication wish to breastfeed their infants, and may feel stigmatized if not allowed to do so. Breastfeeding is also known to improve the maternal mental and physical health as well as the attachment, which is beneficial for both the mother and the infant.[268] However, this field is generally far less studied than the effects of drug use during pregnancy, perhaps because in breastfeeding, there is an option of treating the mother without exposing the infant by recommending against breastfeeding. Considering the benefits of breastfeeding and the strong wish to breastfeed in some of these mothers, it is still important to aim at creating evidence-based recommendations for chronic drug use during lactation.

In study IV, we studied serum lithium concentrations and clinical symptoms in infants exposed to lithium through breastmilk, by retrospectively exploring the medical records of 30 exposed infants followed up at paediatric outpatient clinics. The lithium serum concentrations were stable in all infants after the first month in life, but before that, high serum lithium concentrations were measured in two infants, one born in pregnancy week 35, and one term infant who had been admitted to NICU for observation due to a cyanotic spell at the maternity ward. The high concentration in the preterm infant might be explained by the low GFR leading to slow renal excretion of lithium in preterm infants. The GFR is known to be around 20-40 ml/min/1.73m^2 in the first week in term infants but can be as low as 10 ml/min/1.73m^2 in preterm infants, with a slower post-natal increase than in term infants.[152 153] The previous cyanotic spell in the term infant also presenting with a higher lithium concentration might be connected to the intrauterine lithium exposure, but why this infant was affected was unclear. The mothers to the two infants with high lithium concentrations were treated with adequate doses if lithium sulphate (168 vs 210mg) and were not treated with any drugs known to be interacting with lithium. One of the women was treated with sertraline and the other with levothyroxine, apart from lithium. None of the infants included in the study had any clinical signs of intoxication at the time of the follow-up. These results support the recommendation of restricting breastfeeding to healthy full-term infants only.

Even though the study was relatively small and retrospective to its nature, it is still the largest cohort yet studying infants exposed to lithium through breastmilk. The study comes with limitations due to its retrospective nature, the largest ones being that that the lithium concentrations in infant serum were not documented to be trough concentrations, and that not all the lithium concentrations in maternal serum were measured at the same time as the infants'. The laboratory method for the analysis of lithium serum concentration was the same in the two hospitals, over the whole study period, so the measured concentrations should be technically relatable to each other. However, the long study period imposes a limitation for interpreting the clinical symptoms in the infants, with varying clinical practices for follow-up during the time period Also, interpreting the clinical symptoms is hard without a control group. Even with these limitations, we believe that the results are well generalizable to similar clinical real-life settings.

The long-term effects on infants exposed to lithium through breastmilk are to our knowledge so far unstudied. Long-term effects after fetal lithium exposure have been studied in a few smaller cohorts that have not been able to confirm any neurodevelopmental adversity in the exposed children.[269-272] The dose acquired by the infant through breastmilk is smaller than the fetal exposure, but a cumulative effect of both exposures cannot be excluded. Also, the first months in life is a sensitive period for the brain development, and therefore the postnatal lithium exposure might impose neurodevelopmental risks for the infants not seen after intrauterine exposure. Methodologically, the long-term outcomes are however complicated to study, as a potential causal connection will be confounded by both the severity and a potential continuity of the maternal mood disorder through the infant's childhood, as well as the underlying genetic risks.

When it comes to treatment with other psychotropic drugs during lactation, both antidepressants and antipsychotics are generally considered safe to use while breastfeeding healthy full-term infants, but with a few exceptions.[157 253] Bupropion, an antidepressant acting through inhibition of dopaminergic and noradrenergic reuptake, is shown to be associated with seizures in some infants exposed to it through breastfeeding, especially when in combination with SSRIs.[94] Use of the antipsychotic agent aripiprazole and the psychostimulant lisdexamfetamine are not advised against during breastfeeding per se, but are examples of drugs where the need of studies regarding their safety during breastfeeding is desperate.[157] Also, little is known regarding the effects of polypharmacy with several psychotropic drugs during lactation, which was the case in our study number IV.

6.5 DISCUSSION OF DIFFERENT METHODS TO STUDY DRUG TREATMENT DURING PREGNANCY

There are several methods to study the effects of fetal exposure to psychotropic drugs, of which three are applied within this thesis. All methods have their benefits, drawbacks and difficulties that are discussed in this chapter.

6.5.1 Randomized controlled trials

First, we addressed the question of antidepressant treatment during pregnancy and the effects on the infant with a double-blind RCT where the pregnant women with a moderate depression were randomized to treatment with sertraline or placebo as well as I-CBT offered to all participants. Randomized trials are considered the golden standard of clinical studies. Their results are considered trustworthy, as the study design ensures that the groups are comparable at baseline, with the studied intervention being the only difference between the groups. Therefore, this method is considered to fully eliminate the risk of confounding, which is hard to achieve in naturalistic study designs. However, RCTs are expensive and time-consuming, as we experienced. Us and the Dutch "Stop or Go" study both failed to recruit large enough cohort sizes of pregnant women with depression or antidepressant treatment, to study the long-term effect of the fetal SSRI exposure on the child's psychomotor development.[2] Our experience was, that women refused to participate due to unwillingness to start antidepressant treatment during pregnancy, when the experience from Netherlands was that women treated with SSRIs insisted to continue their drug treatment. Thereby we conclude that this leaves us limited, if any, options to recruit pregnant women to a study with randomization to treatment. Performing RCTs on more severe mental disorders where non-pharmacological treatment is not available would not be ethical.

6.5.2 Clinical observational trials

As mentioned in the introduction, a clinical observational trial was recently published studying the child neurodevelopment at 2.5 years of age after intrauterine exposure to SSRIs, comparing the results of Bayley Scales of Infant Development (BSID) of the exposed infants to the results in children to healthy mothers.[1] In that study, the SSRI-exposed infants had a poorer cognitive and gross-motor development than their non-exposed peers. However, the mean difference between groups was 0.8-0.9 points in the cognitive scale of BSID and 1.1-1.2 points in the gross motor development scale. The clinical significance of these differences is questionable, considering them being less than 0.5 SD (1.5 points), which we in the MAGDALENA study considered a clinically significant difference.[225 273] These differences in BSID were also not statistically significant after adjustment for severity of the maternal mood disorder. Several other observational attempts have also been made to study the neurodevelopment after fetal exposure to SSRIs, all struggling to find an adequate comparison group, i.e., maybe rather ending up comparing apples to pears rather than apples to apples, as drs Oberlander and Vigod so well phrased it.[246] Therefore perhaps, register-based trials with adequate level of information on potential confounders such as the severity and duration of the maternal mood disorder, or with sibling comparisons, are perhaps more reliable in answering this question.[44 45] Observational trials are however essential for studying the drug concentrations in mothers and infants and the duration of symptoms in the exposed infants. These studies need smaller sample sizes and are not as likely to be affected by confounding by indication.

6.5.3 Register-based trials

The Swedish nationwide health registers offer an efficient and robust method to study the effects of intrauterine drug exposure on the exposed infants, when combining the PDR with the MBR and the SNQ.[237 239 242] This is the method we used for studies II and III. Combining these registers and collecting information from not only the MBR but also the PDR and the SNQ improves the quality of both the exposure and the outcome variables. However, there are still methodological drawbacks associated to the register data in studies II and III. Neither MBR nor PDR can guarantee exposure, i.e. that the women actually used the drug. On the other hand, outcomes registered in the MBR and the SNQ are limited to pre-defined ICD-codes and checkboxes, that are scarce for some neonatal conditions, and may be biased by the fact that the exposed infants might have acquired these diagnoses more lightly due to the increased observance held on these infants because of the exposure.

The complexity of covariate selection in a register based study can be exemplified with the role of BMI when studying the association between antipsychotic treatment during pregnancy and the risk for GDM. There is a causal connection between obesity and both antipsychotic treatment and the underlying mental disorder, and obesity is a strong risk factor for GDM. Not adjusting for high BMI will therefore overestimate the risk of developing GDM connected to the drug exposure. However, some of the effect of antipsychotic treatment on GDM are probably also mediated through weight gain caused by the treatment, making BMI both a confounder and a mediator.

The large nationwide registers are constantly improving and their sizes increasing, enabling us to answer new clinical questions through register-based studies. For example, with the PDR being running for 17 years, there are new opportunities to study the long-term effects of intrauterine drug exposure through linking this with the National Patient Register and the School Mark Register. Register-based studies in general are limited by the year-long waiting times to extract data from the registers, as well as the limited predefined variable sets in these registers. A potential future drawback is also the increasing requirements of publishing the dataset at publication of an article, which will not be possible with sensitive population data.

6.5.4 Clinical experimental trials

Another clinical, more experimental, method to study the effects on the infants after intrauterine drug exposure that I got to try is advanced computational analyses of electroencephalographic (EEG) recordings in the infants. These models have shown that exposure to both antiepileptics and SSRIs affect infant brain function, measured with advanced interpretation of signalling patterns in the infant EEG.[274 275] The meaning of this for the long-term neurodevelopmental outcomes is however yet unknown. We aimed in our RCT to include a subgroup of infants with EEG-recordings and study whether the findings were relatable to the neurodevelopment at 2 years of age, but unfortunately the study was terminated after 4 recordings. This, however, is also a potential way forward in studying the effects of intrauterine drug exposure on the infant brain function and development.

6.5.5 Animal and future experimental studies

As the human placenta is difficult to access for research, animal models have been explored for placental research. Many animal placentas are however fundamentally different from the human ones. For example, studying the effects of xenobiotic exposure on malformations in mice is limited by their short pregnancies, leading to the organogenesis being unfinished at birth and continuing postnatally. Guinea pigs have been used to study pregnancy toxaemia, and fetal physiology has been studied in sheep. The placentation and the formation of spiral arteries are fairly similar in monkeys compared to humans, allowing studies on pre-eclampsia and fetal growth restriction in them.[276]

Placental trophoblast organoids are models enabling placental research that is not possible in humans. These organoid cultures of trophoblasts can differentiate into resembling a first trimester placenta. They can be used for studying the placental development, and possibly in the future, fetal toxicology studies to increase the understanding of the placental passage of drugs.[277]

7 CONCLUSIONS

Psychiatric disorders including depression and anxiety disorders with or without pharmacological treatment are common in women of childbearing age. Bipolar and psychotic disorders including postpartum psychosis are severe and can have fatal outcomes if not adequately treated, especially during pregnancy and postpartum. The effects of psychotropic drug treatment during pregnancy and lactation are understudied and not fully understood.

In study I we conclude that there is a large inter-individual variation in sertraline plasma concentrations during pregnancy, but the placental passage of sertraline seems low. TDM during pregnancy could be helpful. Based on our material together with studies covering the long-term effects, we conclude that sertraline is, from a pharmacological standpoint, safe to use during pregnancy. Further, performing randomized trials in this field is very difficult, and register-based studies might give us the needed answers regarding the long-term effects.

Studies II and III, two large population-based register studies, demonstrated that mothers treated with antipsychotics during pregnancy and their infants had a moderately increased risk for pregnancy- and neonatal complications. The high metabolic risk S-GAs olanzapine, clozapine and quetiapine were associated with increased risks for GDM and the infant being LGA, which should be taken in account when prescribing these drugs, as this can have both short- and long-term consequences for the infants. Exposure to any antipsychotics during pregnancy was associated with increased risks for caesarean section, moderate and late preterm delivery, the infant being admitted to NICU, and the infant experiencing withdrawal symptoms, neurological symptoms, and respiratory disorders. Nearly every fifth exposed infant needed to be admitted to NICU, and the median length of stay at NICU was 5 days in exposed infants, slightly longer than in their unexposed peers. The risk for PPHN, a potentially serious complication, was moderately increased for the exposed infants.

Study IV shows that treatment with lithium during lactation can be considered safe for full-term infants if the infants are monitored regarding serum lithium concentrations and clinical status. Breastfeeding in preterm infants during ongoing lithium therapy cannot be recommended.

8 POINTS OF PERSPECTIVE

More studies are needed to understand the pregnancy-related changes in plasma concentrations of psychotropic drugs and the need of dose adjustments during pregnancy. The connection between the altered drug concentrations in pregnancy and the pregnancy-related changes in the activities of the different drug metabolizing enzymes need to be studied further, focusing on the changes in activity of the different genotypes of CYP 2C19 and CYP 2D6. New pharmacokinetic models might complement the clinical studies in this field.[278] These pharmacokinetic studies need however to be complemented with studies clarifying the pharmacodynamic mechanisms leading to the clinical effects of the psychotropic drugs.

Gestational diabetes does seem increased amongst women treated with HR S-GAs during pregnancy. In hindsight, the results of study II could be clouded by the increased diagnostics of GDM in Sweden after the study period, leaving us questioning if the potential under-diagnostics of GDM was similar amongst women with and without antipsychotic treatment during pregnancy in the study period. A prospective study could be possible to examine this association further. With the increasing prescription rates of S-GAs, the effects of these drugs would also be interesting to study separately in the nationwide registers once the cohort size allows it, considering the differing pharmacodynamics of the different S-GAs.

The study on neonatal outcomes after fetal exposure to antipsychotics confirmed the increased neonatal neurological morbidity in exposed infants, but also raised a question regarding how to further study these neurological outcomes in the neonatal period after antipsychotic exposure. Combining data from registers from several countries would increase the cohort size and perhaps enable studying the risks for the neurological diagnoses separately.

Several unanswered questions still remain regarding treatment with lithium during lactation. In study IV, a third of the infants had poor weight gain, but a prospective trial with a control group of infants exposed to lithium in fetal life but not through breastmilk would be needed to fully clarify the cause of these symptoms. Also, the safety of breastfeeding of late preterm infants during lithium therapy, as well as the long-term effects of lithium exposure through breastmilk are so far not studied.

Study IV was a retrospective first part of the MOM-study, (acronym for: Mothers On Medication). Several other psychotropic drugs such as lisdexamfetamine and aripiprazole also lack sufficient safety data for their use during lactation. A second part of the MOM-study will be a prospective study on the use of lithium and these other drugs during lactation, studying the effects on the exposed infants. A third part of the MOM-study will focus on the effects of drug exposure through breastmilk in preterm infants, as this is even less studied than the effects in term infants. The study will start with the effects of antihypertensive drugs, as they are common in mothers to preterm infants.

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