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Doctoral Thesis
Andreas Austgulen Westin

Doctoral theses at NTNU, 2018:303

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The impact of pregnancy on maternal serum concentrations of antiepileptic, antipsychotic and antidepressant drugs

Evidence from therapeutic drug monitoring

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Thesis for the degree of Philosophiae Doctor

Trondheim, October 2018

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Norsk sammendrag

Når man snakker om legemiddelbruk hos gravide – enten det er i dagligtalen eller i vitenskapelig sammenheng – handler det som regel om i hvilken grad legemiddelbruken er trygg for det ufødte barnet. I dette arbeidet skal vi imidlertid ikke rette søkelyset mot barnet, men mot mor.

I løpet av graviditeten skjer det mange forandringer i mors kropp som kan påvirke hvordan denne håndterer legemidler. For eksempel kan opptak av legemidlet fra tarmen forsinkes, kroppsvekten og volumet som legemidlet skal fordele seg i kan øke, «avgiftningen» av legemidlet i leveren kan endres, og legemiddelutskillelsen via nyrene kan øke. Disse endringene kan blant annet resultere i at dosen som en kvinne har brukt før hun ble gravid, blir for lav under svangerskapet. Lave legemiddelnivå kan igjen lede til behandlingssvikt, med potensielt alvorlige konsekvenser for både mor og barn, for eksempel dersom epilepsibehandlingen hos en gravid kvinne svikter og hun får epileptisk anfall.

Hva som skjer med kroppens håndtering av hvert enkelt legemiddel under graviditeten er ikke enkelt å forutsi; det kan avhenge både av egenskaper med legemidlet (for eksempel om det fjernes via leveren eller nyrene), og forhold hos den gravide (for eksempel genetiske faktorer). Derfor er det viktig at det gjøres studier som kan hjelpe oss å kartlegge disse endringene for hvert enkelt legemiddel, slik at vi blir i stand til å tilpasse dosene ut fra den gravides behov.

Men legemiddelstudier hos gravide er ingen enkel affære. Lenge har det vært slik at gravide – av åpenbare etiske hensyn - utelukkes fra legemiddelutprøvningsstudier. Dette kan ved første øyekast synes klokt, men medaljens bakside er at vi på denne måten aldri får den kunnskapen vi trenger for å vurdere dosebehov i nettopp denne pasientgruppen. Derfor, når en gravid kvinne trenger behandling med legemidlet, vet ikke legen sikkert hvilken dose hun bør bruke under svangerskapet.

Kunnskap på dette feltet er sårt tiltrengt. Derfor er det viktig at vi snur oss og ser tilbake på de gravide som faktisk har brukt legemidler under svangerskapet, og vurderer hvordan det gikk med doseringen. I denne avhandlingen presenteres fire slike «retrospektive observasjonsstudier», der vi har gått gjennom ulike pasientmaterialer fra tre store norske klinisk farmakologiske laboratorier. Vi tok for oss to epilepsimedisiner, åtte psykosemidler og ni depresjonsmidler, og så på sammenhengen mellom dosejusterte konsentrasjoner av legemidlet i den gravides blod før, under og etter graviditeten. For noen legemidler (som epilepsimedisinen levetiracetam og psykosemidlene kvetiapin og aripiprazol) fant vi dramatiske fall i konsentrasjonene hos de gravide, noe som betyr at de gravide trolig trenger betydelig høyere dose enn ikke-gravide. For andre legemidler (som psykosemidlet olanzapin og depresjonsmidlet escitalopram) så vi ingen endring, noe som betyr at den gravide trolig kan bruke samme dose som vanlig under svangerskapet.

Arbeidet som er presentert i denne avhandlingen gir oss et verktøy for riktigere dosering av legemidler hos gravide kvinner. Dette vil gjøre legemiddelbehandlingen tryggere for både mor og det ufødte barnet.

Kandidat: Andreas Austgulen Westin
Institutt: Institutt for klinisk og molekylær medisin, NTNU
Veileder: Olav Spigset
Finansieringskilde: St. Olavs Hospital

*Use the lowest **effective** medication dose.*

It is more important for the dose to be effective than to be low.

Leah C. Susser, assistant professor of Clinical Psychiatry at Weill Cornell Medical College, New York, US (1)

Table of contents

Acknowledgements

The work presented in this thesis was carried out in the period from 2007-2017 at the Department of Clinical Pharmacology at St. Olav University Hospital in Trondheim, in collaboration with the Department of Neurology and Clinical Neurophysiology at St. Olav University Hospital, the National Centre for Epilepsy at Oslo University Hospital, the Center for Psychopharmacology at Diakonhjemmet Hospital in Oslo, and the Medical Birth Registry of Norway.

I am grateful to my department for generously providing me with the opportunity and time to conduct this research. Our head of department Trond Aamo always supports our great (and even not so great) ideas with funding and encouragement, and has made our department become a highly merited academic playground, fueled by enthusiasm and not by dictate, which in turn is why I love my job. I also send a warm thank you to all my colleagues (I cannot mention you all) for inspiration, collaboration, and everyday humour. Trond makes our research possible, and you guys make it fun!

I am deeply grateful to my supervisor, Olav Spigset. Not only does he contain a well of knowledge (and publications) in virtually every field of medicine, but briefly put, and needless to say to those who know him, he is the perfect supervisor. 10/10 would use again.

I would like to thank my co-authors Arne Reimers, Eylert Brodtkorb, Grethe Helde, Eirik Skogvoll, Ingrid Castberg, Karl Otto Nakken, Kari-Mette Lillestølen, Svein Johannessen, Malin Brekke and Espen Molden for fruitful discussions and great collaboration. A special thank goes to Arne and Eylert for planting the seed to this project by introducing me to this very interesting field of research, and for guiding me through my first scientific publications. I also thank those who have helped me extracting and preparing the data files, in particular Ludvig Johannessen and Magnhild Hendset.

I am thankful to all my family and friends for all their assistance, and for nodding and smiling while pretending to listen while I have been a bore. A special thank goes to my pharmacological muse in Bergen, Tormod Bjånes, for making me laugh out loud while reading everyday emails, and for always bringing me off the main PhD track with completely unrelated projects. Without you this thesis would have been completed years earlier.

Finally, I am deeply grateful to my fiancé Elin, who deserves a Nobel prize for putting up with me through all of these years of neverending PhD work. The work has occurred on weekends, nights, while on vacation, and other inconvenient times, making the whole family becoming passively exposed to negative health effects of my PhD thesis. I am indebted to our wonderful kids, Othilie and Konrad, who needed to show patience while “daddy was completing his big homework”. Othilie had a hard time understanding why I would voluntarily choose to “send my homework to the meanest teachers” , instead of the ones who would accept it easily. I have to admit there were times I asked myself the same question.

Abbreviations, expressions and acronyms

ATC	Anatomical Therapeutic Chemical Classification System
CDR (or C/D ratio)	Concentration to dose ratio
CRF	Case Record Form (for the EURAP registry)
CV	Coefficient of variation
CYP	Cytochrome P450 enzyme family
DDD	Defined daily dose
EURAP	The European Registry of Antiepileptic Drugs and Pregnancy
LC-MS	Liquid chromatography mass-spectrometry
LC-MS/MS	Liquid chromatography tandem mass-spectrometry
LOQ	Limit of quantification
MAO	Monoamine oxidase
MBRN	Medical Birth Registry of Norway
NAT	N-acetyl transferase
SNRI	Serotonin and norepinephrine reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TDM	Therapeutic drug monitoring
UGT	Uridine diphosphate-glucuronosyltransferase
V_d	Volume of distribution
WHO	World Health Organization

Explanation to the antiepileptic drug name abbreviations is given in Table 2 (page 11).

Explanation to the antipsychotic drug name abbreviations is given in Table 3 (page 14).

Explanation to the antidepressant drug name abbreviations is given in Table 4 (page 17).

List of papers

This thesis is based on the following papers:

Paper I

Andreas Austgulen Westin, Arne Reimers, Grethe Helde, Karl Otto Nakken, Eylert Brodtkorb:

Serum concentration/dose ratio of levetiracetam before, during and after pregnancy.

Seizure 2008;17(2):192-8

Paper II

Andreas Austgulen Westin, Karl Otto Nakken, Svein Johannessen, Kari Mette Lillestølen, Eylert Brodtkorb:

Serum concentration/dose ratio of topiramate during pregnancy.

Epilepsia 2009;50(3):480-5

Paper III

Andreas Austgulen Westin, Malin Brekke, Espen Molden, Eirik Skogvoll, Ingrid Castberg, Olav Spigset:

Treatment with antipsychotics in pregnancy: changes in drug disposition.

Clinical Pharmacology and Therapeutics 2018;103(3):477-84

Paper IV

Andreas Austgulen Westin, Malin Brekke, Espen Molden, Eirik Skogvoll, Olav Spigset:

Treatment with antidepressants in pregnancy: changes in drug disposition.

PLOS One 2017;12(7):e0181082

1. Introduction

1.1 What is this thesis really about?

When discussing drug use in pregnancy – whether it is an everyday conversation, in a scientific discourse or in the media – the primary focus usually concerns the possible dangers the drug may inflict on the unborn child. This is obviously a very important topic, but it is not the topic of this thesis. Our research question is not whether or not a drug causes harm to the baby, but rather how the drug dose should be tailored to meet the mother's need, taking into account the changes related to the handling of drugs that occur in her body throughout pregnancy.

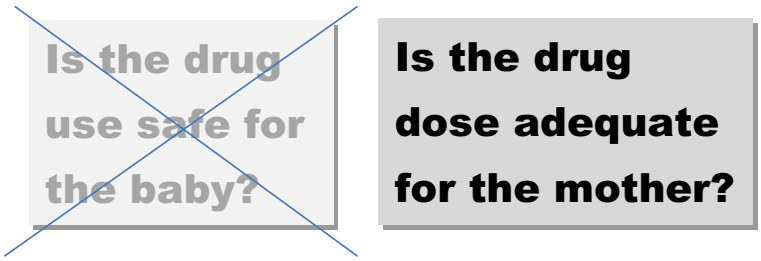


Figure 1. The primary research question of this thesis

1.2 Pharmacokinetics in pregnancy

Pregnancy is associated with a myriad of physiological changes that can alter the pharmacokinetics of several drugs. These changes have been explored in both laboratory studies, animal studies and experimental and observational human studies, and have also been subject for several general review articles (for some recent examples, see (2-6)). An overview of relevant pregnancy-related changes in organ function leading to altered pharmacokinetics is shown in Table 1. Typically, these physiological changes increase progressively throughout pregnancy and peak during the third trimester (5). Of particular relevance for drug exposure are the effects of pregnancy on renal and hepatic drug elimination. Increased renal blood flow and glomerular filtration causes increased clearance and lower serum concentrations of drugs that are mainly eliminated renally, such as lithium (7) and atenolol (8). Similarly, changes in drug metabolic enzymes may cause plasma levels of a drug to increase or decrease in pregnancy, depending on which enzyme is involved in its metabolism (Table 1).

It is essential that clinicians caring for pregnant women are aware of these changes, because their clinical implications may be profound, and sometimes also counterintuitive, such as having to increase the drug dose in pregnancy instead of reducing it.

Table 1. Physiological changes during pregnancy and their impact on drug pharmacokinetics

Physiologic changes	Potential impact on pharmacokinetics
Nausea and vomiting	↓ Absorption (↓ peak concentration and ↓ oral availability)
Delayed gastrointestinal motility	Delayed absorption (↑ time to peak concentration)
Increased total body water	Altered drug disposition; ↑ Vd for hydrophilic drugs
Decreased plasma albumin and α1-acid glycoprotein	↑ Unbound drug concentration for high clearance drugs
Increased renal blood flow and glomerular filtration	↑ Renal clearance for unchanged drug
Changes in activity of drug-metabolizing enzymes:	
- ↑ CYP2B6 activity	↑ Clearance of CYP2B6 substrates (e.g. methadone)
- ↑ CYP2C8 activity	↑ Clearance of CYP2C8 substrates (e.g. pioglitazone)
- ↑ CYP2C9 activity	↑ Clearance of CYP2C9 substrates (e.g. phenytoin)
- ↑ CYP2D6 activity	↑ Clearance of CYP2D6 substrates (e.g. metoprolol)
- ↑ CYP2E1 activity	↑ Clearance of CYP2E1 substrates (e.g. paracetamol)
- ↑ CYP3A4 activity	↑ Clearance of CYP3A4 substrates (e.g. midazolam)
- ↑ UGT1A4 activity	↑ Clearance of UGT1A4 substrates (e.g. lamotrigine)
- ↓ CYP2C19 activity	↓ Clearance of CYP2C19 substrates (e.g. diazepam)
- ↓ CYP1A2 activity	↓ Clearance of CYP1A2 substrates (e.g. caffeine)
- ↓ NAT2 activity	↓ Clearance of NAT2 substrates (e.g. isoniazid)

The table shows some important physiological changes that occur during pregnancy and how they may impact on drug pharmacokinetics. Vd = Volume of distribution; CYP = cytochrome P-450; UGT = uridine diphosphate-glucuronosyltranferase; NAT = N-acetyl transferase. Adopted from references (3-6).

1.3 Methodological limitations in performing drug studies in pregnant women

The vast majority of pregnant women are exposed to medications, and women take an average of 2.6 drugs during pregnancy (9). However, it has been estimated that more than 98% of medications have no or insufficient safety and/or pharmacokinetic data to guide dosing during pregnancy (10). It has even been shown that it may take an average of 27 years from a drug is marketed until there are sufficient data published to make an even crude estimate of its human

teratogenic risk (11). There are several reasons for the dearth of evidence in a field where more knowledge is so badly needed. First, pharmaceutical companies, researchers and institutional review boards are generally reluctant to undertake drug trials in pregnancy out of the obvious concerns of fetal harm. Second, there is no legislation that incites or mandates drug studies in pregnant or lactating women. Since the short duration of pregnancy limits the potential economic return for such studies, it is easier (and less risky) for the drug manufacturers to simply recommend that the drug should not be used in pregnancy (11). Third, ethical arguments are used to exclude pregnant women in drug trials (10). Several researchers have argued that the issue should be viewed the other way around, and that it should be considered unethical *not to* include pregnant women in clinical trials unless the drug is developed for a condition that occurs in males only. Suggestions have also been made as to how such studies should be conducted (10-14). However, we still have a long road ahead of us before these knowledge gaps are bridged.

Regarding the specific field of *pharmacokinetics* in pregnancy, dosing recommendations for pregnant women are usually extrapolated from studies in non-pregnant patients. However, dose extrapolations often fail to take into account the impact of the physiologic changes that occur during pregnancy. These changes need to be studied separately for each drug, in clinical studies with human pregnant subjects. Instead, most of our knowledge derive from “opportunistic studies", i.e. prospective or retrospective case reports or case series based on pregnant women who are already receiving a therapeutic agent. The main limitations to these studies are that they are typically too small, too few, too unstructured, and too late. Nevertheless, in the absence of large and rigorous clinical studies, the small and observational ones represent a crucial source of knowledge.

1.4 Use of antiepileptics, antipsychotics and antidepressants in Norway

1.4.1 Antiepileptics

In the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical (ATC) classification system for drugs (15), antiepileptic drugs are sorted in category N03A. From this group, a total of 25 drugs have been approved in Norway and 21 are currently marketed (16). An overview of these drugs and their year of introduction in Norway is given in Table 2 on page 11.

Figure 2 on page 12 shows the number of users of antiepileptic drugs in Norway in the period from 2004-2016 (17). Although all drugs shown are sorted in ATC category N03A “antiepileptics”, it is important to bear in mind that gabapentin and pregabalin (#1 and #3 in the figure) are mostly used in

treatment of neuropathic pain, and not epilepsy. Similarly, a high number of lamotrigine and valproate users (#2 and #4 in the figure) are treated for bipolar disorder, and not epilepsy (18), and a high number of clonazepam users (#6 in the figure) are treated for psychiatric disorders and not epilepsy.

Figure 3 on page 12 shows the number women of reproductive age (15-49 years) in Norway using antiepileptic drugs. Lamotrigine and gabapentin are by far the drugs most used in this drug class. Of specific interest for the present thesis is the increasing use of the new antiepileptic drugs levetiracetam and topiramate in women of childbearing potential, both with approximately 2,000 female users of reproductive age in 2016.

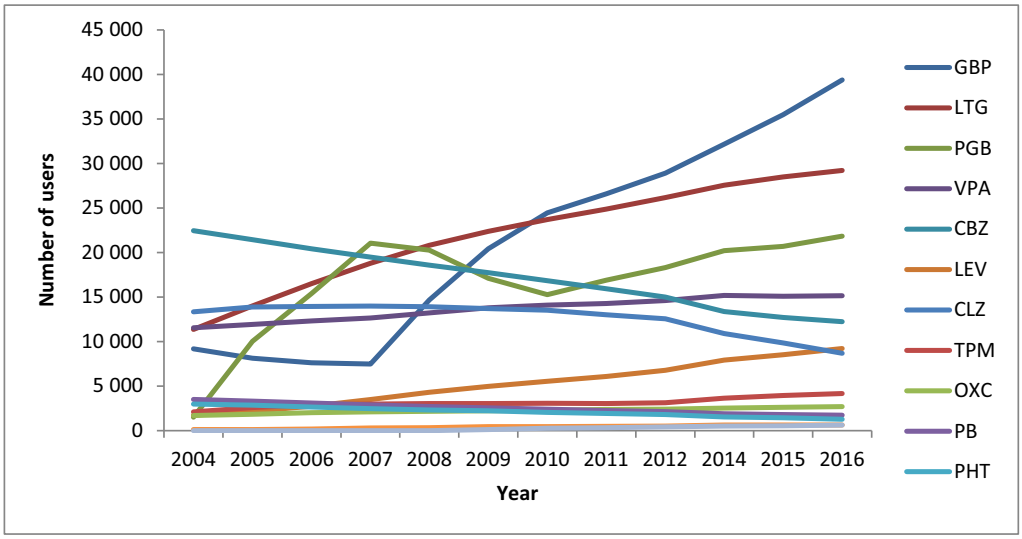
Table 2. Antiepileptic drugs in Norway

Generation of antiepileptic drug	Antiepileptic drug	Abbreviation	Year of introduction in Norway
First generation	Phenytoin	PHT	1944
	Primidone	PRM	1953[1]
	Ethosuximide	ETX	1961[1]
	Ethotoin	ETN	1961[1]
	Carbamazepine	CBZ	1965
	Clonazepam	CLZ	1974
	Phenobarbital	PB	1978
	Valproate	VPA	1980
Second generation	Vigabatrin	VGB	1993
	Lamotrigine	LTG	1994
	Felbamate	FBM	1996
	Gabapentin	GBP	1996
	Topiramate	TPM	1997
	Fosphenytoin	Fos-PHT	1999
	Levetiracetam	LEV	2000
	Oxcarbazepine	OXC	2000
	Pregabalin	PGB	2004
	Zonisamide	ZNS	2005
	Rufinamide	RUF	2007
	Stiripentol	STP	2007
	Lacosamide	LCM	2008
Third generation	Eslicarbazepine	ESL	2009
	Retigabine	RTG	2011[1]
	Perampanel	PER	2012
	Brivaracetam	BRV	2016

The table shows all drugs in the ATC drug class N03A, based on information from The Norwegian Medicines Agency in 2017 (16). Antiepileptic drugs that have not been marketed in Norway are not shown.

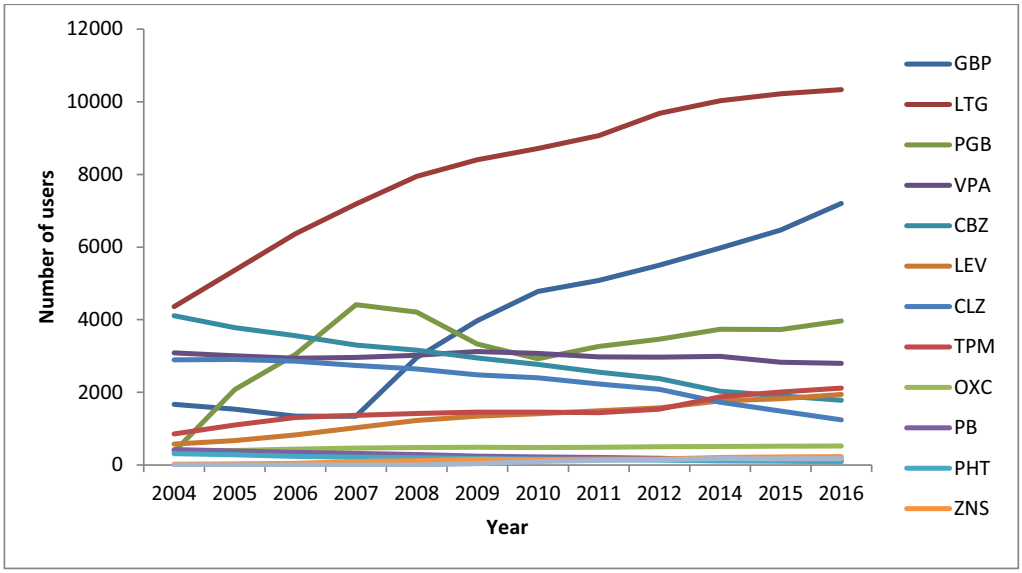
[1] Primidone, ethosuximide, ethotoin and retigabine are no longer marketed in Norway by 2017.

Figure 2. Users of antiepileptic drugs in Norway



The number of antiepileptic drug users (defined as individuals having received the drug on prescription at least once during that year) in Norway in the period from 2004-2016 (17). Explanation to the drug abbreviations are given in Table 2 on page 11. Drugs with no more than 500 users for any year (this includes all drugs that do not have marketing authorization in Norway) are not shown.

Figure 3. Users of antiepileptic drugs in Norway: females 15-49 years



The figure shows the same drugs as Figure 2, but only includes females of reproductive age (15-49 years). Explanation to the drug abbreviations are given in Table 2 on page 11.

1.4.2 Antipsychotics

In the ATC classification system for drugs (15), antipsychotic drugs are sorted in category N05A. From this group, a total of 36 drugs have been approved in Norway and 20 are currently marketed (16). An overview over these drugs and their year of introduction in Norway is given in Table 3 on page 14.

Figure 4 on page 15 shows the number of users of antipsychotic drugs in Norway in the period from 2004-2016 (17). Although all drugs shown are sorted in ATC category N05A "antipsychotics", it is important to bear in mind that many drugs are not used as such. For instance, quetiapine (#1 in the figure) is increasingly used in Norway for off-label non-psychotic indications (19), and prochlorperazine (#6 in the figure) is mostly used in treatment of nausea, and not psychosis. Several of the antipsychotic agents (e.g. quetiapine, olanzapine and aripiprazole) are also used for bipolar disorder.

Figure 5 on page 15 shows the number women of reproductive age (15-49 years) in Norway using antipsychotic drugs. Quetiapine is by far the drug most often used, and its use seems to be still rapidly increasing by 2016, with almost 16,000 users among women of childbearing potential. Also of interest for the present thesis is the rather high number of olanzapine users in this group (more than 3,000 in 2016), and the increasing use of aripiprazole (≈ 2,000 users in 2016).

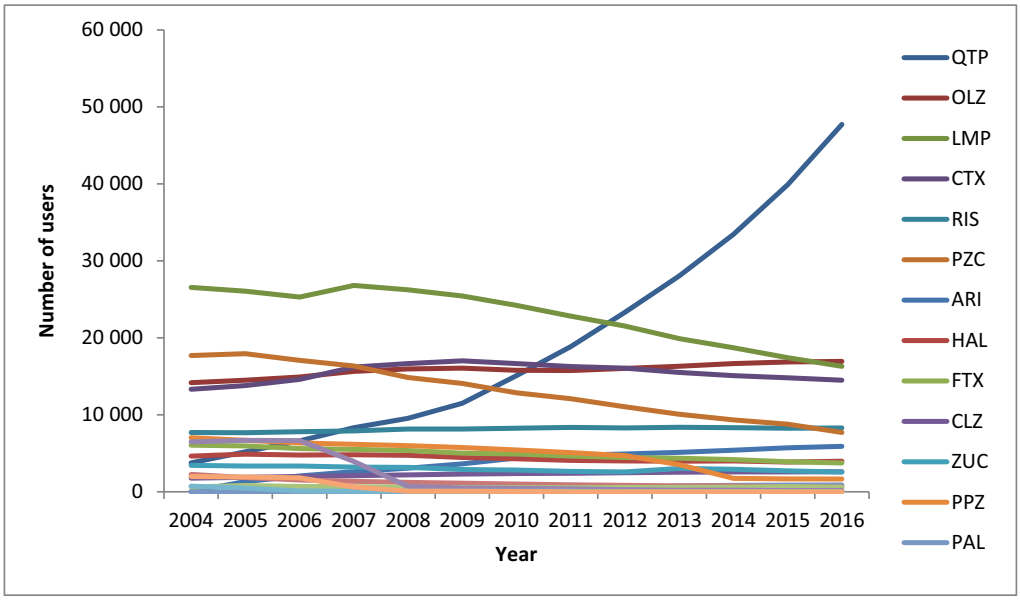
Table 3. Antipsychotic drugs in Norway

Generation of antipsychotic	Antipsychotic	Abbreviation	Year of introduction in Norway
First generation	Chlorpromazine	CPZ	1954[1]
	Promazine	PZ	1957[1]
	Prochlorperazine	PZC	1957
	Perphenazine	PPZ	1958
	Chlorprothixene	CTX	1959
	Levomepromazine	LMP	1960
	Thioridazine	TRZ	1960[1]
	Haloperidol	HAL	1961
	Thiopropazate	TPZ	1961[1]
	Trifluoperazine	TFP	1961[1]
	Sorbitol	SOR	1962[1]
	Fluphenazine	FPZ	1964[1]
	Dixyrazine	DIX	1965[1]
	Flupentixol	FTX	1966
	Pericyazine	PCZ	1966[1]
	Clopoxide	CPX	1968[1]
	Melperone	MEL	1971[1]
	Pimozide	PIM	1973[1]
	Moperone	MOP	1973[1]
	Pipothiazine	PIP	1975[1]
	Fluspirilene	FSP	1976[1]
	Zuclopenthixol	ZUC	1977
Second generation	Clozapine	CLZ	1990
	Risperidone	RIS	1994
	Olanzapine	OLZ	1997
	Sertindole	SDL	1997
	Tiapride	TIA	1998[1]
	Amisulpride	AMS	1999
	Quetiapine	QTP	2000
	Ziprasidone	ZIP	2002
	Aripiprazole	ARI	2004
	Droperidol	DRO	2008
	Asenapine	ASE	2010
	Paliperidone	PAL	2011
	Loxapine	LOX	2013
	Lurasidone	LUR	2014

The table shows all drugs in the ATC drug class N05A, and is based on information from The Norwegian Medicines Agency in 2017 (16). Antipsychotic drugs that have not been marketed in Norway are not shown.

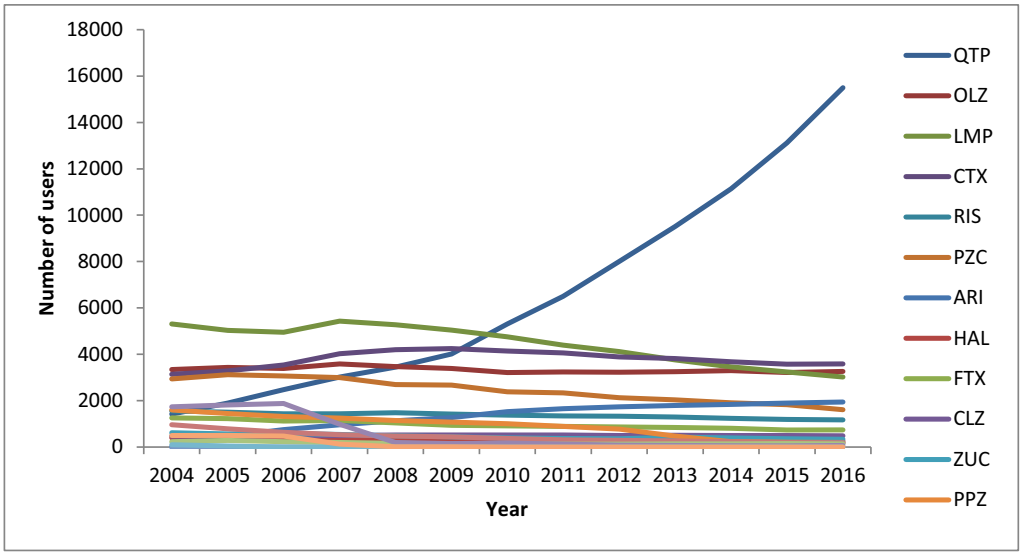
[1] *Drugs no longer marketed in Norway by 2017.*

Figure 4. Users of antipsychotic drugs in Norway



Number of antipsychotic drug users (defined as individuals having received the drug on prescription at least once during that year) in Norway in the period from 2004-2016(17). Explanation to the drug abbreviations are given in Table 3 on page 14. Drugs with no more than 500 users for any year (this includes all drugs that do not have marketing authorization in Norway) are not shown.

Figure 5. Users of antipsychotic drugs in Norway: females 15-49 years



The figure shows the same drugs as Figure 4, but only includes females of reproductive age (15-49 years). Explanation to the drug abbreviations are given in Table 3 (page 14).

1.4.3 Antidepressants

In the ATC classification system for drugs (15), antidepressant drugs are sorted in category N06A. From this group, a total of 24 drugs have been approved in Norway and 20 are currently marketed (16). An overview over these drugs and their year of introduction in Norway is given in Table 4 on page 17.

Figure 6 on page 18 shows the number of users of antidepressant drugs in Norway in the period from 2004-2016 (17). Although all drugs shown are sorted in ATC category N06A "antidepressants", it is important to bear in mind that many drugs have indication overlap with other psychiatric conditions such as generalized anxiety disorder, panic disorder and obsessive compulsive disorder. Some drugs, such as amitriptyline and duloxetine are also used in treatment of neuropathic pain.

Figure 7 on page 18 shows the number women of reproductive age (15-49 years) in Norway using antidepressant drugs. Escitalopram is by far the drug most often used, with more than 30,000 users among women of childbearing potential. The figure also shows a decrease in the use of citalopram (due to the chiral switch from citalopram to escitalopram), and an increasing use of amitriptyline (presumably due to its indication for neuropathic pain). For the remaining antidepressants, the prevalence of use remains largely unchanged in this patient group in this time period. Of particular interest for the present thesis is that all selective serotonin reuptake inhibitors except fluvoxamine had more than 10,000 users among women of childbearing potential in 2016.

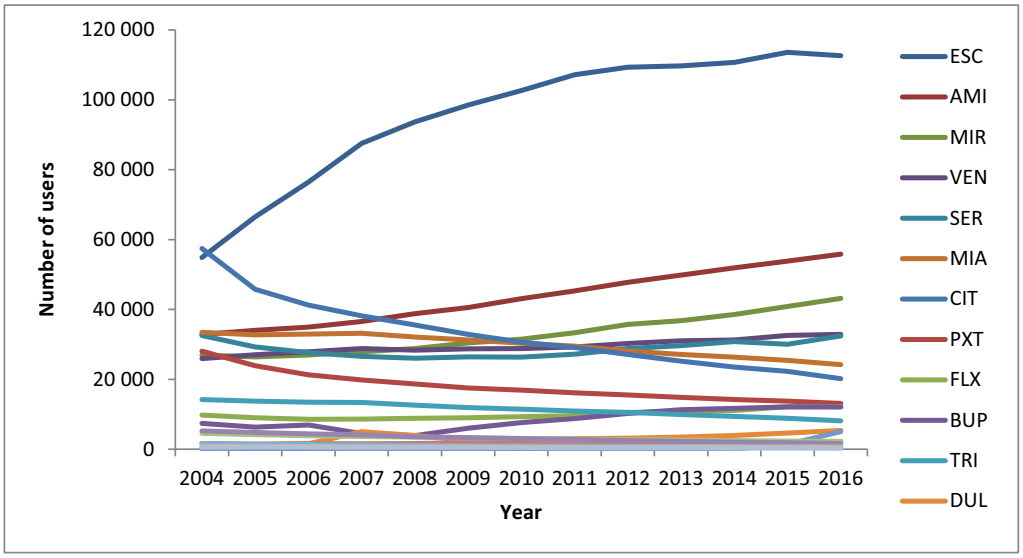
Table 4. Antidepressant drugs in Norway

Type of antidepressant	Antidepressant	Abbreviation	Year of introduction in Norway
TCAs	Imipramine	IMP	1959[1]
	Amitriptyline	AMI	1961
	Opipramol	OPI	1962[1]
	Desipramine	DES	1964[1]
	Nortriptyline	NTP	1965
	Trimipramine	TRI	1966
	Doxepin	DOX	1969
	Clomipramine	CLI	1970
MAO inhibitors	Moclobemide	MOC	1990
SSRIs	Fluvoxamine	FVX	1990
	Paroxetine	PXT	1993
	Citalopram	CIT	1995
	Fluoxetine	FLX	1995
	Sertraline	SER	1996
	Nefazodone	NEF	1996[1]
	Escitalopram	ESC	2002
SNRIs	Venlafaxine	VEN	1996
	Duloxetine	DUL	2004
Other	Mianserin	MIA	1982
	Reboxetine	REB	1999
	Mirtazapine	MIR	2000
	Bupropion	BUP	2000
	Agomelatine	AGO	2009
	Vortioxetine	VOR	2013

The table shows all drugs in the ATC drug class N06A, and is based on information from The Norwegian Medicines Agency in 2017 (16). Antidepressant drugs that have not been marketed in Norway are not shown. TCAs = Tricyclic antidepressants; MAO = Monoamine oxidase; SSRIs = Selective serotonin reuptake inhibitors. SNRIs = Serotonin and norepinephrine reuptake inhibitors.

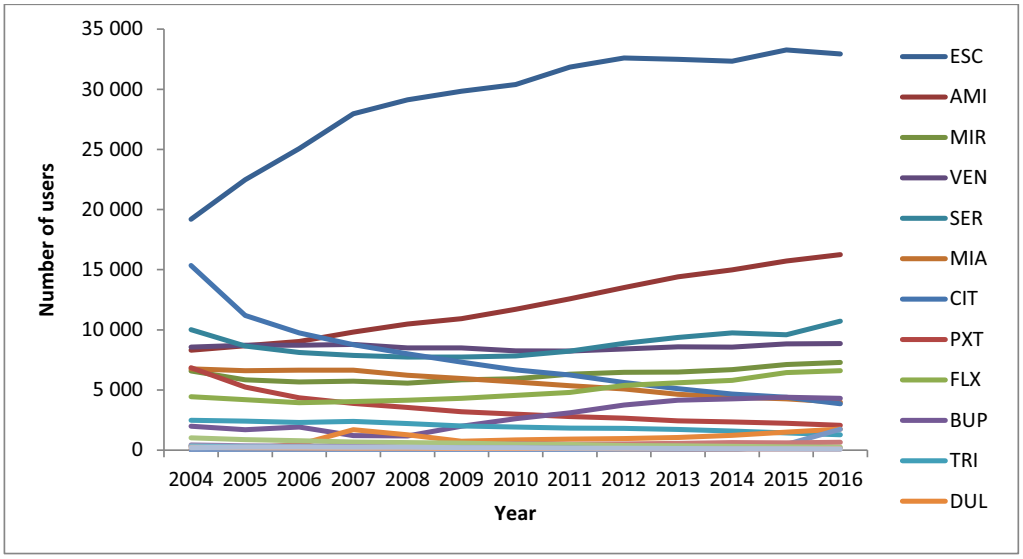
[1] *Drugs no longer marketed in Norway by 2017.*

Figure 6. Users of antidepressant drugs in Norway



Number of antidepressant drug users (defined as individuals having received the drug on prescription at least once during that year) in Norway in the period from 2004-2016 (17). Explanation to the drug abbreviations are given in Table 4 on page 17. Drugs with no more than 500 users for any year (this includes all drugs that do not have marketing authorization in Norway) are not shown.

Figure 7. Users of antidepressant drugs in Norway: females 15-49 years



The figure shows the same drugs as Figure 6, but only includes females of reproductive age (15-49 years). Explanation to the drug abbreviations are given in Table 4 on page 17.

1.5 Therapeutic drug monitoring (TDM)

Therapeutic drug monitoring (TDM) is the quantification and interpretation of drug concentrations in serum, plasma or whole blood (from now on commonly referred to as "serum", for simplicity) in order to optimize pharmacotherapy (20). TDM is based on the assumption that there is a definable relationship between the serum concentration of a drug and its clinical efficacy. TDM is thus a supporting tool for achieving wanted (therapeutic) drug effects while reducing risk of unwanted (adverse) effects.

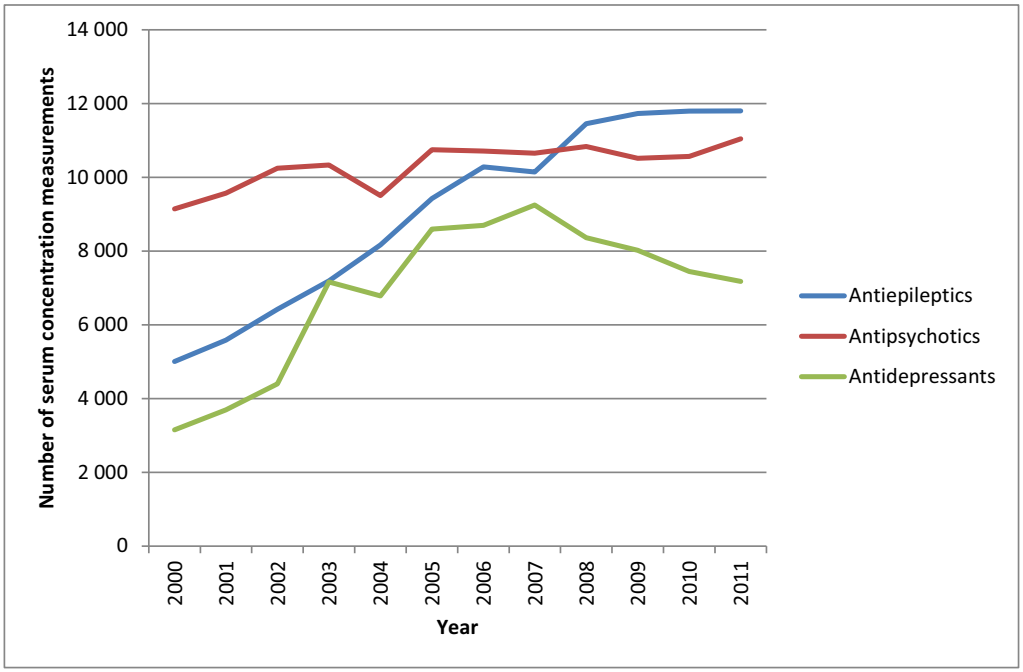
The TDM concept has been embraced as a useful tool in the treatment of epilepsy, and this field of medicine has seen a quite rapid shift with regards to dosing strategies, from the "one dose fits all" thinking before the 1960's (as illustrated by the fixed combination tablets of 300 mg phenytoin + 100 mg phenobarbital) to the implementation of TDM and individualized treatment, which is considered standard of care today (21). Indeed, the International League Against Epilepsy (ILAE) issued its first guidelines for TDM already in 1993, and the guidelines were extensively revised and updated in 2008 (22).

In contrast, psychiatrists seem to be generally more reluctant to employ TDM as a routine tool. This is somewhat puzzling, considering the fact that psychiatric disorders share some important features with epilepsy, such as lack of reliable and easily available surrogate markers of clinical efficacy, and the potentially drastic consequences of therapeutic failure. It is also puzzling considering the fact that psychiatrists were actually among the pioneers of TDM in the 1950's and 1960's, when TDM was introduced as a tool for avoiding lithium (23) and tricyclic antidepressant (24) toxicity. Although TDM is still routinely used for monitoring of lithium and tricyclic antidepressant therapy, TDM is less commonly used for monitoring other psychotropic drugs (20, 25, 26). Possible reasons for the low utilization of TDM in psychiatry may include logistics (e.g. access to laboratory services), lack of interest (and incentives) for pharmaceutical companies to encourage TDM, and prescriber's concerns with the strength of its scientific evidence (25, 27).

Some statistics exist regarding the use of TDM in psychiatry. In the United States, TDM for newer psychiatric drugs is rarely used, except for clozapine (25). In China, some laboratories offer TDM for new psychiatric drugs, but only 10% of the laboratories provide interpretations of the test results, and no consensus guidelines for TDM exist (28). In Europe, there is a stronger tradition for the use of TDM in psychiatry, as illustrated by the wide analytical repertoire in Germany-Austria-Switzerland (29), and also in Norway (30). Although we do not know the exact prevalence of TDM for antidepressants and antipsychotics in Norway, we do have some interesting statistics from our neighboring country, Sweden (31). By the use of aggregated data from a TDM laboratory for

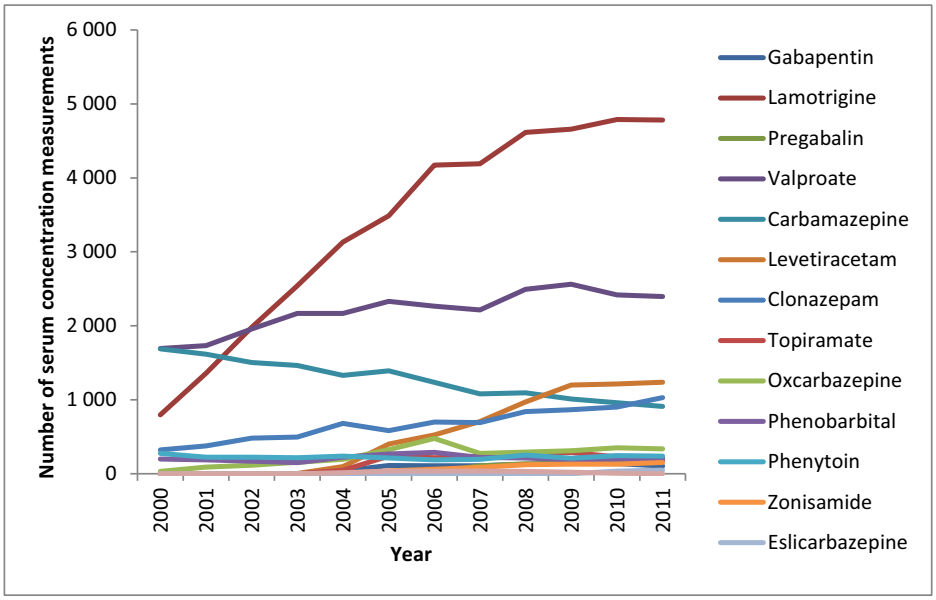
psychotropic drugs in Stockholm region linked to their national prescription database, the authors found that a total of 24,471 TDM measurements for antipsychotics and antidepressants were undertaken during an 8-year period (2006-2013), and they estimated that the prevalence of TDM use was approximately 1 per 200 patients per year for antidepressants and 1 per 20 patients per year for antipsychotics (31). Although we do not possess similar statistics from Norway, we can use the TDM statistics presented in Figure 8 below for comparison: St. Olav University Hospital conducted approximately 18,000 TDM measurements for antipsychotics and antidepressants each year in the mentioned periods, which adds up to about 144,000 measurements in 8 years. This is almost six times the figures from the Stockholm region, even though the region primarily served by St. Olav University Hospital (Mid-Norway; approximately 800,000 inhabitants) is less than half the size of the Stockholm region. Thus, it appears that the Norwegian tradition for TDM in psychiatry is very strong, even for a European country. This makes it an ideal location for studies generating knowledge of TDM in a naturalistic setting, such as the studies on pharmacokinetics in pregnancy presented in this thesis.

Figure 8. TDM for antiepileptic, antipsychotic and antidepressant drugs at St. Olav University Hospital, 2000-2011



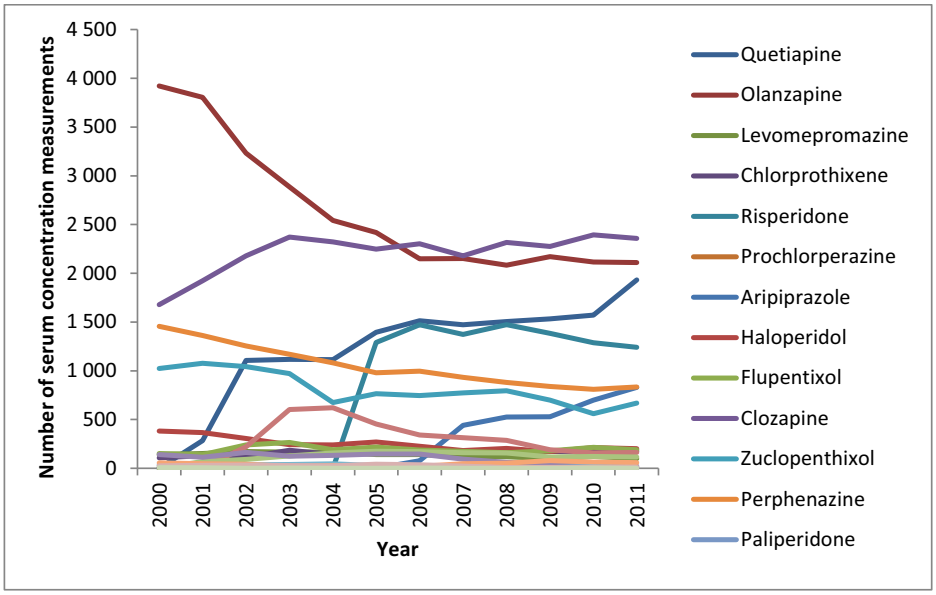
The figure shows the annual total number of serum concentrations measurements undertaken at St. Olav University Hospital for antiepileptic, antipsychotic and antidepressant drugs over the 12 year period 2000-2011.

Figure 9. TDM for antiepileptic drugs at St. Olav University Hospital, 2000-2011



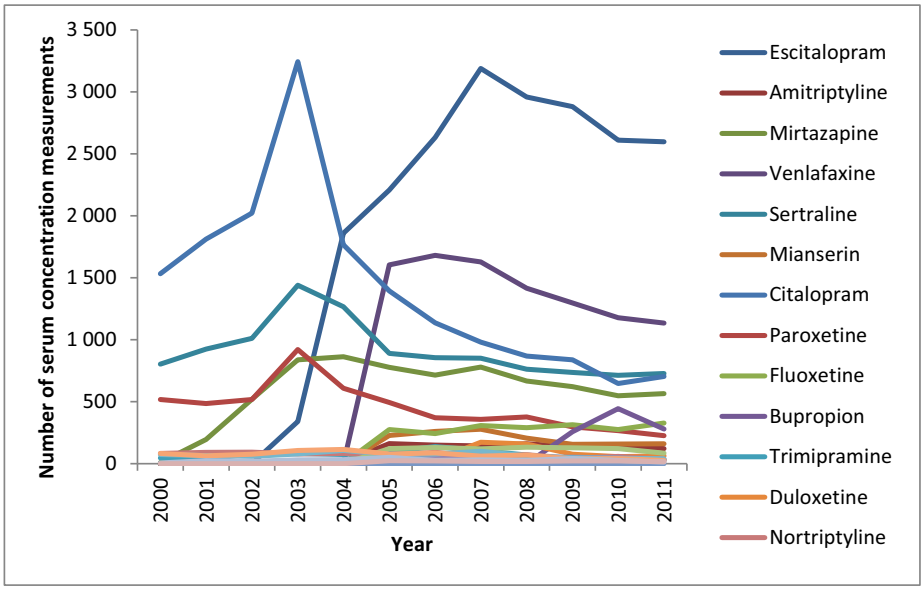
The figure shows the annual total number of serum concentrations measurements undertaken at St. Olav University Hospital for each antiepileptic drug.

Figure 10. TDM for antipsychotic drugs at St. Olav University Hospital, 2000-2011



The figure shows the annual total number of serum concentrations measurements undertaken at St. Olav University Hospital for each antipsychotic drug.

Figure 11. TDM for antidepressant drugs at St. Olav University Hospital, 2000-2011



The figure shows the annual total number of serum concentrations measurements undertaken at St. Olav University Hospital for each antidepressant drug.

1.6 Previous studies on pharmacokinetics in pregnancy

A systematic review on pharmacokinetic changes in pregnancy for all drugs was recently published in *PLoS Medicine* (5). One of the main conclusions was that the overall total number of such studies is small, and that this fact probably relates to the widespread exclusion of pregnant women from clinical studies. Other general findings in the review were that only few pharmacokinetic parameters were available in the studies, and that sample sizes were generally low (5).

These conclusions summarize well the literature for the three main drug categories of this thesis, and for which we will present more details here: A) newer antiepileptic drugs, B) selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, and C) antipsychotics.

1.6.1 Newer antiepileptic drugs

The pharmacokinetics of newer antiepileptic drugs in pregnancy has been covered by several review articles (5, 32-39), although the number of original articles is actually quite modest. Table 5 shows the studies available at the time of the initiation of this project, i.e. before 2008. As shown in

the table, the number of studies and the number of participants in each study were typically low, with the exception for lamotrigine, which was (and still is) by far the most extensively studied antiepileptic drug in conjunction with pregnancy. A significant (50-60%) decline in maternal serum concentrations during pregnancy has been shown for lamotrigine and levetiracetam, but also to a slightly lesser degree (30-36%) for oxcarbazepine and zonisamide. In most studies, there were also large interindividual variations in the concentration changes during pregnancy.

The methodology and outcome variables differ between studies. For instance, some studies (40-43) did not actually follow the course of maternal concentrations throughout pregnancy, but rather consist of maternal plasma concentrations measured at delivery (as an indication of third trimester levels) compared to later measurements. Such studies may be hampered by maternal serum concentration measurements being undertaken at non-trough levels.

Table 5. Previous studies on pharmacokinetics of newer antiepileptic drugs in pregnancy

Drug (references)	Elimination	Protein binding	Total number of pregnancies with pharmacokinetic data	Effect of pregnancy on maternal serum concentrations
Gabapentin (40)	Unchanged in urine	Not bound	3	No change
Lamotrigine (44-49)	Mainly glucuronidation	About 55%	1+10+12+12+14+11=62	Decrease by about 50-60%
Levetiracetam (42, 50)	Mainly unchanged in urine, 1/3 metabolized by peripheral hydrolysis	Not bound	3+12=15	Decrease by about 60%
Oxcarbazepine (51, 52)	Licarbazepine, the metabolite with the primary anticonvulsant properties, is eliminated by glucuronidation	About 40%	9+5=14	Decrease by about 36%
Topiramate (41)	Mainly unchanged in urine, less than 1/3 hepatic biotransformation	About 15%	3	No change
Zonisamide (43)	Mainly hepatic biotransformation, 15-30% unchanged in urine	40-60%	1	Decrease by about 30%

The table shows the previous studies on pharmacokinetics of newer antiepileptic drugs in pregnancy, at the beginning of this project (prior to 2008). Adapted from references (33) and (38).

1.6.2 Antipsychotics

Antipsychotics are among the least studied drug classes regarding pharmacokinetic changes in pregnancy. Indeed, a recent systematic review on pharmacokinetic changes in pregnancy (5) identified no studies at all in this drug class. However, two case reports exist, one for quetiapine (53) and one for aripiprazole (54). These are presented in Table 6 below, together with general

pharmacokinetic information for the other drugs in this class. All drugs are highly protein bound and are eliminated mainly by hepatic biotransformation by various cytochrome P450 enzymes.

Table 6. Previous studies on pharmacokinetics of antipsychotics in pregnancy

Drug (references)	Elimination	Protein binding	Total number of pregnancies with pharmacokinetic data	Effect of pregnancy on maternal serum concentrations
Aripiprazole (54)	Mainly hepatic biotransformation (CYP2D6, CYP3A4)	>99%	3	Decrease by more than 66%
Clozapine	Mainly hepatic biotransformation (CYP1A2, CYP2C19)	>95%	-	-
Haloperidol	Mainly hepatic biotransformation (CYP3A4, CYP2D6)	About 92%	-	-
Olanzapine	Mainly hepatic biotransformation (UGT, CYP1A2)	About 93%	-	-
Perphenazine	Mainly hepatic biotransformation (CYP2D6)	>90%	-	-
Quetiapine (53)	Mainly hepatic biotransformation (CYP3A4, CYP2D6)	About 83%	1	Decrease by 55%
Risperidone	Mainly hepatic biotransformation (CYP2D6, CYP3A4)	About 89%	-	-
Ziprasidone	Mainly hepatic biotransformation (CYP3A4)	>99%	-	-

The table shows the previous studies on pharmacokinetics of antipsychotics in pregnancy. Only two case reports exist. General pharmacokinetic information regarding elimination and protein binding for all drugs was retrieved from references (55) and (56). CYP = cytochrome P450. UGT = uridine diphosphate-glucuronosyltransferase.

1.6.3 SSRIs and venlafaxine

One of the common features of all the selective serotonin reuptake inhibitors (SSRIs) and venlafaxine is that they are all mainly (90% or more) eliminated by hepatic biotransformation (55). The pharmacokinetics of these drugs (and many others) in pregnancy has been covered in a review by Pariente and collaborators in 2016 (5). Table 7 shows the previous studies on this topic. As for newer antiepileptic drugs, the number of studies and the number of participants in each study are typically low, except for paroxetine, for which one study on 74 subjects has been conducted. For citalopram, fluoxetine, paroxetine and venlafaxine serum concentrations in pregnancy have been

observed to decline by roughly one third, whereas for escitalopram and sertraline there appears to be no clear change during pregnancy, and for fluvoxamine, the topic remains unexplored.

Table 7. Previous studies on pharmacokinetics of SSRIs and venlafaxine in pregnancy

Drug (references)	Elimination	Protein binding	Total number of pregnancies with pharmacokinetic data	Effect of pregnancy on maternal serum concentrations
Citalopram (57, 58)	Mainly hepatic biotransformation (CYP2C19, CYP2D6), about 10% unchanged in urine	80%	11+3=14	26-42% decline
Escitalopram (58)	Mainly hepatic biotransformation (CYP2C19), about 10% unchanged in urine	56%	5	Minor/no decline
Fluoxetine (59-61)	Mainly hepatic biotransformation (CYP2D6, CYP2C9)	94%	11+9+17=37	32% decline in active moiety. S-fluoxetine declines more than R-fluoxetine)
Fluvoxamine	Mainly hepatic biotransformation (CYP2D6, CYP1A2)	80%	-	-
Paroxetine (62, 63)	Mainly hepatic biotransformation (CYP2D6, CYP3A4)	95%	12+74=86	30% decline
Sertraline (58, 64)	Mainly hepatic biotransformation, through multiple enzymes (CYP2B6, CYP2C19, CYP2C9, CYP2D6, MAO oxidases, UGT)	98%	8+6=14	Conflicting results: slight increase, no change, or slight decline
Venlafaxine (53, 65)	Mainly hepatic biotransformation (CYP2D6, CYP3A4)	About 30% for both parent drug and metabolite	1+7=8	13-50% decline in parent compound. No change in active moiety

The table shows previous studies on pharmacokinetics of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine in pregnancy. Adapted from reference (5), with addition of some studies (53, 60, 61, 63) that were not included in the systematic review. General pharmacokinetic information regarding elimination and protein binding for all drugs was retrieved from references (55) and (56). CYP = cytochrome P450. MAO = monoamine oxidase. UGT = uridine diphosphate-glucuronosyltransferase.

2. Aims

It is known that many drugs are commonly administered as part of clinical care during pregnancy. One can take advantage of that fact by using an opportunistic study design to obtain clinical data of drugs in pregnancy. TDM has a very strong position in Norway as a routine tool in clinical care of patients using antiepileptic, antidepressant and antipsychotic drugs. Since these services have now been provided for more than two decades, the TDM laboratories possess unique and valuable data in terms of population pharmacokinetics. These data may be used to address research questions for which the answers are hard to find by other means, such as how to provide optimal drug dosing during pregnancy. In this study we will make use of the three largest TDM databases in Norway for antiepileptic and psychotropic drugs in order to assess to what degree serum concentrations change during pregnancy. This information may in turn be used to provide optimal dosing for pregnant women using these drugs in the future.

- The aim of study I was to investigate the changes in the maternal serum concentrations of the antiepileptic drug **levetiracetam** in relation to pregnancy, using data from the TDM databases and clinical information from the European antiepileptic drug and pregnancy registry (EURAP).
- The aim of study II was to investigate the changes in the maternal serum concentrations of the antiepileptic drug **topiramate** in relation to pregnancy, using data from the TDM databases and clinical information from EURAP.
- The aim of study III was to investigate the changes in the maternal serum concentrations of **antipsychotics** in relation to pregnancy, using data from the TDM databases linked to the Medical Birth Registry of Norway (MBRN), for identification of pregnant subjects.
- The aim of study IV was to investigate the changes in the maternal serum concentrations of **selective serotonin reuptake inhibitors and venlafaxine** in relation to pregnancy, using data from the TDM databases linked to the MBRN for identification of pregnant subjects.

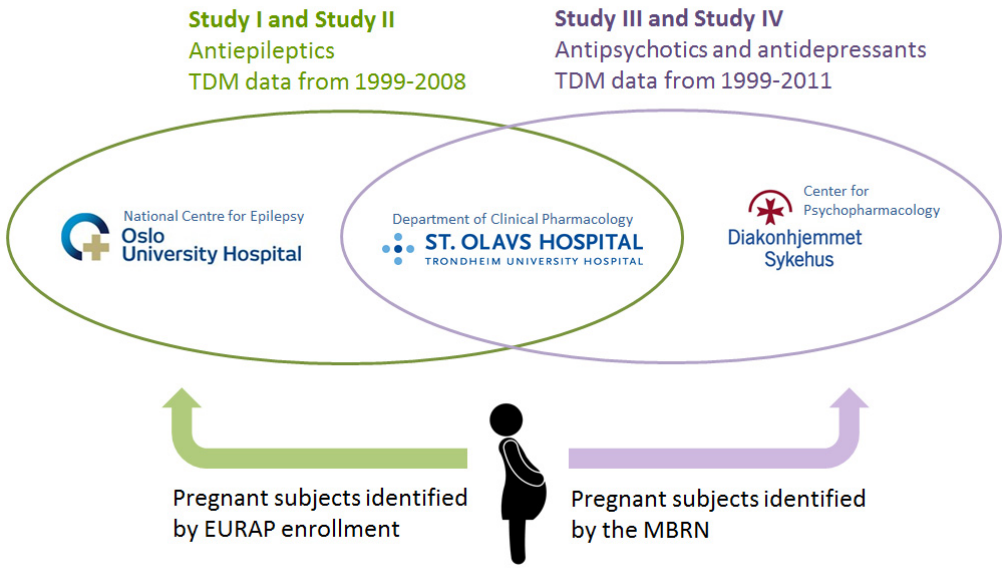
3. Materials and methods

3.1 The TDM databases

The data used in all studies was collected from the routine TDM databases at the Department of Clinical Pharmacology at St. Olav University Hospital in Trondheim (study I-IV), the National Centre for Epilepsy at Oslo University Hospital (study I and II), and the Center for Psychopharmacology at Diakonhjemmet Hospital in Oslo (study III and IV). The National Centre for Epilepsy together with St. Olav University Hospital constitute the two largest TDM services in Norway for antiepileptic drugs, whereas the Center for Psychopharmacology and St. Olav University Hospital constitute the two largest TDM services in Norway for antipsychotic and antidepressant drugs. As an example of the TDM activity in these laboratories, the annual number of TDM analyses provided at St. Olav University Hospital is shown in Figure 8-Figure 11 on page 20-22.

Samples sent to the TDM laboratories are accompanied by a requisition form, shown in Appendices 1-3 for the three laboratories, respectively. In these forms, the requisitioners are asked to provide demographic information about the patient as well as information regarding drug dose, time of last drug intake, mode of administration, time of last drug dose alteration, time of sampling, and concomitant use of other drugs. The requisition forms also contain various other items of clinical information, such as indication for sampling (e.g. routine measurement, adverse events, or suspected non-adherence), diagnosis, hepatic and renal function, pregnancy, smoking status, and other relevant clinical information. However, all items are not always filled in by the requisitioners. For instance, if a patient is pregnant at the time of sampling, this piece of information is not always provided on the requisition form. Therefore, for all studies in this thesis, other and more reliable sources of information were used in order to identify samples from pregnant women and estimate the gestational week at the time of sampling, as is shown in Figure 12. These sources will be presented in the following sections.

Figure 12. The TDM databases and the sources of study subject selection



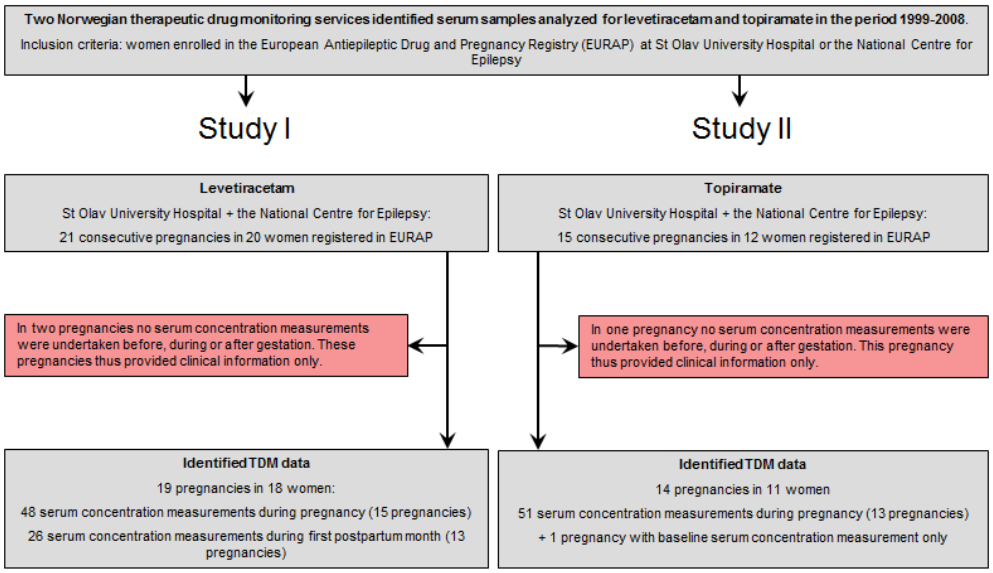
The figure shows which of the Norwegian TDM databases provided data for each of the studies I-IV in this thesis, and the time span for each study. The figure also shows how pregnant subjects were identified in the TDM databases (further elaborated in Figure 13 and Figure 15. EURAP = European Antiepileptic Drug and Pregnancy Registry. MBRN = the Medical Birth Registry of Norway.

3.2 Identification of pregnant subjects by EURAP

EURAP is a prospective observational study of pregnancies with antiepileptic drugs, with a primary goal of comparing the safety of different antiepileptic drugs during pregnancy with respect to birth defects (66). It was launched in 1999, and has now become a global registry with participating physicians from 42 countries, and more than 23,000 pregnancies have been registered. All women taking antiepileptic drugs at conception are eligible for inclusion. Assigned national coordinators collect data from study centers in each contributing country and report the data to a central study database (66-68). EURAP does not interfere with the treatment prescribed by the patient's physician. Instead, observational data are collected and reported using a standardized Case Record Form (CRF), collecting information on the patient's demographics, type of epilepsy, seizure frequency, family history of malformations, as well as drug therapy and dosage. Follow-up data are collected on separate sub-forms once at each trimester, at birth and at one year after delivery. The CRF used for collecting information is shown in Appendix 4.

In Norway, neurologists at St. Olav University Hospital in Trondheim and the National Centre for Epilepsy in Oslo have enrolled pregnant women in the EURAP registry since 2001. As contributors to EURAP, these centers keep their own copy of the CRFs of their enrolled subjects, and may publish results of their own subsets of data. Thus, for study I and study II, our study population consisted of consecutive pregnancies enrolled in the EURAP registry, for levetiracetam and topiramate respectively, at both Norwegian locations. The TDM measurements before, during and after pregnancy from these subjects were identified in the databases at each location, as shown in Figure 12 and Figure 13.

Figure 13. Study population selection for studies I and II



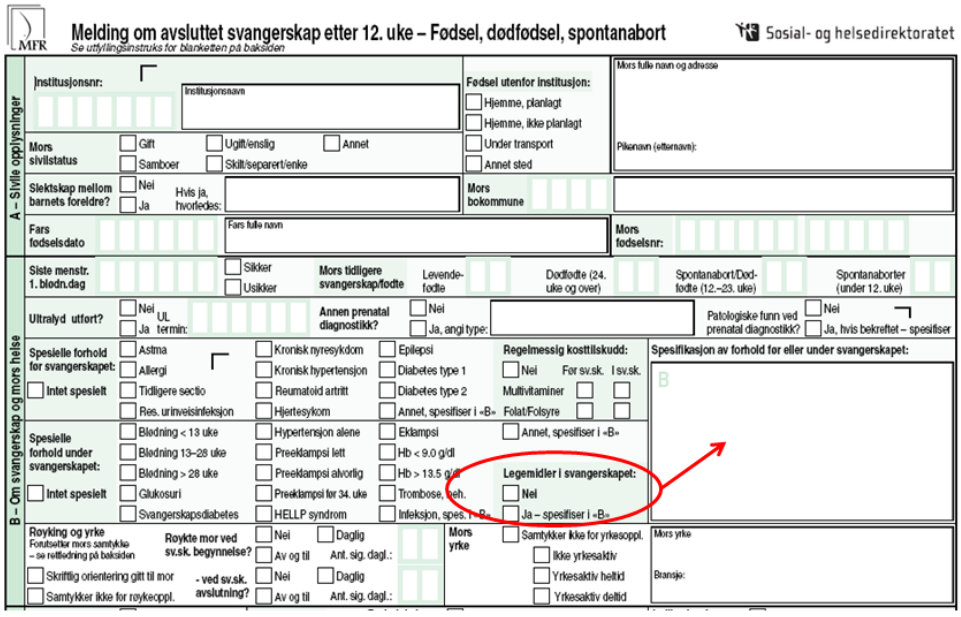
The figure shows how the study populations were selected to studies I and II of this thesis. All consecutive pregnancies enrolled in the EURAP registry at the two locations were included.

3.3 Identification of pregnant subjects by the MBRN

The Medical Birth Registry of Norway (MBRN) is a population based registry containing information on all births in Norway since 1967 (69). The registry is based on compulsory notification of every birth or late abortion from 12 completed weeks of gestation onwards. The report form includes date of delivery and length of pregnancy as well as other information regarding the mother and infant. The report form is shown in Appendix 5.

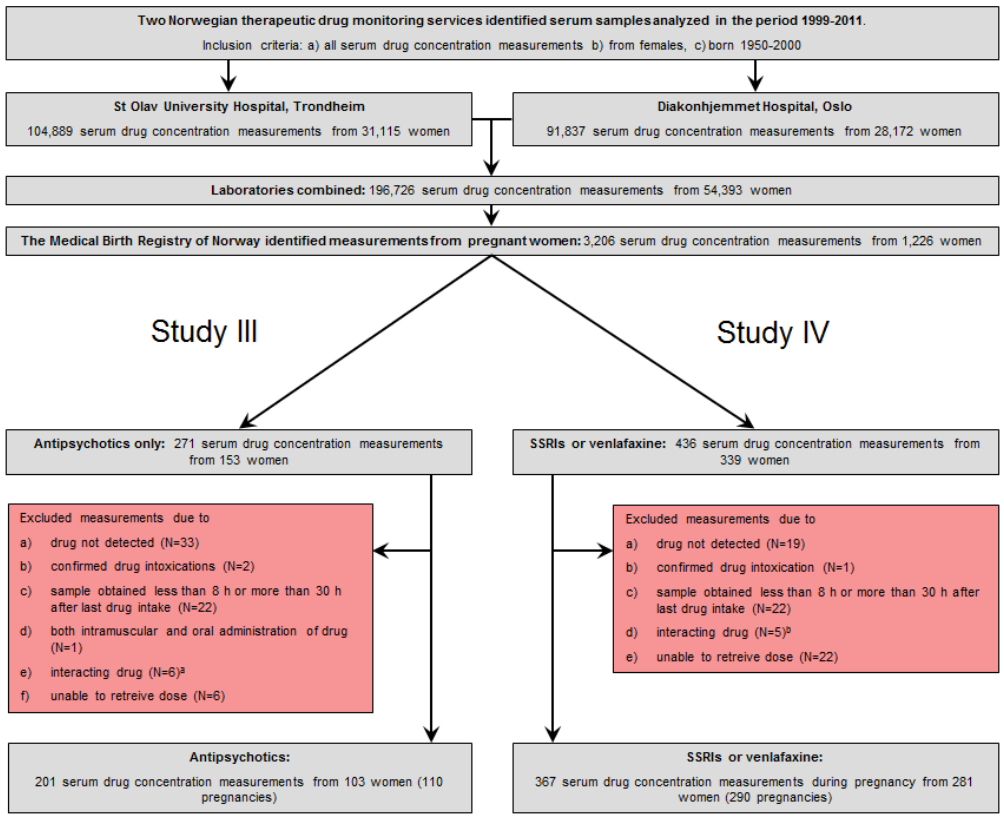
In the making of our study protocol for studies III and IV, we originally planned to identify pregnant subjects by the information provided in the MBRN birth notification form (Figure 14): we intended to identify pregnancies by reported use of antipsychotics and antidepressants in pregnancy, and then look for their serum drug concentrations measurements in our TDM databases. However, another Norwegian research group showed that the medication use recorded in the MBRN was an unreliable source of information, with just 50% concordance with the information in Norwegian Prescription Database (70). Therefore, after consulting both the MBRN and the Regional Committee for Medical and Health Research Ethics, we changed our research protocol, and sent the entire TDM databases (all serum drug concentration measurements from all women of reproductive age) to the MBRN, and let them identify samples from pregnant women, as shown in Figure 15. This approach not only eliminated the uncertainty of self-reported drug use; it also provided information regarding the exact gestational time for each sample drawn.

Figure 14. Medication use recorded in the MBRN



The figure shows part of the Medical Birth Registry of Norway notification form. The form contains a separate item for drug use during pregnancy (red circle and arrow), but this has been shown to be an unreliable source of information, and was therefore not used in our studies.

Figure 15. Study population selection for studies III and IV



The figure shows how the study populations were selected to studies III and IV of this thesis.

[a] In Study III, six analyses were excluded due to the following drug interactions: clozapine + fluvoxamine (n=1), olanzapine + carbamazepine (n=1), perphenazine + paroxetine (n=2), perphenazine + fluoxetine (n=1) and risperidone + fluoxetine (n=1). In Study IV, five analyses were excluded due to the following drug interactions: sertraline + carbamazepine (n=1), venlafaxine + bupropion (n=4).

3.4 Bioanalytical methods

Study I: Serum samples were analyzed using the routine methods applied at the two sites involved in the study, as part of their daily therapeutic drug monitoring service: At the National Centre for Epilepsy at Oslo University Hospital, levetiracetam serum concentrations were measured by an isocratic liquid chromatographic method (71). Levetiracetam was extracted from 200 µL serum with 600 µL methanol with internal standard. After mixing and centrifugation 200 µL of the supernatant was transferred to autosampler vials. An Ultimate 3000 (Dionex) with a Varian HPLC column, OmniSper 5 C18 S250x3 mm and a precolumn, ChromSep Guard Column, S10x2 mm, was used. The mobile phase consisted of acetonitrile: phosphate buffer (40:60), pH=5.6. Chromatography

was run at 35 °C, and the column eluent was monitored at 220 nm. The coefficient of variation (CV) calculated from between-batch precision of spiked concentrations was 5.0% and 5.9% at 50 µM and 300 µM, respectively. The limit of quantification was 10 µM.

At the Department of Clinical Pharmacology at St. Olav University Hospital, serum samples were analyzed with a liquid chromatography—mass spectrometry (LC—MS) method. Levetiracetam was extracted from 100 µL serum with 500 µL dichloromethane: isopropanol (90:10) after addition of internal standard solution (d_6-levetiracetam). After mixing and centrifugation the organic extract was evaporated to dryness with air, the residue was reconstituted in 100 µL acetonitrile, transferred to vials and injected on an Agilent MSD 1100 LC— MS system (Agilent, Palo Alto, CA, USA). The LC—MS system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a G1316A column oven and a G1946A mass spectrometer. Separation was performed on a Zorbax XDB-C8 (150 mm x 4.6 mm) column with a mobile phase consisting of acetonitrile: formic acid (55:45). Levetiracetam was monitored after positive electrospray ionization at m/z 171.1, the internal standard d_6-levetiracetam at m/z 132.1. The calibrated range of the method was from 5 to 500 µM. Six quality control samples covering the range from 25 to 250 µM were analyzed with every batch of unknown samples. Between-day relative standard deviation calculated from quality control samples was better than 16.9% at 25 µM and 7.7% at 250 µM. The limit of quantification of the method was 5 µM.

Study II: Serum samples were analyzed using the routine methods applied at the two sites involved in the study, as part of their daily therapeutic drug monitoring service: At the National Centre for Epilepsy at Oslo University Hospital, topiramate serum concentrations were measured by a fluorescence polarization immunoassay. The assay was based on the competitive binding principle (Innofluor Topiramate Assay System, Seradyn, Indianapolis, IN, USA), and was used on a TDx analyzer (Abbott, Abbott Park, IL, USA). The lower limit of detection was 0.3 µg/mL (0.89 µM). Precision studies have shown a CV of <5%.

At the Department of Clinical Pharmacology at St. Olav University Hospital, serum samples were analyzed with a liquid chromatography—mass spectrometry (LC—MS) method. Topiramate was extracted from 100 µL serum with 500 µL dichloromethane: isopropanol (90:10) after addition of internal standard solution (griseofulvin). After mixing and centrifugation the organic extract was evaporated to dryness with air, the residue was reconstituted in 100 µL acetonitrile, transferred to vials and injected on an Agilent MSD 1100 LC— MS system (Agilent, Palo Alto, CA, USA). The LC—MS system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a

G1316A column oven and a G1946A mass spectrometer. Separation was performed on a Zorbax XDB-C8 (150 mm x 4.6 mm) column with a mobile phase consisting of acetonitrile: formic acid (55:45). Topiramate was monitored after positive electrospray ionization at m/z 357.2, the internal standard griseofulvin at m/z 152.7. The calibrated range of the method was from 5 to 500 µM. The detection limit was 0.34 µg/mL (1.0 µM) with a CV of 7.5%.

Study III and *study IV:* Serum samples were analyzed using the routine methods applied at the two sites involved in the study, as part of their daily therapeutic drug monitoring service: Quantification of the drug concentrations was performed with LC-MS/LC-MS/MS. The analytical methods have been described in detail previously (72-75). In brief, the drugs were extracted from serum by liquid-liquid extraction, using a mixture of hexane, acetonitrile and/or butanol, or dichloromethane and isopropanol. Thereafter, the analytes were separated on C18 columns using methanol, acetonitrile, formic acid or ammonium acetate as mobile phases, and quantified on LC-MS or LC-MS-MS systems. Calibration curves were constructed for each assay with drug-free human serum by the addition of varying concentrations of the substances and their respective metabolites. All methods were linear in the therapeutic range of the various drugs, and the limits of quantification were generally well below the lower limits of the reference intervals. The inter-day coefficients of variability were in most cases below 10%. During the timespan of study 3 and study 4, some assays had been improved and adjusted, but all modifications were cross-validated with the previous method used for the same drug.

3.5 The concentration/dose ratio (CDR) concept

The serum concentration-to-dose ratio (CDR) was chosen as the primary outcome measure in all studies. The CDR was calculated by dividing the measured serum concentration of the drug (in µM or ng/mL) by the total daily drug dose (in mg). Thus, the CDR expresses the serum drug concentration per milligram drug administered daily. By using CDRs as output measures instead of the actual serum drug concentrations, the estimated values could be compared directly within as well as between subjects, irrespective of any variations in dosage. In studies III and IV, the CDRs were multiplied by the defined daily dose (DDD), which is the assumed average maintenance dose per day for that drug used for its main indication in adults (15). Since all CDRs for the same drug were multiplied by the same factor, this did not affect the actual ratios. The intention was to make the resulting values

easier to understand for clinicians, by providing expected serum concentration per typical daily dose of a drug instead of per milligram.

3.6 Calculations and statistical methods

In studies I and II, CDRs were presented as means for each trimester and for the baseline. Baseline values were defined as the CDR in the last sample drawn before pregnancy, or (if missing), the first sample taken at least one month after delivery. If more than one sample per trimester was analyzed for a single patient, the CDRs were averaged, in order to produce a single value for that pregnancy for that trimester. Student's paired t-test and independent samples t-test were used to compare mean CDRs in each trimester with the mean baseline CDR. P-values of < 0.05 were considered statistically significant in study I, and <0.017 (after Bonferroni correction) in study II. Statistical analyses were conducted in SPSS for Windows, version 16.0.

In studies III and IV a more sophisticated statistical model was used, allowing for multiple observations from the same pregnancies, and using gestational time as a linear variable. Due to a heavily right skewed distribution of CDR data, the logarithm of the CDRs was employed as the outcome variable in the statistical model, in order to achieve near normality. Then, the $\log_e$ CDR values were assessed in a linear mixed model. This model assumes that each individual patient possesses a random intercept (i.e., an individual "offset" CDR) in addition to being affected by the gestational week at the time of sampling. Any baseline measurements (i.e. samples drawn when the woman was not pregnant and not the first weeks after pregnancy) were set to gestational week 0 in the model. This way, the effect of gestational week on concentration compared to baseline could be estimated for each drug. The model assumes that changes in drug concentrations on the logarithmic scale are linear throughout pregnancy. For drugs where both the parent drug and the metabolite were measured, parent drug/metabolite concentration ratios during pregnancy were compared to baseline values as described above; ratios were log transformed and fitted into a linear mixed model, estimating the baseline ratios and effect of each gestational week. All model parameters, including variance components, were estimated by the method of maximum likelihood using STATA 13 command "mixed". Data are presented as means with 95% confidence intervals. P values less than 0.05 were considered statistically significant.

3.7 Clinical information

For studies I and II, clinical information about drug use and dosage, seizure frequency and pregnancy outcome was collected from the CRFs and the patients' medical records. Pregnancy outcome was presented in the articles as a secondary study variable.

For studies III and IV, no clinical information (neither regarding the condition of the mother nor the offspring) was available, except the information provided on the request form to the laboratories, which typically consisted of drug use and dosage only. However, if the requisition form lacked information on drug dose, the authors contacted the requesting clinician, who attempted to obtain this information from the medical record. No other information was exchanged in this dialogue.

3.8 Ethics

None of the studies included in this thesis involved direct contact or interventions with patients. As the studies did not involve direct handling of biologic material, it was not necessary to apply for the establishment of a research biobank.

Study I: The authors consulted the Regional Committee for Medical and Health Research Ethics, and described the planned project. The committee considered the project to be a quality control study, and stated that no further approval was needed.

Study II: When the project expanded to a second study, the authors made a formal and detailed written request to the Regional Committee for Medical and Health Research Ethics. The study was approved by the committee.

Studies III and IV were approved by the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data (Data Protection Official), the Norwegian Directorate of Health, and the Medical Birth Registry of Norway (MBRN).

For studies I and II, informed consent had been given by all study participants as a part of the EURAP enrollment. For studies III and IV, the need for informed consent was waived by the Regional Committee for Medical and Health Research Ethics (Ref. No. 08/8544–2) and the Norwegian Directorate of Health (Ref. No. 08/10184), according to Norwegian legislation.

4. Results

4.1 Summary of study I

Serum concentration/dose ratio of levetiracetam before, during and after pregnancy.

Andreas Austgulen Westin, Arne Reimers, Grethe Helde, Karl Otto Nakken, Eylert Brodtkorb.

Seizure (2008) 17, 192—198

Purpose: To study the impact of pregnancy on dose-adjusted maternal serum concentrations of levetiracetam.

Methods: By retrospective use of the EURAP registry in Norway, we retrieved therapeutic drug monitoring results from altogether 21 consecutive pregnancies in 20 women with epilepsy receiving levetiracetam. Levetiracetam serum concentrations/dose ratios for each trimester were compared with baseline (non-pregnant) ratios, using Student's t-tests. Additional variables were changes in levetiracetam dose, concomitant use of other antiepileptic drugs, seizure frequency, and pregnancy outcome. Clinical and pharmacological data were obtained from the women's medical records.

Results: Dose-adjusted serum concentrations declined by 50 %, from 0.42 (±0.018) µmol/L/mg at baseline to 0.021 (±0.009) µmol/L/mg in the third trimester ($p < 0.001$, $n = 11$), and returned to baseline levels within the first weeks after pregnancy. The interindividual variability was pronounced. A clear correlation between lowered levetiracetam levels and seizure breakthrough could not be demonstrated, nor ruled out.

Conclusions: The change in dose-adjusted levetiracetam serum concentrations is likely to be of clinical significance. Our results warrant close clinical monitoring throughout pregnancy, preferentially supported by therapeutic drug monitoring.

4.2 Summary of study II

Serum concentration/dose ratio of topiramate during pregnancy.

Andreas Austgulen Westin, Karl Otto Nakken, Svein I. Johannesen, Arne Reimers, Kari Mette Lillestølen, Eylert Brodtkorb. Epilepsia (2009) 50, 480—485

Purpose: To study the impact of pregnancy on dose-adjusted maternal serum concentrations of topiramate.

Methods: By retrospective use of the EURAP registry in Norway, we retrieved therapeutic drug monitoring results from altogether 15 consecutive pregnancies in 12 women with epilepsy receiving topiramate. Topiramate serum concentrations/dose ratios for each trimester were compared with baseline (non-pregnant) ratios, using Student's t-tests. Additional variables were changes in topiramate dose, concomitant use of other antiepileptic drugs, seizure frequency, and pregnancy outcome. Clinical and pharmacological data were obtained from the women's medical records.

Results: The average dose-adjusted topiramate serum concentrations in the second and third trimester were 30% ($p = 0.002$, $n = 11$) and 34% ($p = 0.001$, $n = 8$) lower than the baseline values, respectively. The interindividual variability was pronounced. Increased seizure frequency was common in pregnant women using topiramate, but a correlation to the decline in topiramate serum concentrations could not be established from our data.

Conclusions: Dose-adjusted serum concentrations of topiramate appear to decline gradually throughout pregnancy. Clinical monitoring and therapeutic drug monitoring of patients using topiramate in pregnancy may be useful, particularly in patients with brittle seizure control.

4.3 Summary of study III

Treatment with antipsychotics in pregnancy: Changes in drug disposition

Andreas Austgulen Westin, Malin Brekke, Espen Molden, Eirik Skogvoll, Ingrid Castberg, Olav Spigset. Clinical Pharmacology and Therapeutics 2018;103(3):477-84

Purpose: To study the impact of pregnancy on dose-adjusted maternal serum concentrations of antipsychotics.

Methods: Using patient data from two routine therapeutic drug monitoring (TDM) services in Norway with linkage to the national birth registry, dose-adjusted serum drug concentrations of antipsychotics during pregnancy were compared to the women's own baseline (non-pregnant) values, using a linear mixed model.

Results: We identified 201 routine serum antipsychotic therapeutic drug monitoring concentration measurements obtained from a total of 110 pregnancies in 103 women, and 512 measurements from the same women before and after pregnancy. Serum concentrations in the third trimester were significantly lower than baseline for quetiapine (-76%; confidence interval [CI], -83%, -66%; $P < 0.001$)

and aripiprazole (-52%; CI, -62%, -39%; P < 0.001), but not for olanzapine (-9%; CI, -28%, +14%; P = 0.40). For the remaining antipsychotics (perphenazine, haloperidol, ziprasidone, risperidone, and clozapine), our dataset was limited, but it indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol.

Conclusions: Even though the clinical consequence of the serum concentrations decline remains to be elucidated, our results warrant close clinical monitoring throughout pregnancy, preferentially supported by therapeutic drug monitoring.

4.4 Summary of study IV

Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: Changes in drug disposition

Andreas Austgulen Westin, Malin Brekke, Espen Molden, Eirik Skogvoll, Olav Spigset.

PLoS One (2017) Jul 14; 12 (7): e0181082.

Purpose: To study the impact of pregnancy on dose-adjusted maternal serum concentrations of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine.

Methods: Using patient data from two routine therapeutic drug monitoring (TDM) services in Norway with linkage to the national birth registry, dose-adjusted serum drug concentrations of SSRIs and venlafaxine during pregnancy were compared to the women's own baseline (non-pregnant) values, using a linear mixed model.

Results: We identified 367 routine serum SSRI and venlafaxine therapeutic drug monitoring concentration measurements obtained from a total of 290 pregnancies in 281 women, and 420 measurements from the same women before and after pregnancy. Serum concentrations in the third trimester were significantly lower than baseline for paroxetine (-51%; 95% confidence interval [CI], -66%, -30%; p<0.001), fluvoxamine (-56%; CI, -75%, -23%; p = 0.004) and citalopram (-24%; CI, -38%, -7%; p = 0,007), and higher than baseline for sertraline (+68%; CI, +37%, +106%; p<0.001). For escitalopram, fluoxetine and venlafaxine concentrations did not change significantly.

Conclusions: For paroxetine and fluvoxamine the pronounced decline in maternal drug serum concentrations in pregnancy may necessitate a dose increase of about 100% during the third trimester in order to maintain stable concentrations. For fluoxetine, venlafaxine, citalopram, escitalopram and sertraline, the present study indicates that dose adjustments are generally not necessary during pregnancy.

5. Discussion

5.1 Methodological considerations

The primary target variable in all studies of this thesis was the dose-adjusted serum concentrations for each drug. This variable expresses the serum drug concentration per milligram per day, or per typical daily dose (DDD). The dose-adjusted serum concentrations enable us to compare drug concentrations within and between subjects, irrespective of any variations in dosage. However, even though it is a useful marker for pharmacokinetic changes in pregnancy, it is only a surrogate marker for what matters the most: the wellbeing of the patient. Controversy still exists regarding use of serum drug concentration measurements as markers of clinical efficacy, both for antiepileptic drugs (38) but even more so for antipsychotics (26, 27) and antidepressants (27, 76). Even though the evidence for the use of TDM is continuously growing (for a recent overview of TDM recommendations for all neuropsychopharmacological drugs, see (20)), more evidence is needed to overcome the "we are treating patients, not serum concentrations" argument. For pregnant women in particular, we need more studies to elucidate the clinical relevance of pharmacokinetic changes. We do know that the total drug concentration in serum may change - as was clearly demonstrated in all of our studies - but other important *pharmacokinetic* variables still remain to be elucidated, such as the drug concentration unbound to proteins, and the drug concentrations inside the blood-brain barrier, i.e. at the actual site of pharmacological action. Moreover, many *pharmacodynamic* factors also remain to be elucidated. For instance, the pregnant state could alter drug concentration requirements, for instance through altered receptor sensitivity. In other words, a therapeutic drug range for a non-pregnant woman may not necessarily be the same for a pregnant woman. Thus, translating serum concentration measurements into drug dosing guidelines is still based on assumptions that have yet to be scientifically verified. In a recent review article on drug pharmacokinetics in pregnancy (5) the authors conclude as follows: "[There is] a significant gap between the accumulating knowledge of pharmacokinetic changes in pregnant women and our understanding of their clinical impact for both mother and fetus". Unfortunately, this gap also applies to the studies in the present thesis: Even though we provide unprecedented knowledge on pharmacokinetics in pregnancy for many drugs, we had no clinical data in the antipsychotics and antidepressants studies (studies III and IV) and only a limited patient material in the antiepileptics studies (studies I and II). Thus, our studies enable us to provide drug dosing guidelines for how to *maintain stable serum drug concentrations* in pregnancy, but accepting this as a guideline for *maintaining stable therapeutic effect* still requires a leap of faith.

Our studies have several other limitations, as thoroughly discussed in each paper, and also summarized in Table 8. Most limitations relate to the observational and non-experimental design of the studies. In all studies, routine patient data from a naturalistic setting was retrospectively assessed. Thus, the authors had no role in designing sampling schemes or subject recruitment, nor could we affect the amount or quality of information input from the requisitioners. We had to make use of the data the way it was. Even though many of the limitations for studies III and IV (e.g. unknown indication for sampling, unknown drug adherence, variable time interval from intake of last dose to sampling, and possibility of inaccurate dose information) could introduce bias, we believe that the effects of these factors are to a high degree counterbalanced by the large number of observations in the studies. For instance, we find it unlikely that there should be a gradually declining drug adherence (or increasing time from last dose to sampling) throughout pregnancy, and that this should be confined to some drugs (e.g. levetiracetam, citalopram and quetiapine, for which the concentrations decreased during pregnancy) and not others (e.g. sertraline and olanzapine).

Table 8. Study limitations

Study limitation	**Study I**	**Study II**	**Study III**	**Study IV**	**Comment**
Observational design	X	X	X	X	The authors had no role in designing sampling schemes or subject recruitment, nor could we affect the amount or quality of information input from the requisitioners. We had to make use of the data the way it was.
No clinical data			X	X	Without clinical data we do not know if the reduced serum drug concentrations in pregnancy actually caused clinical deterioration.
Small study populations	X	X	(X)		Even though our data material is of unprecedented size for almost all drugs in our study, our sample sizes were still too small to draw firm conclusions regarding the clinical consequences of reduced serum concentrations (studies I and II) and for some drugs it was also too small to make a firm assessment of changes in pharmacokinetics in pregnancy (e.g. ziprasidone and risperidone in study III).
Unknown drug adherence	(X)	(X)	X	X	We cannot rule out that declining serum drug concentrations in pregnancy relates to non-adherence. However, samples with no detected drugs were excluded, and we consider it unlikely that a gradually declining drug adherence throughout pregnancy should be confined to some drugs (e.g. levetiracetam, citalopram and quetiapine) and not others (e.g. sertraline and olanzapine).
Unknown indication for sampling			X	X	We cannot rule out a selection bias in observations, i.e. overrepresentation of samples taken because of treatment failure. However, our impression is that serum concentration measurements in pregnancy are conducted in the same way as in non-pregnant patients, and that most samples are taken as routine follow-up. Also, we consider it being unlikely that such a selection bias should be confined to some drugs only.

High variability in time interval from last dose to sampling			X	X	Some of the variability in our serum concentration measurements probably relates to non-uniform time of sampling, but we found no systematical differences in the post-dose time interval for blood sampling between pregnant and non-pregnant women.
Possibility of inaccurate dosing information from requisitioners			X	X	Dosage information on request forms was not double-checked with requisitioners unless it appeared obviously incorrect. Although all measurements lacking information on drug dose were excluded, we cannot exclude the possibility of erroneous dose information in the data set.
Only one pharmacokinetic variable	X	X	X	X	The serum concentration-to-dose ratio was the only pharmacokinetic (PK) variable available in all studies. With a prospective design, other PK variables, such as the maximum concentration and time (C_{max} and t_{max}), area under the curve (AUC) and free drug concentration could have been measured.
Statistical limitations	X	X			In studies I and II mean observations per trimester were calculated for each trimester and compared by t tests. Although the approach was sufficient for detecting serum concentration changes for both drugs, a mixed-model regression analysis could have been better suited, in order to make use of repeated observations from each subject, and to include gestational week as a linear variable.

5.2 Expected versus observed pharmacokinetic changes in pregnancy

Although a myriad of physiological changes may alter drug disposition during pregnancy (2, 5, 6, 77), total clearance of a drug is – in addition to the dose – the primary determinant of the its serum concentration at steady state. We therefore anticipated that the route of elimination for each drug would be crucial for whether or not serum concentrations would change, and in what direction and to what degree. For most drugs this turned out to be true, and the observed change in serum drug concentrations was in accordance with what was expected on the basis of knowledge about its route of elimination, but for some it did not. An overview of expected and observed changes in serum drug concentrations in pregnancy for all drugs in our studies is shown in Table 9.

Table 9 Expected and observed pharmacokinetic changes in pregnancy

Drug	Route of elimination, in order of relative importance (expected direction of change of serum concentrations in pregnancy)	Expected net change in serum drug concentrations in pregnancy	Observed change in serum drug concentrations in pregnancy
Levetiracetam	Renal elimination (↓) Extrahepatic hydrolysis (↕)	Major decline	Major decline
Topiramate	Renal elimination (↓) Hepatic biotransformation, unknown pathway (↕)	Major decline	Moderate decline
Aripiprazole	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP3A4 (↓)	Major decline	Major decline
Clozapine	Hepatic biotransformation, CYP1A2 (↑) Hepatic biotransformation, CYP2C19 (↑)	Increase	No change[1]
Haloperidol	Hepatic biotransformation, CYP3A4 (↓) Hepatic biotransformation, CYP2D6 (↓)	Major decline	No change[1]
Olanzapine	Hepatic biotransformation, UGT1A4 (↓) Hepatic biotransformation, CYP1A2 (↑)	No change	No change
Perphenazine	Hepatic biotransformation, CYP2D6 (↓)	Major decline	No change[1]
Quetiapine	Hepatic biotransformation, CYP3A4 (↓) Hepatic biotransformation, CYP2D6 (↓)	Major decline	Major decline
Risperidone	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP3A4 (↓)	Major decline	No change[1]
Ziprasidone	Hepatic biotransformation, CYP3A4 (↓)	Major decline	No change[1]
Citalopram	Hepatic biotransformation, CYP2C19 (↑) Hepatic biotransformation, CYP2D6 (↓)	No change	Minor decline
Escitalopram	Hepatic biotransformation, CYP2C19 (↑)	Increase	No change
Fluoxetine	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP2C9 (↓)	Major decline	No change
Fluvoxamine	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP1A2 (↑)	No change	Major decline[1]
Paroxetine	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP3A4 (↓)	Major decline	Major decline
Sertraline	Hepatic biotransformation, CYP2B6 (↓) Hepatic biotransformation, CYP2C19 (↑) Hepatic biotransformation, CYP2C9 (↓) Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, UGT (↓)	Moderate decline	Major increase
Venlafaxine	Hepatic biotransformation, CYP2D6 (↓) Hepatic biotransformation, CYP3A4 (↓)	Major decline	No change

The table summarizes the routes of elimination for all drugs of this thesis, as presented in Table 5, Table 6 and Table 7. The expected direction of change in drug serum concentration in pregnancy, based on previous knowledge, is shown in parentheses for each elimination route. The third column shows the net expected change in drug serum concentrations in pregnancy, whereas the forth column shows what we actually found. We have made the following definitions: Major change = more than 50 % change. Moderate change = 30% - 50% change. Minor change = less than 30% change.

[1]For each of the drugs clozapine, haloperidol, oral perphenazine, intramuscular perphenazine, risperidone, ziprasidone and fluvoxamine, the total number of pregnancies in our data set were less than 10, and results should be interpreted with caution.

Drugs eliminated primarily by renal excretion

Two drugs in our studies (levetiracetam and topiramate) are excreted primarily unchanged by the kidneys, with less than 30% biotransformation. Due to the increase in renal blood flow and glomerular filtration in pregnancy, both drugs would be expected to undergo declining serum drug concentrations in pregnancy, and both did.

Drugs eliminated primarily by CYP2D6 and/or CYP3A4

Many drugs in our studies (aripiprazole, haloperidol, perphenazine, quetiapine, risperidone, ziprasidone, fluoxetine, paroxetine and venlafaxine) are predominantly metabolized by the hepatic cytochrome P450 enzymes CYP2D6, CYP3A4, or both. These enzymes have been shown to undergo extensive induction (having up to twofold activity or more) in pregnancy (6, 78). Thus, the listed drugs would be expected to undergo declining serum drug concentrations in pregnancy. However, in our studies some did an some did not. Dramatic declines in serum drug concentrations were observed for quetiapine, aripiprazole and paroxetine, whereas no significant changes were found for haloperidol, perphenazine, risperidone, ziprasidone, fluoxetine and venlafaxine. For haloperidol, perphenazine, risperidone and ziprasidone we believe that the absence of change probably relates to small study sizes, as we had less than 10 women in each study group. We did observe a trend towards declining concentrations (over 50% in the third trimester) for all four drugs, and we believe that with larger study groups these differences would probably become statistically significant. On the other hand, the unchanged concentrations for fluoxetine and venlafaxine remains somewhat puzzling. For these drugs we had a relatively high number of study subjects (43 pregnancies for fluoxetine, and 33 for venlafaxine), yet only minor changes in serum drug concentrations (less than 30% reduction) was found for both drugs during pregnancy, and the changes did not reach statistical significance. Thus, for these two drugs, the anticipated change in drug serum concentration did not match what would be expected from a theoretical perspective. We believe our results to be valid, due to the sample size and the fact that our results match prior observations made for venlafaxine (53, 65) and fluoxetine (59-61) in pregnancy, but we do not know why CYP2D6 and CYP3A4 induction does not affect these drugs more than they apparently do, or if these effects could be counterbalanced by other physiologic changes in pregnancy.

Drugs eliminated primarily or partly by CYP1A2

Three drugs in our study are metabolized primarily or partly by the hepatic cytochrome P450 enzymes CYP1A2, namely olanzapine, clozapine and fluvoxamine. CYP1A2 activity has been shown to decrease in pregnancy (6, 78). Thus, if this enzyme represented the only elimination pathway in pregnancy for these drugs, serum concentrations would be expected to increase during pregnancy. However, none of the drugs in our study are metabolized by CYP1A2 alone.

Olanzapine, the drug for which we had most observations (29 pregnancies) is metabolized by CYP1A2, but is also glucuronidized by the enzyme UGT1A4, which has shown to exhibit *increased* activity in pregnancy (6, 78). In theory, these two physiological changes could counterbalance each other in pregnancy regarding net change in olanzapine serum concentrations. And indeed, in our study, olanzapine serum concentrations did not change in third trimester, and we believe this could be the reason.

Also for fluvoxamine, metabolized by both CYP1A2 and CYP2D6, a counterbalancing of effects has been hypothesized to occur (79), although no prior studies have actually explored its pharmacokinetic changes in pregnancy. In our study, we observed a major decline in serum drug concentrations in the third trimester. This could imply that the increased CYP2D6 activity has a greater influence on the net serum concentrations than the decreased CYP1A2 activity. However, it is important to bear in mind that our results derive from observations in three pregnancies only, and thus should be interpreted with caution.

Clozapine is metabolized by CYP1A2 and CYP2C19. Both these enzymes have been shown to have decreased activity in pregnancy (6, 78), and clozapine serum concentrations would thus be expected to increase. In our study clozapine concentrations did not change in pregnancy. However, our patient population consisted of four pregnancies only, and it is possible that a change could be revealed in a larger material.

Drugs eliminated primarily or partly by CYP2C19

In addition to clozapine, which has already been discussed, three drugs in our study are metabolized primarily or partly by the hepatic cytochrome P450 enzymes CYP2C19. These are citalopram, escitalopram and sertraline.

Citalopram undergoes stereoselective metabolism; the pharmacologically active S-enantiomer (escitalopram) is metabolized primarily by CYP2C19, whereas the inactive R-enantiomer is

metabolized primarily by CYP2D6 (58). In our study, escitalopram concentrations did not change during pregnancy. However, there was a trend towards a minor increase, as would be expected due to decreased CYP2C19 activity. For citalopram, we observed a minor decrease in serum concentrations in pregnancy. This implies that the increased CYP2D6 activity has a greater influence on the net serum concentrations than the decreased CYP2C19 activity. Our findings also imply that the chiral composition of citalopram may change in pregnancy, and that the concentrations of the R-enantiomer and the S-enantiomer may change in different directions. This means that for citalopram, declining concentrations do not necessarily translate into need for higher doses, since the decline is probably due to a decline the inactive enantiomer concentrations only.

For sertraline, in contrast to the other antidepressants, we found a statistically significant *increase* in serum concentrations in pregnancy compared to baseline. Sertraline is metabolized by multiple enzymes, including CYP2B6, CYP2C19, CYP2C9, CYP2D6, monoamine oxidases, and several UGT enzymes (56, 80). The effect of pregnancy on these enzymes is divergent and to some extent unknown (6). However, since we found increasing levels of both sertraline and the metabolite desmethylsertraline in pregnancy, we suspect CYP2C19 inhibition to play a crucial role.

5.3 Implications of our findings

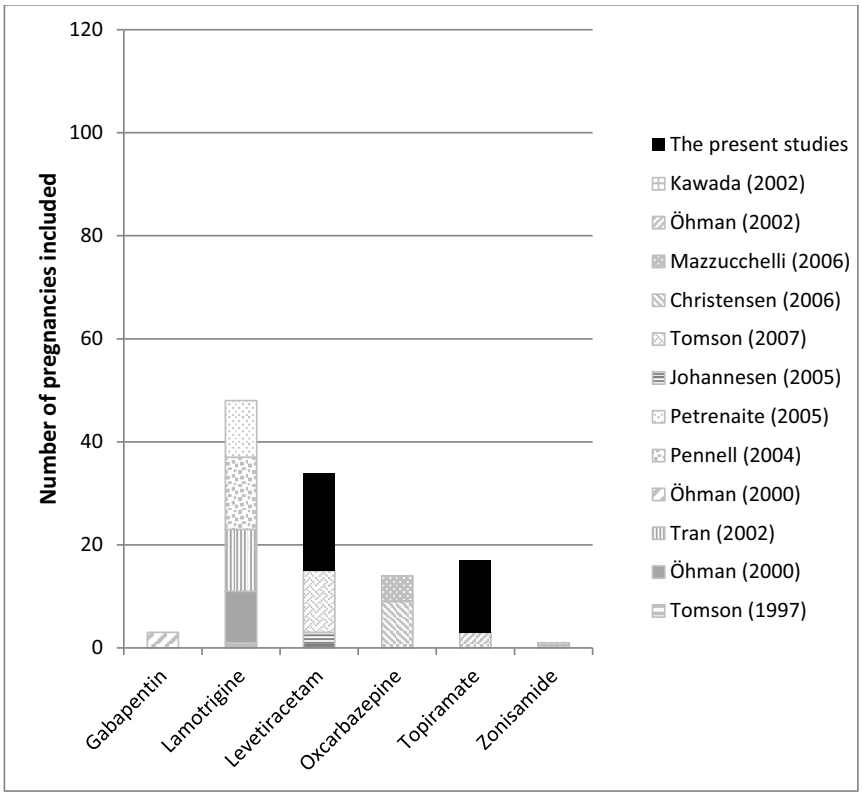
Due to the ethical issues involved in clinical drug trials during pregnancy (10, 11), retrospective studies of samples taken in a naturalistic setting is one of the very few available tools for obtaining information on drug disposition in pregnancy. In the absence of robust clinical trials, this «opportunistic approach» enables us to generate sorely needed knowledge, which in turn may help clinicians provide optimized dosing regimens for pregnant women, instead of extrapolating dose recommendations from non-pregnant adults.

Figures 16-18 provide an overview of the basis of our knowledge on the pharmacokinetics in pregnancy for the drugs in the study, in terms of number of pregnancies included in each of the prior studies. The figures clearly illustrate the overall minuscule number of pregnancies from which our knowledge on pharmacokinetics in pregnancy derives. Even lamotrigine, typically characterized as «the most extensively characterized antiepileptic drug in conjunction with pregnancy» (33) had pharmacokinetic data from 50 pregnancies only, when our project started in 2008 (Figure 16). And for antipsychotic drugs, there were case reports only (Figure 17).

Figures 16-18 also illustrate how knowledge is added in a brick by brick manner for each drug, providing more and more reliable and extensive insight into the pharmacokinetics of each drug. The

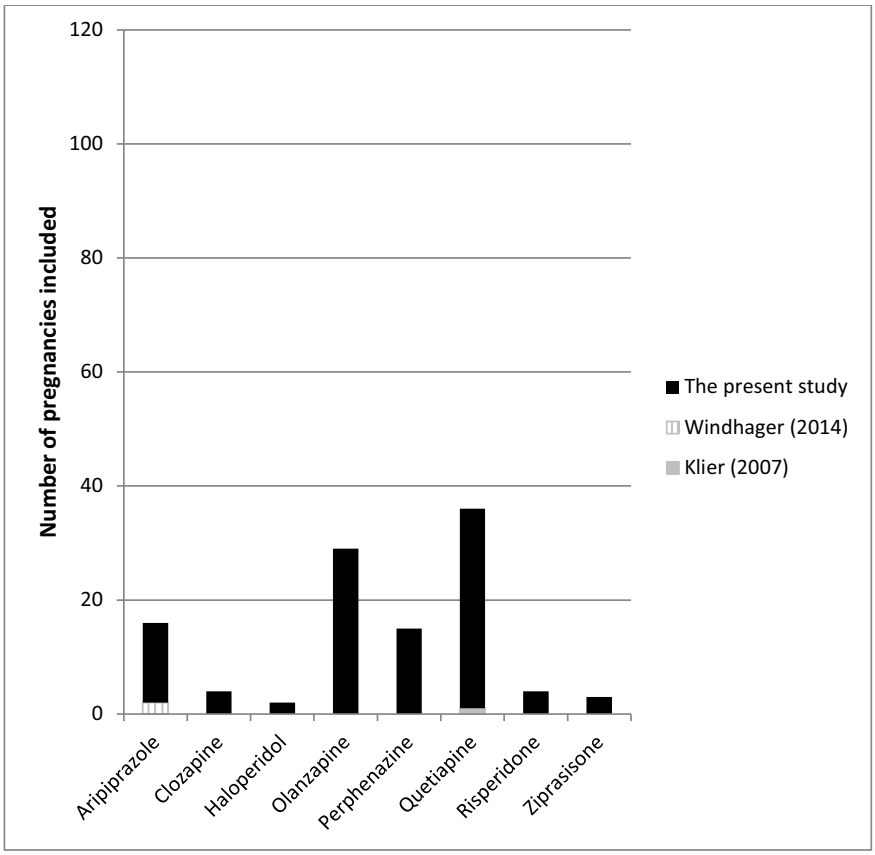
figures also clearly show what our studies add: For all drugs studied (except paroxetine), our data provides more pregnancies to the «pillars of knowledge» than any prior study, and for many drugs, even more than all previous studies added together.

Figure 16. What this study adds: Antiepileptic drugs



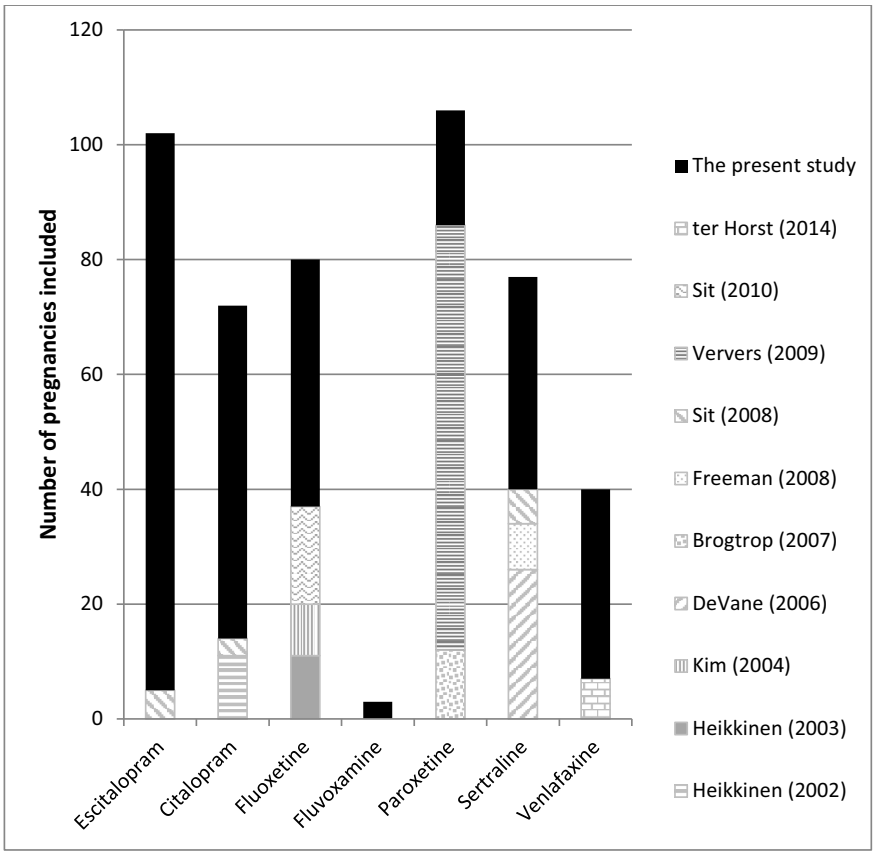
The figure shows the available literature (measured as the number of pregnancies studied) on pharmacokinetics of newer antiepileptic drugs in pregnancy at the beginning of our project in 2008. The black bars show what our studies I and II add.

Figure 17. What this study adds: Antipsychotic drugs



The figure shows the available literature (measured as the number of pregnancies studied) on pharmacokinetics of antipsychotic drugs at the time of publishing of our Study III, in 2018. The black bars show what Study III adds.

Figure 18. What this study adds: Antidepressant drugs



The figure shows the available literature (measured as the number of pregnancies studied) on pharmacokinetics of SSRIs and venlafaxine at the time of publishing of our Study IV, in 2017. The black bars show what Study IV adds.

Some years have passed since the first two publications of this thesis, and other research groups have also added separate "bricks" to our shared knowledge for newer antiepileptic drug disposition in pregnancy. The same year as we published our Study II on topiramate, Öhman and collaborators published a study on 17 topiramate pregnancies with very similar results to ours: they found third trimester concentrations to decline by approximately 40%, with large interindividual variations (81). Another study group found more modest changes in topiramate clearance, but had data from three pregnancies only (82). Another important recent event for topiramate is that the U.S. Food and Drug Administration has given it a label change, from pregnancy category C ("risk not ruled out") to D ("positive evidence of risk") due to the high prevalence of small for gestational age births following in utero exposure (83). Topiramate is thus not among the first-line drug choices for treating epilepsy pregnant women (83-85).

Also for levetiracetam, further studies have been published after ours, with similar results. The first one, published by López-Fraile and collaborators in 2009, presented data from five pregnancies. They found that third trimester concentrations were approximately half of those measured at baseline (86). The second one, by Reisinger and collaborators in 2013, presented pharmacokinetic data from 15 pregnancies with levetiracetam monotherapy, and they found that the average peak clearance during pregnancy was increased by 207% from the non-pregnant baseline (82). Furthermore, they reported that a high number of patients (7 of 15) on levetiracetam monotherapy experienced increased seizure frequency during pregnancy, a finding that has also been reported from a North Irish research group (87), and which is could be related to the pharmacokinetic changes in pregnancy. Increased seizure frequency following declining levetiracetam concentrations in pregnancy has also been described in detail in two case reports (88, 89). Levetiracetam still remains one of the preferred antiepileptic drugs (together with lamotrigine) for the management of epilepsy in pregnancy, due to its advantageous teratogenic risk profile (83-85, 90).

Recent studies have also elaborated on the pharmacokinetics in pregnancy for lamotrigine (82, 91-101), oxcarbazepine (82, 100, 102), and zonisamide (82, 103, 104). For lamotrigine, the total number of pregnancies studied with regards to pharmacokinetics now exceeds 200 (5).

5.4 Future perspectives

The work presented in this thesis, and many similar articles published by others, provide insights into drug-specific pharmacokinetic changes in pregnant women. However, the studies seldom provide information on the *clinical impact* of the observed pharmacokinetic changes (5). We need future studies to explore this "missing link" between what we see and what it means, i.e. between our surrogate markers (such as TDM concentrations) and the actual wellbeing of the patients. Ideally, this research question would be addressed in clinical drug trials combining clinical assessment and pharmacokinetic measurements. However, pregnant women are rarely included in such trials, due to ethical and legal concerns (11). The second best option would thus be to make use of "opportunistic" observational data in the best way possible. These studies would require access to structured clinical data (e.g. depression rating scales or other quantifiable clinical parameters), and in order to obtain the statistical power to reveal correlations between pharmacokinetic parameters and clinical outcome, they need to be done on a much larger scale than most studies so far.

We also need more mechanistic-oriented (human and animal) studies to further explore the pharmacokinetic changes in pregnancy, and shed light on matters like a) protein binding and free drug concentrations, b) drug concentrations in cerebrospinal fluid and the role of the blood-brain

barrier, and c) enzyme activity and genetic variability, and many more. Exploring the mechanisms affecting pregnancy pharmacokinetics will enable us not only to better understand some of the intriguing results of the present studies (such as the increasing sertraline concentrations in our study IV), but also enable us to better predict the pharmacokinetic outcome of new and so far unstudied drugs in pregnancy.

Another matter that deserves attention in a future perspective is the use of TDM in general, and psychiatry TDM in particular. Although the use of TDM is rather widespread for antiepileptic drugs, its clinical use and benefits appear to remain a somehow controversial issue for antipsychotics (26, 27) and antidepressants (27, 76). We believe that this difference in the traditions for TDM has also impacted pregnancy research. Indeed, looking at the overall literature on drugs use in pregnancy, it is striking to see how much concern is devoted to the issues of pharmacokinetics and dosing in pregnancy in the literature for antiepileptic drugs, compared to that of antidepressants and antipsychotics. There appears to be a common awareness of the pharmacokinetics changes in pregnancy in the field of neurology (33, 37, 38, 83, 85, 90, 105-107), that is somewhat still lacking in the field of psychiatry (6, 108, 109). In a recent review article entitled "Treating depression during pregnancy: are we asking the right questions?", two psychiatrists point out that research questions in perinatal psychiatry have been too largely focused on risk of medication exposure instead of the risk of disease exposure for the mother and fetus (110), and the authors suspect that the high rates of depression relapse in pregnant women may be due to inadequate dose adjustments to the pharmacokinetic changes occurring in pregnancy. An increased use of TDM in psychiatry would probably lead to increased awareness among clinicians regarding drug disposition in pregnancy, and possibly also better patient care.

Another reason to increase the use of TDM in pregnancy is that it helps us generate knowledge. In Scandinavia the tradition for TDM is strong (30, 31), as also demonstrated by the high number of works cited in this thesis originating in Finland (57, 59), Denmark (36, 49, 51, 99, 102), Sweden (21, 33, 38, 40, 50, 81, 93, 94, 111-113) and Norway (7, 37, 96, 114-119). Especially in Norway, the combination of the very extensive use of routine TDM on the one hand, and the availability of a national birth registry on the other, provides us with a unique possibility of generating knowledge on serum concentration changes in pregnancy for a wide range of drugs (30), in an extent that probably cannot be generated otherwise and elsewhere today. In the future, we would love to see more collaboration between Scandinavian TDM laboratories, in order to combine small data sets into bigger and more robust ones.

I hope the studies in the present thesis may increase the awareness regarding pharmacokinetics and drug dosing in pregnancy, especially in the field of psychiatry. At our department, we have made a recommendation for routine TDM analyses in pregnancy (in brief, recommending one serum concentration measurement at baseline, one for each trimester, and one for week 1,2 and 4 following delivery), and distributed this (Appendix 6) to all our requisitioners in the field of psychiatry. However, we always make sure that our requisitioners are informed that TDM is a supplement to, and not a substitute for clinical assessment.

6. Conclusions

Pregnant women are often advised to use the lowest effective dose of therepautic drugs during pregnancy. However, marginally sufficient drug levels may turn into subtherapeutic levels when drug clearance increases throughout pregnancy. Our studies show that there are pronounced declines in serum concentrations of levetiracetam, topiramate, quetiapine, aripiprazole, paroxetine and fluvoxamine during pregnancy. In order to maintain stable serum drug concentrations for these drugs in pregnancy, doses may need to be roughly doubled in the third trimester. For olanzapine, escitalopram, citalopram, fluoxetine, venlafaxine and sertraline, dose adjustments are generally not necessary in pregnancy. For other antipsychotics our dataset was more limited, but indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol.

Even though the clinical consequence of the serum concentration declines remains to be elucidated, our results call for close clinical monitoring of therapeutic effect during pregnancy. If available, TDM could be undertaken, preferentially beginning when the woman is well prior to or in an early stage of pregnancy.

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8. Errata of the published papers

In Figure 1 in paper I it is stated that the boxplot shows the serum concentration/dose ratio of all *samples* prior to, during and post pregnancy, and that the number of *samples* available in each group are given at the bottom of the figure. The word *sample* should be substituted with *individual mean concentrations* in order to be accurate. As explained in the statistics part of the Methods section of the paper, results are presented as means for each patient for each trimester. Thus, if a patient had two observations in the same trimester, with the numerical values 2 and 4, the *individual mean concentration* presented in the paper for this patient for this trimester would be 3. In retrospect, we see that the explanation we provided to this in the Methods section of paper II should also have been provided in paper I. The explanation reads: "If more than one sample per trimester was analyzed for a single patient, the C/D-ratios of these were averaged."

In Figure 1 in paper I the correct number of individual mean concentrations for first trimester should read "n=11", not "n=10".

In paper I the bioanalytical method is described for one participating laboratory only (the Department of Clinical Pharmacology at St. Olav University Hospital). The bioanalytical method for the other participating laboratory (the National Centre for Epilepsy at Oslo University Hospital) is provided in the methods section of this thesis.

In Figure 1 in paper II the legend reads "Scatter plot and regression line showing the topiramate serum concentration/dose ratios of all samples (n=62) from all *patients* (n=14) at baseline and during pregnancy". The word *patients* should be substituted with the word *pregnancies*.

PAPER I

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Serum concentration/dose ratio of levetiracetam before, during and after pregnancy

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KEYWORDS
Epilepsy;
Levetiracetam;
Pregnancy;
Pharmacokinetics;
Clearance;
Elimination

Summary

Purpose: To investigate changes in levetiracetam (LEV) serum concentration/dose ratio (C/D-ratio) in relation to pregnancy.
Methods: Altogether 21 consecutive pregnancies in 20 women with epilepsy receiving LEV during gestation were studied retrospectively. The main target variable was the C/D-ratio before and during pregnancy, and in the post partum period. Secondary target variables were changes in LEV dose, concomitant use of other antiepileptic drugs and seizure frequency. Student's paired *t*-test and two-sample *t*-test for independent samples were used to test for statistically significant changes in C/D-ratio means.
Results: Mean C/D-ratio in the third trimester was 50% of the mean C/D-ratio at baseline ($p < 0.001$, $n = 11$). Baseline levels were reached within the first weeks after pregnancy. The interindividual variability was pronounced.
Conclusions: Serum concentrations of LEV declined significantly in the third trimester of pregnancy and increased rapidly after delivery.

Introduction

Levetiracetam (LEV) is a newer antiepileptic drug (AED) with efficacy in various seizure types.[1] Due to its rapidly increasing use, a growing number of women receive LEV during pregnancy. The volume of distribution of LEV is close to intra- and extracellular water and the protein binding is minimal. The major metabolic pathway (applying to 24% of an administered dose) is extrahepatic hydrolysis of the acetamide group. Most of the drug is excreted unchanged by the kidneys.[2]

A range of pharmacokinetic alterations may result from the pregnant state. Some important factors are changes in plasma volume and volume of distribution, altered drug protein binding, changes in metabolic

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capacity as well as increased renal blood flow with enhanced glomerular filtration rate.[3,4] While gestation-related factors are known to influence the pharmacokinetic properties of older generation AEDs,[4,5] relatively little is known about their impact on the newer AEDs, with the exception of lamotrigine, which has been extensively studied (for an overview, see Tomson and Battino[4]). A marked increase in apparent clearance has been demonstrated for lamotrigine. A similar finding has been made for the monohydroxy derivative of oxcarbazepine.[6,7]

Limited data on the pharmacokinetics of LEV during pregnancy has so far been reported. Two case series, of which one only has been presented as an abstract, suggest that the apparent clearance of LEV also increases.[8,9] This increase appears to be higher than can be accounted for by enhanced renal blood flow alone.[9]

The objective of the present study was to confirm the previously published results, and to provide further information on the course of the maternal LEV serum concentration/dose ratio (C/D-ratio) throughout pregnancy and the post partum period. Additionally, we aimed to gather information on the pattern of seizure control in pregnant women using LEV.

Material and methods

Women from two Norwegian epilepsy outpatient clinics, participating in the European antiepileptic drug and pregnancy registry (EURAP) were screened for the use of LEV. Altogether 21 consecutive pregnancies in 20 women were identified. Nineteen of the pregnancies were completed; spontaneous abortions occurred in two. Mean age at time of delivery was 29 years (range: 21–38 years). Data on drug use and dosage, seizure frequency, seizure type and the occurrence of status epilepticus were obtained prospectively at each trimester according to the EURAP protocol.[10] Seizures were recorded by patient diaries. Supplementary clinical and pharmacological data were retrospectively collected from the medical records of each subject. LEV was used in monotherapy in five pregnancies, and in combination with other AEDs in the remaining 16. Treatment characteristics (maximum doses in each trimester) are summarized in Table 1.

Blood samples were taken drug fasting (10–14 h after last dose) at different stages prior to, during and after gestation in 19 pregnancies. They were analyzed with a liquid chromatography–mass spectrometry (LC–MS) method. Levetiracetam was extracted from 100 μL serum with 500 μL dichlorometane:isopropanol (90:10) after addition of internal standard solution (d6-levetiracetam). After mixing and centrifugation the organic extract was evaporated to dryness with air, the residue was reconstituted in 100 μL acetonitrile, transferred to vials and injected on an Agilent MSD 1100 LC–MS system (Agilent, Palo Alto, CA). The LC–MS system consisted of a G1379A degasser, a G1311A quaternary pump, a G1313A autosampler, a G1316A column oven and a G1946A mass spectrometer. Separation was performed on a Zorbax XDB-C8 (150 mm × 4.6 mm) column with a mobile phase consisting of acetonitrile:formic acid 55:45. Levetiracetam was monitored after positive electrospray ionization at m/z 171.1, the internal standard d6-levetiracetam at m/z 132.1. The calibrated range of the method was from 5 to 500 μM. Six quality control samples covering the range from 25 to 250 μM were analyzed with every batch of unknown samples. Between-day relative standard deviation calculated from quality control samples was better than 16.9% at 25 μM and 7.7% at 250 μM. The limit of quantification of the method was 5 μM.

Informed consent was given by all patients.

The serum concentration/dose ratio (C/D-ratio) was used as the primary outcome measure, as doses were not kept constant during the study. The LEV C/D-ratio was calculated by dividing the serum concentration of LEV (expressed as μmol/L) by the total daily dose (in mg). Thus, the LEV C/D-ratio expresses the serum concentration per milligram LEV given. The last sample prior to pregnancy, or (if missing) a sample taken 2 or 4 weeks after pregnancy served as the baseline value for each subject. Thus, the term baseline refers to the non-pregnant state, which might be either before or after pregnancy.

Statistics

Results are presented as mean (±SD) or median, as appropriate, for each trimester and for the baseline. Student's paired t-test and independent samples t-test were used to compare mean LEV C/D-ratios in each trimester with the mean C/D-ratios before and after pregnancy.

A p-value ≤ 0.05 was considered statistically significant.

Results

C/D-ratio during pregnancy

The box plot in Fig. 1 shows the median C/D-ratio at each sampling time. It indicates a gradual decrease throughout pregnancy, with an almost immediate

Table 1 Treatment characteristics and clinical course during pregnancy

Patient number	Antiepileptic drug	Doses (mg/day)				Seizures (3 months prior to pregnancy and during pregnancy
		At conception	First trimester	Second trimester	Third trimester	
1	Levetiracetam	1500	1500	1500	1500	SPS: 8—10/month
	Carbamazepine	1200	1200	1200	1200	
2	Levetiracetam	2000	2500	2500	2500	CPS: 1/month prior to pregnancy, but none during
	Valproate	900	900	0	0	
	Lamotrigine	0	200	200	200	
3	Levetiracetam	3000	3000	3000	3500	CPS: 1/month prior to pregnancy and during the first trimester SPS: Sporadic in the third trimester
	Carbamazepine	1200	1200	1200	1200	
4	Levetiracetam	0	0	1500	2000	None prior to pregnancy
	Valproate	1800	1800	1800	1800	CPS: 8—10/month in the first trimester
	Topiramate	300	300	300	300	GTC: 2 in the second trimester, 4 in the third trimester
5	Levetiracetam	1500	1500	1500	2000	None prior to pregnancy Myoclonic: 1/month in the first trimester, 4/month in the second, but none in the third trimester
6	Levetiracetam	0	0	2000	2500	SPS: Daily prior to and during pregnancy
	Gabapentin	1200	1200	1200	1200	
	Lamotrigine	300	400	600	600	
7	Levetiracetam	2000	2000	2000	2000	None prior to pregnancy
	Lamotrigine	550	600	700	800	GTC: 1 in the first trimester, 2 in the second CPS: Sporadic
8	Levetiracetam	2000	2500	2500	2500	None
	Lamotrigine	150	300	300	400	
9	Levetiracetam	1500	1500	1500	1500	None
10	Levetiracetam	500	1000	500	0	GTC: 1/month prior to and during pregnancy CPS: Several prior to pregnancy and during the first and second trimester, less in third
	Oxcarbazepine	0	1200	2400	2400	
	Pregabaline	450	450	450	450	
11	Levetiracetam	1500	1500	1500	1500	None
12a[a]	Levetiracetam	1500	1500	n.a.	n.a.	GTC: One prior to pregnancy, but none during first trimester
	Lamotrigine	200	200			
12b	Levetiracetam	1500	1500	1500	2000	None prior to pregnancy CPS: 1/month during the third trimester
	Lamotrigine	200	200	300	300	
13	Levetiracetam	1750	1750	2500	2500	None prior to pregnancy GTC: 1 in the third trimester
14	Levetiracetam	1500	1500	1500	1500	None
	Valproate	900	1800	1800	1800	
15	Levetiracetam	2500	2500	2500	2500	CPS: 1/week prior to and during pregnancy
	Lamotrigine	150	150	150	150	

Table 1 (*Continued*)

Patient number	Antiepileptic drug	Doses (mg/day)				Seizures (3 months prior to pregnancy and during pregnancy
		At conception	First trimester	Second trimester	Third trimester	
16	Levetiracetam Carbamazepine	1000 500	2000 500	2000 400	2000 800	None prior to pregnancy GTC: 1/month in the first trimester CPS: Increasing from weekly to daily throughout pregnancy
17	Levetiracetam Oxcarbazepine	2000 1200	2000 1200	2000 1200	2000 1200	CPS: 4/month prior to pregnancy and during the first and second trimester, 2/month in the third trimester
18	Levetiracetam Topiramate Valproate	1000 200 1200	1000 200 1200	1000 200 1200	0 200 1200	GTC: 1/month before and during the first two trimesters Absences: Several prior to pregnancy and during the first two trimesters, rare in the third trimester
19[a]	Levetiracetam	1500	1500	n.a.	n.a.	None prior to or during first trimester
20	Levetiracetam	1500	1500	2000	2500	CPS: 1/week prior to and throughout pregnancy
	Topiramate	400	400	450	400	GTC: Several/month prior to pregnancy, less than 1/month in the first and second trimester, weekly in the third trimester Status epilepticus: Convulsive in the second and non-convuslive in the third trimester

[a] Spontaneous abortion in first trimester; n.a., not applicable; SPS, simple partial seizures; CPS, complex partial seizures; GTC, generalized tonic-clonic seizures.

increase after delivery. However, complete sets of C/D-ratios, i.e. pre-pregnancy, all three trimesters, and post-pregnancy values, were not available from all patients (Table 2). In seven patients we obtained sets from all trimesters and at baseline. The mean C/D-ratio (±SD) in these patients at baseline was 0.036 (±0.015). In all trimesters it was lower than at baseline, although not significantly lower in the first and second trimester. In the third trimester, the mean C/D-ratio was 0.022 (±0.010), which was significantly lower than at baseline ($p = 0.005$, $n = 7$). In addition to these seven patients, four patients provided blood samples from the third trimester and at baseline, but not from the first and second trimester. The C/D-ratio changes from baseline to the third trimester in these altogether 11 patients (seven with complete data from all trimesters plus four with third trimester data only) are shown in Fig. 2. Among these patients, the mean C/D-ratio (±SD) in the third trimester was 0.021 (±0.009), that is significantly lower than the baseline value of 0.042 (±0.018) ($p < 0.001$).

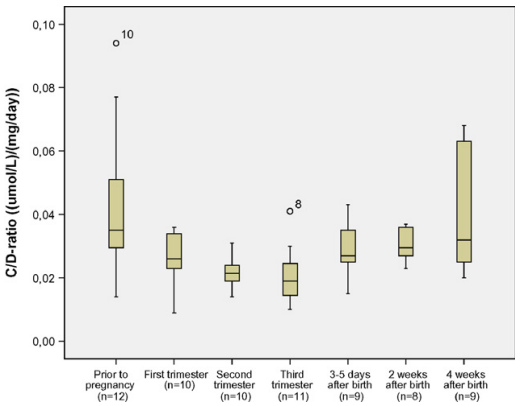

Figure 1 Boxplot showing the serum concentration/dose ratio [(μmol/L)/(mg/day)] of all samples prior to, during and post pregnancy. Numbers of samples available in each group are given at the bottom. Circles denominate outliers.

C/D-ratio after delivery

Blood samples were collected 3–5 days after birth ($n = 9$), 2 weeks after birth ($n = 8$) and 4 weeks after birth ($n = 9$) (some data previously reported by Johannessen et al.[11]). The mean C/D-ratios at these

Table 2 Serum concentration/dose ratio [(μmol/L)/(mg/day)] of levetiracetam during and after pregnancy

Patient number	Prior to pregnancy	First trimester	Second trimester	Third trimester	3–5 days after birth	2 weeks after birth	4 weeks after birth
1	–	–	–	–	0.025	0.027	0.039
2	–	–	–	–	0.025	0.027	0.032
3	0.019	0.009	0.022	0.018	0.019	0.023	0.020
4	–	–	–	–	0.035	–	0.022
5	–	–	–	0.020	0.015	0.037	–
6	–	–	–	––	0.034	0.036	0.068
7	0.032	0.023	0.024	0.020	–	–	0.030
8	–	0.027	0.024	0.041	–	–	0.064
9	0.077	0.034	–	0.030	–	–	–
10	0.094	0.036	–	–	––	–	–
11	0.035	0.025	0.014	0.010	–	–	–
12a	0.048	0.028	n.a.	n.a.	n.a.	n.a.	n.a.
12b	0.048	0.027	0.021	0.029	–	0.032	–
13	0.054	–	0.016	0.015	–	–	0.063
14	0.041	–	–	0.013	–	–	–
15	–	–	–	–	–	–	–
16	0.029	0.023	0.021	0.014	0.027	0.036	–
17	0.030	–	0.019	–	0.038	–	–
18	0.014	0.015	0.030	–	–	–	–
19	–	–	n.a.	n.a.	n.a.	n.a.	n.a.
20	–	0.034	0.031	0.019	0.043	0.027	0.025
Mean	0.043	0.026	0.022	0.021	0.029	0.031	0.040
St. dev.	0.022	0.008	0.005	0.009	0.009	0.005	0.018

n.a., not applicable (spontaneous abortions).

sampling times were compared to the 11 samples from the third trimester using an independent samples *t*-test. The mean (±SD) C/D-ratio was 0.031 ± 0.005 ($n = 8$) 2 weeks after birth and 0.040 ± 0.019 ($n = 9$) 4 weeks after birth. These values were both significantly higher than the third trimester value of 0.021 ± 0.009 ($n = 11$; $p = 0.02$ and 0.01, respectively). There was a trend towards a statistically significant difference already 3–5 days after birth (mean (±SD) C/D-ratio was 0.29 ± 0.009 ($n = 9$); $p = 0.06$).

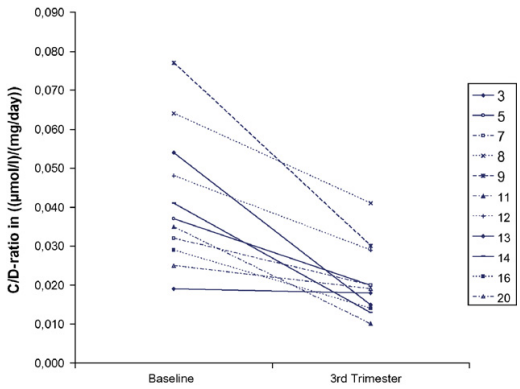

Figure 2 Individual serum concentration/dose ratios [(μmol/L)/(mg/day)] at baseline and during the third trimester, in 11 women on levetiracetam.

Dose adjustments

In 11 pregnancies, the LEV dose was increased (in two of them LEV therapy was started during pregnancy); four increments were performed in the first trimester, four in the second and six in the third trimester. In a total of 14 pregnancies, the dose of either LEV or concomitant AEDs was increased at least once (Table 1). AED dose increase was conducted during the first trimester in seven, during the second in six, and during the third trimester in 10 pregnancies. In two pregnancies, LEV was withdrawn.

Seizure frequency

Increased seizure frequency was observed in seven of the 19 completed pregnancies (Patients 4, 5, 7, 12, 13, 16, 20), in five of them during the third trimester. Reduced seizure frequency was observed in five (Patients 2, 3, 10, 17, 18); In the remaining pregnancies, the subjects were either seizure free prior to conception and throughout pregnancy, or their seizure frequency remained stable during the study period (Table 1). Among the seven patients

with increased seizure frequency, five had an increased number of generalized tonic-clonic seizures. One (Patient 20) experienced an incident of convulsive status epilepticus in the second trimester, and of non-convulsive status epilepticus in the third trimester, respectively. AED doses were increased in all seven patients with increased seizure frequency during pregnancy, and LEV was increased in six of them. However, the observed decline in LEV C/D-ratio was not more pronounced in the patients with increased seizure ratio than in the other subjects.

Discussion

Our data show a significant decline of the maternal LEV C/D-ratio in the third trimester, and a rapid increase within the first 2 weeks post partum (Table 2, Fig. 1). The drop of the C/D-ratio was pronounced, with the mean value being reduced to 50% compared to baseline ($n = 11$). In other words, on average a doubling of the LEV dose would be required to maintain baseline serum concentrations during the third trimester. However, as reflected by Fig. 2 and Table 2, the extent of these changes shows considerable intersubject variability. An accurate prediction of the course of the LEV serum concentrations in pregnancy in individual patients is therefore not possible. Our findings are in accordance with previous data on the impact of pregnancy on the apparent clearance of LEV. In a conference abstract, Pennell et al.[8] reported a prospective study of five pregnancies from the U.S., in which blood samples were obtained in each trimester and post partum. Serum concentrations were adjusted for different dosage and for weight changes, by calculating apparent LEV clearance [(dose/body weight)/serum concentration]. Mean LEV clearance in the third trimester was 154% of the baseline value, indicating that in the third trimester about 1.5 times the original LEV dose would be needed to keep serum concentrations at baseline levels. This finding is supported by a recently published case series from Sweden.[9] In 12 pregnancies, it was found that the apparent LEV clearance in the third trimester was 342% of the baseline value, indicating a need for an increase of the LEV dose of almost 3.5 times to keep serum concentrations unchanged. Pennell's, Tomson's and our study suggest that the dose-corrected serum levels of LEV during the third trimester are between 29% and 65% of baseline values, with the present findings close to the mean (50%). However, neither the present nor the Swedish study applies adjustments for body weight changes. As suggested by Tomson et al.,[9] this might partly explain the more prominent change in apparent LEV clearance compared to the U.S. study.

Increased renal blood flow may contribute to the observed decline in LEV serum concentrations during pregnancy. The kidneys are the primary organ responsible for the excretion of LEV, as 66% of an administered LEV dose is found unchanged in the urine.[12] Since glomerular filtration rate increases approximately 50% during pregnancy, renal LEV clearance is likely to increase, but the extent is unknown. Generally, the effect of pregnancy on renal drug clearance is highly variable, ranging from 20% to 65% for most drugs.[3] Another possible explanation for the decline in LEV serum concentration could be an increased metabolism during pregnancy. The primary site for the hydrolysis of LEV appears to be in the blood, and the metabolism does not involve the hepatic cytochrome P450 (CYP) system.[12] However, enzyme-inducing AEDs have been shown to decrease LEV serum concentrations by about 20–30%.[13,14] Thus, since LEV metabolism appears to be inducible, it cannot be ruled out that metabolic/endocrine changes during pregnancy may induce LEV metabolism.

Whatever the mechanism, a change in LEV serum concentrations of the found magnitude is likely to be of clinical significance. In our study, an increase in seizure frequency occurred in seven of 19 completed pregnancies; one patient had recurrent status epilepticus. However, a clear correlation between lowered LEV levels and seizure breakthrough could not be demonstrated, conceivably as LEV doses usually were increased as a response to seizures, and because only two patients used LEV as monotherapy. Nevertheless, similar observations from the EURAP registry concerning seizure control during pregnancy have recently been published.[10] Among the enrolled women, two thirds had a stable seizure frequency (the majority was seizure free), whereas one third experienced a change, half of them improved, the other half got worse. As expected, incomplete seizure control appeared to be associated with polytherapy and AED dose changes.

In conclusion, our results confirm the findings of earlier studies. We have shown that dose-corrected LEV serum concentrations drop to about 50% of baseline values in the third trimester of pregnancy, and rapidly increase within the first weeks post partum. Consequently, serial measurements of LEV serum concentrations throughout pregnancy and in the first weeks post partum are advisable, particularly in patients with brittle seizure control. A considerable number of women using LEV during pregnancy may experience worsening of their seizure frequency. The present findings are essential

for appropriate counselling and follow-up of women who need treatment with LEV during pregnancy.

Policy and ethics

The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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PAPER II

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FULL-LENGTH ORIGINAL RESEARCH

Serum concentration/dose ratio of topiramate during pregnancy

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SUMMARY

Purpose: To study the impact of pregnancy on the serum concentration/dose ratio (C/D-ratio) of topiramate (TPM).

Methods: Twelve women with epilepsy using TPM during pregnancy, and 15 pregnancies were studied. The main target variable was the C/D-ratio at baseline and during pregnancy. Additional variables were changes in TPM dose, concomitant use of other antiepileptic drugs, seizure frequency, and pregnancy outcome. Clinical and pharmacological data were obtained from the women's medical records.

Results: The average C/D-ratios in the second and third trimester were 30% ($p = 0.002$, $n = 11$) and 34% ($p = 0.001$, $n = 8$) lower than the baseline values, respectively. The interindividual variability was pronounced. Increased seizure frequency was common in pregnant women using TPM, but a correlation to the decline in TPM C/D-ratio could not be established from our data.

Discussion: Dose-corrected serum concentrations of TPM appear to decline gradually throughout pregnancy. The underlying mechanisms are not known. Increased glomerular filtration may play a major role. During pregnancy, therapeutic drug monitoring of TPM may be useful.

KEY WORDS: Anticonvulsants, Antiepileptic drugs, Drug monitoring, Epilepsy, Pharmacokinetics, Pregnancy outcome.

The treatment of pregnant women with epilepsy is a challenge. Except for lamotrigine, data on the human teratogenicity of newer antiepileptic drugs (AEDs) is generally scarce (Tomson & Hiilesmaa, 2007). Moreover, apart from lamotrigine, oxcarbazepine, and levetiracetam, information on their pharmacokinetic properties during pregnancy is limited, and for some drugs nonexistent (Tomson & Battino, 2007). Nevertheless, an increasing number of women of childbearing age, including pregnant women, are treated with newer AEDs.

Topiramate (TPM) is one of several newer AEDs introduced after 1990. It has a broad-spectrum antiepileptic profile to which several mechanisms are considered to contribute, although its precise mechanisms of action are not known. It has established efficacy as monotherapy or adjunctive therapy in the treatment of adult or pediatric patients with generalized tonic–clonic seizures, partial seizures with or without generalization, and seizures associated with Lennox-Gastaut syndrome. The volume of distribution of TPM is close to intra- and extracellular water, and the protein binding is minimal (approximately 15%). Most of the drug is excreted unchanged by the kidneys. Approximately 20%–30% of orally administered TPM is metabolized in the liver, and this fraction may increase up to 50%–70% in the presence of enzyme-inducing drugs (Lyseng-Williamson & Yang, 2008).

There have been no systematic studies on the effect of pregnancy on the pharmacokinetics of TPM. The only indication we have so far is the results of a case series where maternal plasma concentrations were measured at

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delivery and while breastfeeding 2–3 weeks after delivery in three women treated with TPM (Öhman et al., 2002). No decline in TPM plasma concentrations at the time of delivery was observed compared to postdelivery concentrations. However, the number of patients was small, and the time of sampling varied.

Knowledge of the pharmacokinetic properties of AEDs during pregnancy is important in order to optimize drug therapy. The aim of the present study was to provide information on the course of maternal serum concentration relative to the daily dose of TPM throughout pregnancy. Additionally, we aimed to gather information on the pattern of seizure control in pregnant women using TPM and on the pregnancy outcome.

Materials and Methods

Female patients from two Norwegian epilepsy outpatient clinics were screened for the use of TPM during pregnancy. Twelve patients and 15 pregnancies were identified. Fourteen of the pregnancies were completed; one resulted in spontaneous abortion. Mean age at the time of conception was 28 years (range: 21–38 years). Data on drug use and dosage, seizure frequency, and seizure types were obtained prospectively for each trimester according to the European Antiepileptic Drug and Pregnancy Registry (EURAP) protocol (The EURAP Study Group, 2006). Supplementary clinical and pharmacological information were collected from the medical records of each subject. TPM was used in monotherapy in seven pregnancies, and in combination with other AEDs in the remaining eight. Treatment characteristics are summarized in Table 1.

Blood samples were drawn 10–14 hours after the last dose, at different stages prior to, during, and after gestation. TPM serum concentrations were measured using the routine methods applied at the two sites involved in the study, which were a fluorescence polarization immunoassay at one site, and a liquid chromatography mass spectrometry (LC-MS) method at the other. The fluorescence polarization immunoassay was based on the competitive binding principle (Innofluor Topiramate Assay System, Seradyn, Indianapolis, IN, U.S.A.). The assay system was used on a TDx analyzer (Abbott, Abbott Park, IL, U.S.A.). The lower limit of detection was 0.3 μg/ml (0.89 μmol/L). Precision studies have shown a coefficient of variation (CV) of <5%. For the LC-MS analysis, the detection limit was 0.34 μg/ml (1.0 μmol/L) with a CV of 7.5%.

Table 1. Antiepileptic treatment at conception and maximum prescribed daily dose at each trimester

		Maximum dose (mg/day)			
Patient number	Antiepileptic drug	At conception	First trimester	Second trimester	Third trimester
1	Topiramate	350	350	0	0
	Lamotrigine	300	300	300	300
	Primidone	1000	1000	1000	1000
2	Topiramate	200	200	200	200
	Lamotrigine	400	400	400	400
3	Topiramate	175	175	175	175
	Carbamazepine	1200	1200	1200	1200
4a	Topiramate	400	400	400	400
4b	Topiramate	400	400	400	400
5	Topiramate	200	200	200	225
	Valproate	1200	1200	1200	1200
	Levetiracetam	1000	1000	1000	1000
6	Topiramate	400	400	450	450
	Levetiracetam	1750	1750	1750	2500
7	Topiramate	200	200	n.a[a]	n.a[a]
	Oxcarbazepine	1200	1200	–	–
8a	Topiramate	100	100	100	100
8b	Topiramate	100	100	100	100
9a	Topiramate	150	150	150	150
9b	Topiramate	150	150	150	150
10	Topiramate	300	300	300	300
	Valproate	1800	1800	1800	1800
	Levetiracetam	0	0	1500	2000
11	Topiramate	150	150	150	150
12	Topiramate	200	200	400	400
	Oxcarbazepine	1800	1800	2100	2700

[a]Spontaneous abortion in the first trimester; n.a., not applicable.

Table 2. Mean serum C/D-ratio in (μmol/L)/(mg/day) of TPM at baseline and at each trimester of pregnancy

Patient number	Baseline	First trimester	Second trimester	Third trimester
2	0.0905	0.0755 (2)	0.0645 (1)	0.0640 (1)
3	0.0286	0.0328 (3)	0.0314 (1)	–
4a	0.0540	0.0569 (2)	0.0448 (1)	0.0370 (1)
4b	0.0600	–	0.0285 (1)	0.0133 (1)
5	0.0755	0.0755 (2)	0.0470 (1)	–
6	0.1037	0.0464 (4)	0.0469 (7)	–
7	0.0547	0.0675 (1)	n.a	n.a
8a	0.1050	0.1030 (1)	–	0.0610 (1)
8b	0.0890	–	–	–
9a	0.0880	0.1100 (1)	0.0730 (2)	–
9b	0.0927	0.0967 (1)	0.0760 (1)	0.0707 (1)
10	0.0560	0.0433 (1)	0.0497 (2)	0.0427 (1)
11	0.0867	0.0800 (1)	0.0533 (1)	0.0667 (1)
12	0.0408	0.0360 (1)	0.0336 (3)	0.0251 (3)
Mean	0.0732	0.0686 (20)	0.0499 (21)	0.0476 (10)
SD	0.0240	0.0262	0.0160	0.0213

Number of samples in brackets; n.a., not applicable (spontaneous abortion).

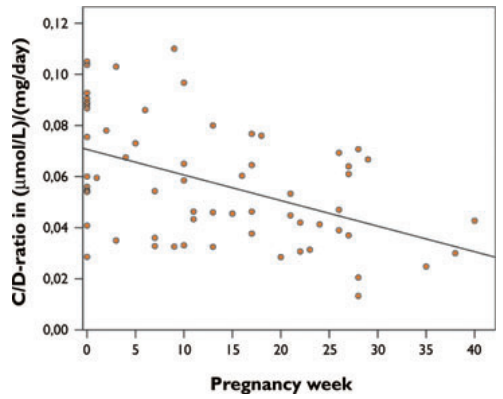

Figure 1.
Scatter plot and regression line showing the topiramate serum concentration/dose ratios of all samples (n = 62) from all patients (n = 14) at baseline and during pregnancy.
Epilepsia © ILAE

As TPM doses were not always kept constant during the pregnancies, the serum concentration/dose-ratio (C/D-ratio) was chosen as the primary outcome measure. The C/D-ratio was calculated by dividing the measured serum concentration of TPM (in μmol/L) by the total daily dose (in mg) taken by the patient at that time. Thus, the TPM C/D-ratio expresses the serum concentration per milligram TPM given. In the following text, baseline values are defined by the calculated C/D-ratio in samples drawn from the subjects in a nonpregnant state. This might be either the last sample before pregnancy (n = 11) or (if missing), first sample taken at least 1 month after delivery (n = 3). The 1-month limit was chosen since serum concentrations of other AEDs have been shown to reach nonpregnant values within that time frame (Tomson & Battino, 2007).

Results are presented as mean (±SD) for each trimester and for the baseline. If more than one sample per trimester was analyzed for a single patient, the C/D-ratios of these were averaged (Table 2). Separate, paired-samples Student's *t*-tests were used to compare the mean TPM C/D-ratios in each trimester with the mean C/D-ratio at baseline. Bonferroni adjustments for multiple tests were applied, and a p-value of ≤0.017 was considered significant.

The study was approved by the regional ethics committee, and informed consent was given by all patients.

Results

C/D-ratio during pregnancy

Sixty-two blood samples from 11 patients (14 pregnancies) were collected. The scatter plot in Fig. 1 shows the time of sampling (pregnancy week) and the calculated C/D-ratio for all samples. As shown by the regression line in the figure, there appears to be a gradual decline in the dose-corrected TPM serum concentrations throughout pregnancy. However, complete sets of C/D-ratios (i.e., baseline and all three trimesters) were available from only six patients (Table 2). Therefore, the mean C/D-ratios of each trimester were compared to the mean C/D-ratio of the same patients at baseline, using separate paired-samples Student's *t*-tests. For the first, second, and third trimesters, samples were available from 12, 11, and 8 pregnancies, respectively (Table 2). All patients provided baseline values for comparison. The mean C/D-ratio in the first trimester was not significantly different from baseline (p = 0.45, n = 12). The mean C/D-ratio in the second trimester was 0.050 (± 0.016), which was lower than the 0.071 (±0.024) at baseline, and the difference was statistically significant [p = 0.002, confidence interval (CI) = 0.01–0.31, n = 11]. The mean C/D-ratio in the third trimester was 0.048 (±0.021), compared to 0.073 (±0.023) at baseline, and this difference also was statistically significant (p = 0.001, CI = 0.02–0.036, n = 8).

The mean C/D-ratio drop from baseline to the second and third trimester was 30% (CI: 14%–43%) and 34% (CI: 27%–49%), respectively. For a typical 200 mg daily dose of TPM, this would translate to a decline in TPM serum concentration from approximately 14 to 10 μmol/L (CI: 8–12) and 9 μmol/L (CI: 7–10) in the second and third ztrimester, respectively. An average 42% and 52% dose increase from baseline would be needed in the second and third trimester, respectively, to maintain baseline serum concentrations throughout pregnancy.

Dose adjustments

In four pregnancies, the dose of TPM and/or concomitant AEDs were increased at least once (Table 1). The TPM dose was increased in three pregnancies; two increments were performed in the second trimester and one in the third trimester. Among the other AED increments, two were performed in the second trimester and three in the third trimester. In one pregnancy, TPM was withdrawn due to psychosis (Patient 1). Otherwise, no AED dose reductions were performed during the 15 pregnancies.

Seizure frequency

Increased seizure frequency was observed in seven of the 15 pregnancies (Patients 1, 4b, 6, 8a, 8b, 10, and 12), three of which used TPM monotherapy. An increased number of generalized tonic–clonic seizures was observed in six pregnancies. In all pregnancies where a deterioration of seizure control was observed, seizure frequency increased during the second or third trimester. Four of these patients also had increased seizure frequency during the first trimester. Reduced seizure frequency was observed in two pregnancies (Patients 3 and 5). In the remaining six pregnancies (including one spontaneous abortion), the subjects were either seizure-free prior to conception and throughout pregnancy or their seizure frequency remained stable during the observed period (Table 1).

Among the eight patients from whom blood samples were drawn during the third trimester (shown in Fig. 2), four experienced an increased number of seizures during the third trimester, while the other four had an unchanged seizure frequency throughout pregnancy. The average C/D-ratio reduction from baseline to third trimester was 34% in the prior group and 26% in the latter, the differences being not statistically significant.

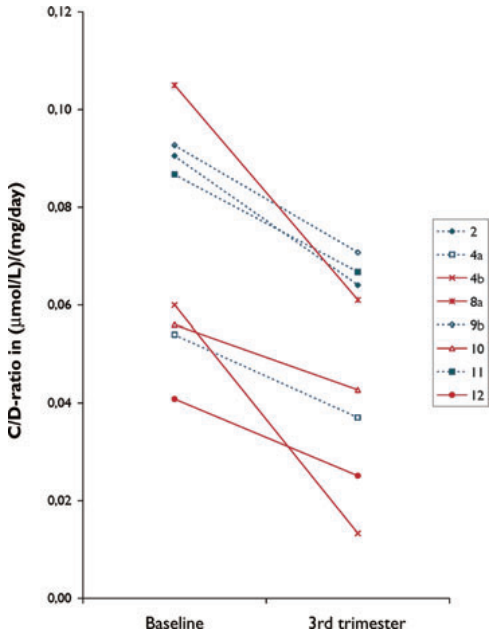

Figure 2.
Individual topiramate serum concentration/dose ratios at baseline and during the third trimester in eight women on topiramate. Solid lines, patients with increased seizure frequency in the third trimester; dotted lines, patients with unchanged seizure frequency throughout their pregnancy.

Pregnancy outcome

One woman had a spontaneous abortion in the first trimester (Patient 7). Another woman (Patient 9b) gave birth to a child with two small cardiac ventricular septum defects (VSDs). The defects had no clinical significance, and by 1 year of age the closure was almost complete, and cardiologists expected the defects to close spontaneously. Another woman gave birth to a healthy child 4 weeks before term (Patient 11). The remaining 12 pregnancies resulted in uneventful deliveries and healthy children. Normal health and development was reported by the mothers of the 14 children that were assessed 1 year after delivery. The pregnancy outcome and child health at 1-year follow-up is shown in Table 3.

Discussion

To our knowledge, this is the first study to describe changes in the pharmacokinetic properties of TPM during pregnancy. Our data show a significant decline of the maternal TPM C/D-ratio in the second and third trimester (Figs. 1 and 2, and Table 2). The mean C/D-ratio drop from baseline to the second and third trimester was 30% and 34%, respectively. Thus, an average 42% and 52% dose increase would be needed in the second and third trimesters, respectively, to maintain baseline serum concentrations throughout pregnancy. However, as reflected by Fig. 2 and Table 2, the extent of the changes in TPM concentrations shows considerable intersubject variability. An accurate prediction of the course of the TPM serum concentrations in pregnancy in individual patients is therefore not possible on the basis of the present study.

A recent Swedish study reported TPM plasma concentrations of three women during delivery and lactation (Öhman et al., 2002). Those data did not indicate any decline in TPM concentrations in late pregnancy compared to the baseline plasma concentrations. In fact, two of the women had higher TPM plasma concentrations at delivery than 2–3 weeks postpartum, a finding most probably explained by a systematic difference in the sampling time.

Table 3. Clinical course during pregnancy and pregnancy outcome

Patient number	Seizure frequency (3 months prior to and during pregnancy)	Pregnancy outcome		
		Uneventful delivery	Abnormalities at birth	Abnormalities after 1 year
1	GTC: 1/month prior to pregnancy, weekly in first and second trimester, 1/month in third Myoclonic: 1/month prior to and during pregnancy, less than 1/month in third trimester	Yes	No	No
2	None	Yes	No	No
3	GTC: Less than 1/month prior to and during pregnancy, none in third trimester Absences: Several/week prior to pregnancy and in first trimester, daily in second and third trimester	Yes	No	No
4a	None	Yes	No	No
4b	GTC: Less than 1/month prior to and during first and third trimester. None in second CPS: Increasing from weekly to daily throughout pregnancy	Yes	No	No
5	GTC: 2 prior to pregnancy, 2 in first trimester, monthly in second, none in third CPS: 5 prior to pregnancy, 1 in first trimester, daily in second, monthly in third	Yes	No	No
6	GTC: Less than 1/month prior to and during pregnancy, weekly in third trimester SPS/CPS: Weekly prior to and during pregnancy	Yes	No	No
7	SPS: Daily prior to and during first trimester[a]	Spontaneous abortion	n.a	n.a
8a	None prior to pregnancy GTC: 1 in second trimester, 1 in third CPS: 1 in first trimester, 1 in third	Yes	No	No
8b	None prior to pregnancy GTC: 1 in second trimester	Yes	No	No
9a	None	Yes	No	No
9b	None	Yes	Two small ventricular septum defects (VSDs)	Spontaneous closure almost complete
10	GTC: Monthly prior to pregnancy, 3 in second trimester, 6 in third	Yes	No	No
11	None prior to or during pregnancy	4 weeks preterm delivery	No	n.a.[a]
12	Sporadic CPS prior to pregnancy GTC: 1 in first trimester, 1 in third CPS: Increasing from weekly to daily throughout pregnancy	Yes	No	No

[a]Child less than 1 year of age at time of submitting this article; n.a, not applicable; SPS, simple partial seizures; CPS, complex partial seizures; GTC, generalized tonic–clonic seizures.

The main finding in our study is a significant decline of the dose-corrected TPM serum concentrations during pregnancy. However, the decline is less pronounced than what has been shown for other new AEDs, such as lamotrigine (see, Tomson & Battino, 2007), the monohydroxy derivative of oxcarbazepine (Christensen et al., 2006; Mazzucchelli et al., 2006), and for levetiracetam (Tomson et al., 2007; Westin et al., 2008). It should be noticed that our second and third trimester data are based on observations from only 11 and eight pregnancies, respectively, and additional studies are needed to confirm our observations.

The pregnant state induces a variety of physiological changes. Alterations in the plasma volume and the volume of distribution, altered drug protein binding, changes in the metabolic capacity, and increased renal blood flow with enhanced glomerular filtration rate are all important factors known to alter the pharmacokinetic properties of AEDs in pregnancy (Anderson, 2005; Tomson & Battino, 2007;

Brodtkorb & Reimers, 2008). TPM is eliminated mainly through the kidneys, and 70%–80% of an administered TPM dose is found unchanged in the urine (Lyseng-Williamson & Yang, 2008). Since glomerular filtration rate increases approximately 50% during pregnancy, renal TPM clearance is also likely to increase. The renal clearance of most drugs increase 20%–65% during pregnancy (Anderson, 2005). Thus, increased renal blood flow might, in itself, explain the observed decline in TPM serum concentrations during pregnancy. Another possible explanation might be increased drug metabolism during pregnancy. Approximately 20%–30% of a TPM dose undergoes hepatic metabolism. In patients receiving enzyme-inducing AEDs, the metabolized proportion of the given dose has been shown to rise to 50%–70% (Lyseng-Williamson & Yang, 2008). Thus, since TPM metabolism appears to be inducible, it cannot be ruled out that metabolic/endocrine changes during pregnancy may induce TPM metabolism.

It may be speculated that the observed decline in TPM C/D-ratio during pregnancy could be of clinical significance. Among the 15 pregnancies in our study, an increase in seizure frequency occurred in seven (Table 3), and TPM doses were increased in three (Table 1). A decline in seizure frequency was observed in two, and no change was observed in the remaining six. Among the seven pregnancies with increased seizure frequency, TPM monotherapy was used in three. In the remaining four, comedication consisted of other AEDs with a marked tendency to decrease during pregnancy (Tomson & Battino, 2007; Brodtkorb & Reimers, 2008); namely lamotrigine, oxcarbazepine, and levetiracetam. However, a clear statistical correlation between lowered TPM C/D-ratio and seizure breakthrough could not be demonstrated in the present study.

Among the enrolled women in the EURAP registry (n = 1956 pregnancies), two-thirds had a stable seizure frequency during pregnancy, whereas one-third experienced a change, half of them improved, the other half deteriorated (The EURAP Study Group, 2006). In our study, almost 50% of the women experienced a deterioration of seizure control in pregnancy. This observation may be biased due to patient selection. Women using TPM during pregnancy may have a more difficult-to-treat epilepsy than the average female patient in the EURAP registry.

Little has been known about the outcome of pregnancy following TPM treatment. Studies in rodents have caused concern (Ornoy et al., 2008). Preliminary reports in humans are difficult to interpret due to polytherapy, differences in their methods, and small pregnancy numbers. In the UK Epilepsy and Pregnancy Register, malformations were found in two of 28 live births (7.1%) in women with TPM monotherapy (Morrow et al., 2006). In another recent study, two of 41 women (4.9%), 29 with monotherapy, gave birth to children with malformations (Ornoy et al., 2008). The present study adds 14 completed consecutive pregnancies without major malformations (Table 3). The outcome release from the large-scale EURAP study is awaited.

In conclusion, our limited data suggest that dose-corrected TPM serum concentrations drop by 30%–35% in the second and third trimester of pregnancy. Consequently, serial measurements of TPM serum concentrations throughout pregnancy and the first weeks postpartum appear advisable, particularly in patients with brittle seizure control. A considerable number of women using TPM during pregnancy may experience a worsening of their seizure control. The present findings may be useful for appropriate counseling and follow-up of women who need treatment with TPM during pregnancy.

Acknowledgments

Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. E.B. and K.O.N. have received speaker fees and financial support for conference attendance from Janssen-Cilag, manufacturer of topiramate. The remaining authors have no conflicts of interest to disclose.

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PAPER III

Treatment With Antipsychotics in Pregnancy: Changes in Drug Disposition

Andreas A. Westin[1], Malin Brekke[2], Espen Molden[2,3], Eirik Skogvoll[4,5], Ingrid Castberg[6] and Olav Spigset[1,7]

Although pregnancy is known to cause changes in drug pharmacokinetics, little is known about its impact on serum levels of antipsychotics. In this study we retrospectively assessed 201 routine serum antipsychotic therapeutic drug monitoring concentration measurements obtained from a total of 110 pregnancies in 103 women, and 512 measurements from the same women before and after pregnancy. Serum concentrations in the third trimester were significantly lower than baseline for quetiapine (−76%; confidence interval (CI), −83%, −66%; $P < 0.001$) and aripiprazole (−52%; CI, −62%, −39%; $P < 0.001$), but not for olanzapine (−9%; CI, −28%, +14%; $P = 0.40$). For the remaining antipsychotics (perphenazine, haloperidol, ziprasidone, risperidone, and clozapine), our dataset was limited, but it indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol. Even though the clinical consequence of the serum concentrations decline remains to be elucidated, our results warrant close clinical monitoring throughout pregnancy, preferentially supported by therapeutic drug monitoring.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Drug pharmacokinetics may undergo pronounced alterations in pregnancy, and dose requirements may change. For antipsychotics, only case reports are available to provide guidelines for dose adjustments.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We used routine therapeutic monitoring data to explore the impact of pregnancy on serum levels of antipsychotics.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ With data from 110 pregnancies, this study is by far the largest to date. There was a pronounced decline in the serum concentrations of quetiapine and aripiprazole, whereas concentrations of olanzapine did not change. The study also provides limited data for other antipsychotics.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ Our results warrant reconsideration of the general advice of using the prepregnancy "minimum effective dose" of antipsychotics during pregnancy. Increased drug clearance in pregnancy may cause subtherapeutic concentrations. Although the clinical implications of the lowered drug levels require further research, our results call for close clinical monitoring of all patients using antipsychotics in pregnancy.

Whether or not to prescribe antipsychotic drugs during pregnancy is a challenging dilemma. One the one hand, treating the mother necessarily implies exposing the fetus to the drug, thereby potentially causing harmful effects to the unborn child. On the other hand, abstaining from treatment puts the mother at risk of a worsened psychiatric condition, with the dangers this involves for the mother and child. Weighing these options against each other, the recommendation has often been to discontinue treatment, especially during the first trimester.[1] However, during the past decade more safety data have accumulated suggesting that antipsychotics are relatively safe to use in pregnancy.[1–3] It has also been demonstrated that discontinuing ongoing maintenance treatment for severe mood and psychotic disorders during pregnancy carries a high risk of disease recurrence.[2] Thus, for women with substantial psychiatric morbidity and good treatment response, maintained use of an antipsychotic during pregnancy might often represent the best risk–benefit option.

When a decision has been made to commence or continue pharmacological treatment during pregnancy, there is a paucity of data to ensure appropriate dosing. Numerous physiological changes occur during pregnancy, some of which may cause changes in drug disposition, e.g., due to alterations in body weight, plasma volume, hepatic metabolic capacity, and renal function.[4–7] Thus, the right drug dose for a woman prior to conception or for the patient group in general is not necessarily the right dose during pregnancy. For antipsychotics, evidence on changes in drug disposition in pregnancy is extremely

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Table 1 The study population

	Mode of administration	Number of serum drug concentration measurements			Number of pregnancies	Number of women
		During pregnancy	First 12 weeks following delivery	At baseline		
Quetiapine	PO	66	11	144	35	33
Olanzapine	PO	47	11	84	29	28
Aripiprazole	PO	31	5	44	14	12
Perphenazine	IM	13	1	40	8	8
Perphenazine	PO	7	1	17	7	5
Clozapine	PO	10	2	114	4	4
Ziprasidone	PO	7	4	14	3	3
Risperidone	PO	5	1	9	4	4
Haloperidol	PO	5	0	2	2	2
Other antipsychotics[a]	PO/IM	10	0	8	10	10
Total		201	36	476	110[b]	103[b,c]

PO, oral; IM, intramuscular depot injections.
[a]Other antipsychotics included chlorprothixene ($n = 5$), risperidone intramuscular depot injections ($n = 2$), flupentixol ($n = 1$), zuclopenthixol ($n = 1$), and levomepromazine ($n = 1$). [b]In six pregnancies serum drug concentrations were measured for two different antipsychotics in the same pregnancy. [c]Four women contributed with two pregnancies each, and one woman contributed with four pregnancies.

scarce and confined to one case report on quetiapine[8] and a small cases series on aripiprazole.[9] The aim of this study was to elucidate to what extent pregnancy affects serum concentrations of antipsychotic drugs in a large target population in a naturalistic setting.

RESULTS

Table 1 and **Figure 1** provide an overview of all serum drug concentration measurements and pregnancies included in the study. Overall, the mean duration of pregnancy was 274 ± 19 days, and the mean maternal age at delivery was 29.8 ± 6.6 years.

The model estimates for the $\log_e$-transformed serum concentrations across pregnancy for nine antipsychotics are given in **Supplementary Table S1**. **Table 2** shows the estimated serum concentrations at baseline and by trimester during pregnancy, as well as the relative changes from baseline in percent. For the three drugs with the most observations (>10 pregnancies) there were statistically significant decreases in serum concentrations in mid-third trimester compared to baseline for quetiapine (−76%) and aripiprazole (−52%), but not olanzapine. For the remaining drugs our dataset was more limited (**Table 2**).

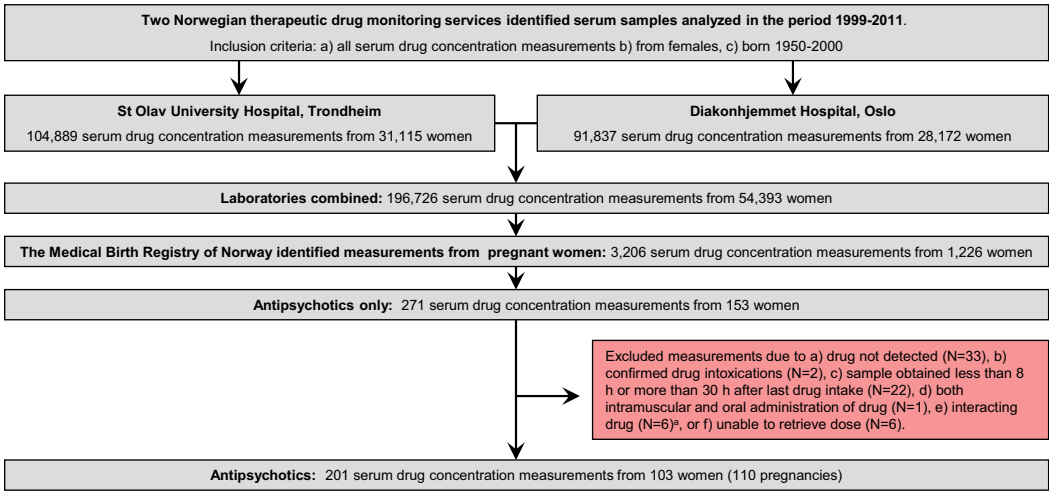

Figure 1 Flow of sample identification and inclusion of therapeutic drug monitoring samples of antipsychotic drugs obtained during pregnancy. [a]Six measurements were excluded due to the following drug interactions: clozapine + fluvoxamine ($n = 1$), olanzapine + carbamazepine ($n = 1$), perphenazine + paroxetine ($n = 2$), perphenazine + fluoxetine ($n = 1$), and risperidone + fluoxetine ($n = 1$). [Color figure can be viewed at wileyonlinelibrary.com]

Table 2 Serum antipsychotic concentrations across pregnancy

			Estimated serum concentrations													
			Baseline	1st trimester		2nd trimester		3rd trimester								
	Number of pregnancies	Dose[a]	Conc	Conc	Change	Conc	Change	Conc	CI low	CI high	Change	CI low	CI high		
Measure	*N*	mg/day	ng/mL	ng/mL	%	ng/mL	%	ng/mL	ng/mL	ng/mL	%	%	%	*P*[c]	CF[b]
Quetiapine	35	400	75.6	58.7	−22	32.5	−57	18.0	12.6	25.7	−76	−83	−66	<0.001	2.61
Olanzapine	29	10	21.3	20.9	−2	20.1	−6	19.3	15.3	24.3	−9	−28	+14	0.40	3.20
Aripiprazole[d]	14	15	232.4	204.2	−12	151.1	−35	111.7	87.6	142.6	−52	−62	−39	<0.001	2.23
Perphenazine IM	8	7[e]	2.1	1.8	−15	1.2	−41	0.9	0.6	1.2	−59	−71	−42	—	2.48
Perphenazine PO	7	30	2.5	2.1	−18	1.3	−48	0.8	0.4	1.9	−67	−85	−25	—	2.48
Clozapine	4	300	418.6	399.7	−5	358.8	−14	322.1	227.3	456.6	−23	−46	+9	—	3.06
Ziprasidone	3	80	56.7	50.1	−12	37.5	−34	28.0	13.1	59.9	−51	−77	+6	—	2.42
Risperidone[d]	4	5	24.4	23.2	−5	20.7	−15	18.4	8.9	37.7	−25	−63	+54	—	2.35
Haloperidol	2	8	5.0	4.4	−12	3.2	−35	2.4	1.3	4.5	−52	−74	−10	—	2.66

The column "baseline" provides the model estimates for the dose-adjusted serum antipsychotic concentrations at day 0 (nonpregnant). The first, second, and third trimester columns provide the model estimates for the concentrations in gestational weeks 6, 20, and 34, respectively. The columns "change" provide the change from baseline concentration, in percent.
IM, intramuscular depot injections; PO, oral; Conc, concentration; CI, 95% confidence interval limits.
[a]Dose = defined daily dose. [b]Serum concentrations in mass units can be converted to molar units by multiplication with the conversion factor (CF). Nanomol/L = ng/mL x CF. [c]*P*-value for the regression line in the statistical model. *P*-values are not given for drugs with observations from less than 10 pregnancies. [d]For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e., aripiprazole plus dehydroaripiprazole and risperidone plus 9-hydroxyrisperidone). [e]For perphenazine intramuscular depot injections the 7 mg dose corresponds to ~100 mg perphenazine decanoate given every 14 days.

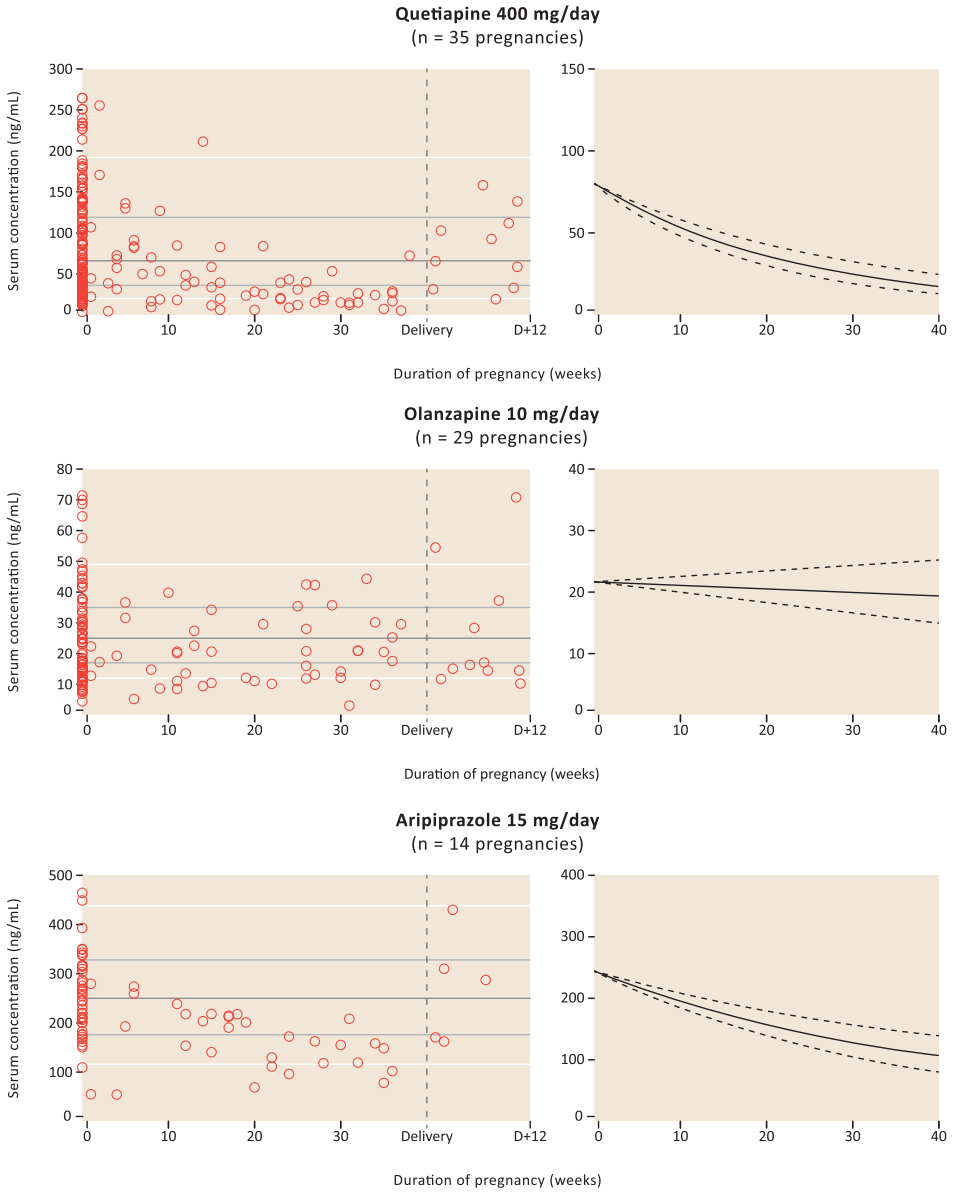

Figure 2 Quetiapine, olanzapine, and aripiprazole serum concentrations in pregnancy. The figures to the left show each of the observed serum concentrations of the study, adjusted to the doses presented in the figure headings. Measurements from the same women in a nonpregnant state (baseline values) are shown as pregnancy week 0. Delivery is set to pregnancy week 40. Thus, for a woman who gave birth in week 38, a sample drawn *t* weeks after delivery would be shown *t* weeks to the right of the vertical dashed line. For aripiprazole the concentrations shown represent the active moiety (parent drug + metabolite). Six outliers for quetiapine are not shown in the figure. These were four measurements at week 0 (concentrations of 554, 536, 470, 440 ng/mL), one measurement at week 7 (302 ng/mL), and one measurement at week D+3 (315 ng/mL). The horizontal lines represent the median (dark gray), 25- and 75-percentiles (light gray), and 10- and 90-percentiles (white) for concentration measurements (adjusted to the doses presented in the figure headings) for all women aged 18–45 years from the St Olav University Hospital TDM database. The figures to the right show the expected serum concentrations across pregnancy for women using the antipsychotic doses presented in the figure headings. The regression lines are shown with solid lines, and the 95% confidence limits with dashed lines. For aripiprazole the concentrations shown represent the active moiety (parent drug + metabolite). D+12 = Delivery + 12 weeks. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3 Parent compound / metabolite ratios across pregnancy

		Estimated ratios							
		Baseline	1st trimester		2nd trimester		3rd trimester		
Ratio	Number of pregnancies N	ratio	ratio	%	ratio	%	ratio	%	P^a
Quetiapine / norquetiapine	12	0.44	0.42	−5	0.38	−15	0.34	−24	0.16
Olanzapine / N-demethylolanzapine	8	6.87	8.06	+17	11.70	+70	16.98	+147	—
Aripiprazole / dehydroaripiprazole	14	3.20	2.99	−6	2.57	−20	2.20	−31	<0.001
Clozapine / norclozapine	2	1.31	1.34	+2	1.41	+8	1.49	+14	—
Risperidone / 9-hydroxyrisperidone	4	0.09	0.08	−8	0.07	−24	0.05	−37	—

Only analyses with available metabolite data (see Table S2) are included. The column "baseline" provides the model estimates for the parent compound / metabolite ratio at day 0 (nonpregnant). The first, second, and third trimester columns provide the model estimates for the parent compound / metabolite ratios in gestational weeks 6, 20, and 34, respectively.

[a]*P*-value for the regression line in the statistical model. *P*-values are not given for drugs with observations from fewer than 10 pregnancies.

Individual concentrations related to gestational week, as well as when the women were not pregnant, are shown in **Figure 2** for quetiapine, olanzapine, and aripiprazole, and in **Figure S1** for the remaining drugs. The figures also show the percentile values derived from the concentrations in the general female reference population. The regression lines with 95% confidence limits showing the expected serum concentrations for each antipsychotic drug during pregnancy are shown in **Figure 2** for quetiapine, olanzapine, and aripiprazole, and in **Figure S2** for the remaining drugs.

For quetiapine, olanzapine, aripiprazole, clozapine, and risperidone, metabolites had been measured in all or some samples, allowing us to study parent compound / metabolite ratios. The original $\log_e$-transformed values (**Table S2**) are converted to actual ratios in **Table 3**. For aripiprazole, there was a statistically significant decline in parent compound / metabolite ratio throughout pregnancy (**Table 3**).

DISCUSSION

The present study, including antipsychotic serum concentration data from 110 pregnancies, is by far the largest study to date regarding the disposition of antipsychotics in pregnancy. The principal finding is that the serum concentrations of quetiapine and aripiprazole decrease by more than 50% during pregnancy, a change that is likely to be of clinical relevance. In contrast, olanzapine concentrations did not change during pregnancy. For the remaining antipsychotics (perphenazine, haloperidol, ziprasidone, risperidone, and clozapine) our dataset was limited, although some information may be drawn from **Figures S1** and **S2**.

A myriad of physiological changes may occur during pregnancy and alter drug disposition.[4–7] Changes in volume of distribution may alter the concentration after the first dose and the loading dose requirements, and alter peak concentrations and elimination half-life,[6] but generally have little influence on the trough concentration at steady state. Concentrations of binding protein for drugs in plasma (albumin and α-1-acid glycoprotein) may be reduced by 20–30% in the third trimester.[10] This effect might be relevant for antipsychotics, which are all highly protein bound,[11] but it is still not sufficient to fully explain the extent of changes in the observed total drug levels, nor the differences between them. Renal filtration in pregnancy is also considered to be of minor relevance for our results, as all drugs in our study have a negligible degree of unmetabolized urinary excretion (<10%).[11]

In contrast, we consider changes in hepatic clearance to be of high relevance for our results. Since all drugs in our study are predominantly eliminated by hepatic cytochrome P450 (CYP) enzymes,[11–13] we believe these enzymes to be the crucial explanatory factor for changes (or lack thereof) in the observed drug concentrations in our study. Our findings are also largely in line with what could be expected from data on the activity of drug-metabolizing enzymes in pregnancy.

Quetiapine is metabolized mainly by CYP3A4,[13] an enzyme known to be induced during pregnancy.[4–7] Similar drug concentration declines in pregnancy have also been reported for other CYP3A4 substrates,[14,15] and also in a previous case report for quetiapine.[8] In that publication, trough serum levels of quetiapine in the first, second, and third trimester were 42%, 55%, and 53% lower than the nonpregnant levels, respectively. Our study confirms and extends the observed decline in that case report, and suggests that the quetiapine serum concentration decline in the third trimester may in fact be even greater than previously described.[8] We also found that the observed decline in our study was not caused by use of different formulations of quetiapine (extended release vs. immediate release), as a separate analysis for each of these groups provided similar results (data not shown).

Aripiprazole is metabolized by CYP2D6 to the active metabolite dehydroaripiprazole, which is in turn further metabolized by CYP3A4.[13] CYP2D6 expression and activity also increase during pregnancy,[4–6,16] and for other CYP2D6 substrates a 2–13-fold increase in clearance has been described.[17] A previously published case series described aripiprazole plasma concentrations in three pregnancies in two women.[9] Aripiprazole concentrations declined by more than two-thirds during pregnancy, and returned to baseline within 2–3 weeks after delivery.[9] In the present study, we found a 52% reduction of the active moiety (aripiprazole + dehydroapiprazole) concentration in the third trimester compared to baseline, and a similar reduction also for the parent compound as such (data not shown).

None of the remaining drugs of our study have previously been investigated with respect to changes in serum levels in pregnancy. From a theoretic perspective, the major CYP enzymes involved in

the metabolism of perphenazine (CYP2D6), ziprasidone (CYP3A4), and haloperidol and risperidone (CYP2D6 and CYP3A4)[13] suggest that their serum levels could decline in pregnancy, as they do for aripiprazole and quetiapine. We did find a trend towards declining perphenazine concentrations in pregnancy. For instance, in **Figure S2** almost all serum perphenazine intramuscular concentrations in pregnant women were below the median (gray line) of the nonpregnant population. This is particularly interesting, as nonadherence is not an issue for intramuscular administration. Also for oral perphenazine and haloperidol, a corresponding trend was found. However, it should be emphasized that the number of observations was low, thus being vulnerable to variations caused by confounding factors in single subjects, such as outlier observations due to nonadherence or erroneous dose information. For ziprasidone and risperidone the numbers were even smaller and the trends even less clear.

For olanzapine and clozapine the estimates for alterations in the serum concentrations during pregnancy were closer to zero, indicating no or little change. Although the confidence intervals for these estimates are narrower for olanzapine (with observations from 29 pregnancies) than for clozapine (with observations from four pregnancies only) it is interesting to note that both these drugs have a metabolism largely dependent on CYP1A2,[13] an enzyme that has been shown to have a *decreased* activity during the second and third trimesters.[6,18] This could explain why our results for these drugs may differ from the others. Another explanation that cannot be excluded is reduced cigarette smoking during pregnancy, which would also result in decreased CYP1A2 activity.[19] Unfortunately, information on smoking habits was not available in our dataset.

It is also of importance to explore when and how maternal serum concentrations return to normal following delivery. Some researchers have provided evidence of a postpartum drop in metabolic capacity that could result in briefly elevated drug concentrations (i.e., higher than baseline) for some antidepressants during the first 6–8 weeks following delivery.[20–24] Due to few postpartum observations our study can neither confirm nor rule out that such a refractory period occurs for antipsychotic agents. However, our data do indicate that serum concentrations return back to baseline values within the first weeks after delivery (**Figure 2** and **Figure S1**), as also shown previously for aripiprazole.[9]

Our study has some limitations that need to be addressed. First, as we did not have access to any clinical data we do not know whether the reduced serum antipsychotic concentrations actually caused clinical deterioration. Although it is reasonable to assume that this could occur, and similar studies on antidepressants[8,20,23,25] have indicated such an effect, this subject should be explored in future studies on antipsychotics.

Second, it is unknown to which degree patients were adherent to the prescribed medication; a challenge that not least could be of relevance during pregnancy.[26–28] In particular, for the drugs with low number of observations in our study, the results could be vulnerable to variations caused by variable adherence in single subjects. However, all measurements with a serum concentration of zero ($n = 33$, **Figure 1**) were excluded from the study. Also, even though an increased degree of nonadherence during pregnancy would cause lower concentrations, we consider it unlikely that such a situation should be confined to, e.g., quetiapine and aripiprazole and not to olanzapine.

Third, our study relies on correct information from the requesting clinicians regarding drug doses. Although all measurements lacking information on drug dose ($n = 6$, **Figure 1**) were excluded from the study, we cannot exclude that erroneous dose information exists among the remaining measurements, and again, the results for drugs with the lowest number of observations would be most vulnerable to variations caused by this factor.

Fourth, there is a variability of the time interval from last dose to sampling. Ideally, this interval should have been standardized to 12 h, and all values calculated to such using drug-specific elimination half-lives, as in a previous publication from our group.[29] However, information for calculating the time interval was often missing on the requisition form, and excluding all such measurements would result in loss of precious data. We believe that some of the variability in our results (**Figure 2** and **Figure S1**) derives from variations in these time intervals, an inevitable factor given the retrospective nature of our study, but we found no systematic difference in the postdose time interval between measurements in pregnancy and measurements at baseline (**Table S3**).

Fifth, the statistical model used in our study assumes a linear change in the logarithm of serum concentrations for each week of pregnancy. It is possible that the changes in pregnancy may be better described by a more sophisticated function. However, we did not investigate this possibility further.

On the other hand, this study also has some strengths, the most obvious being the very large sample size. Due to the ethical issues involved in clinical drug trials during pregnancy,[30,31] retrospective studies of samples taken in a naturalistic setting are often the only available tool to obtain information on drug disposition in pregnancy. Due to the variability often seen in observational studies a large sample size is crucial, such as in our use of data from two large routine therapeutic drug monitoring (TDM) services over a time span of 11 years. It is also a strength that we could link the TDM data a national birth registry, thereby allowing precise identification of pregnant women in the dataset, and making misclassification of gestational week unlikely.

In conclusion, our results show that for quetiapine and aripiprazole, there is a pronounced decline in serum concentrations throughout pregnancy. These changes may warrant reconsideration of using the prepregnancy "minimum effective dose" during pregnancy. As drug clearance increases subtherapeutic drug levels may ensue, potentially exposing the mother and unborn child to both the medication and the illness. Based on our data, doubling the daily dose may be needed in order to compensate for the increased drug clearance in the third trimester for these drugs. For olanzapine, serum concentrations seem to remain largely unchanged during pregnancy, and dose adjustments might not be necessary. For the remaining antipsychotics our dataset was more limited, but indicates that concentrations may decline at least for perphenazine and possibly also for haloperidol. Even though the clinical consequence of the serum concentration declines remains to be elucidated, our results call for close clinical monitoring of all patients using antipsychotics in pregnancy. If available, therapeutic drug monitoring could be undertaken, preferentially beginning when the woman is well prior to or in an early stage of

pregnancy. The measured drug level could be used as that woman's target concentration across pregnancy, in a similar approach to what is already used for lamotrigine and other anticonvulsants.[32]

METHODS

A model relating dose-adjusted serum concentrations of antipsychotics to gestational week was developed in order to elucidate to what extent pregnancy affects drug disposition. To study infant outcomes was beyond the scope of the present study.

Therapeutic drug monitoring data

The Norwegian healthcare system has a tradition for routine TDM of psychotropic drugs.[33] After obtaining approval from the Regional Committee for Medical and Health Research Ethics, the Norwegian Centre for Research Data (Data Protection Official), the Norwegian Directorate of Health, and the Medical Birth Registry of Norway (MBRN) publication council, serum concentration data for antipsychotic drugs were collected from the two largest TDM services for psychotropic drugs in Norway (i.e., Department of Clinical Pharmacology at St. Olav University Hospital in Trondheim, and Center for Psychopharmacology at Diakonhjemmet Hospital in Oslo). The antipsychotics TDM data contain serum concentrations measured in a naturalistic setting from psychiatry inpatients and outpatients. In addition to measured serum concentrations, the TDM databases contain information obtained from the requisition forms, such as the prescribed antipsychotic drug dose, its mode of administration, time of last drug intake, time of blood sampling, and types and doses of concomitant drugs. Although a complete set of information is not always provided by the requisitioner, it is a general recommendation from the laboratory that TDM samples are collected as trough levels at steady state.

The Medical Birth Registry of Norway (MBRN)

The MBRN is a population-based registry containing information on all births in Norway since 1967.[34] The registry is based on compulsory notification of every birth or late abortion from 12 completed weeks of gestation onwards. The report form includes date of delivery and length of pregnancy as well as other information regarding the mother and infant.

Data linkage and available data

First, a combined laboratory TDM file was created, containing all serum concentration measurements (for any drug) in the period October 1999 to December 2011 for all women of reproductive age (i.e., born 1950–2000). The file consisted of a total of 196,726 measurements from 54,393 women (**Figure 1**). Using the unique 11-digit identification number assigned to all individuals living in Norway, the MBRN could identify all pregnant women in the dataset. By applying this procedure, 3,206 measurements from 1,226 pregnant women were identified (**Figure 1**). For the current study we retrieved the following information: the personal identification number, the measured drug serum concentration, time of last dose, time of sampling, drug dose, concomitant drug use, other clinical information, name of the responsible physician, gestational week at the time of sampling, and date of delivery.

Inclusion criteria

The basis of the present study is all samples analyzed for an antipsychotic agent, defined as a drug classified in the World Health Organization Anatomical Therapeutic Chemical group N05A,[35] except lithium. Then 271 measurements from 153 pregnant women were available (**Figure 1**). Measurements were excluded if 1) no drug was detected, 2) the sample was obtained as a result of drug intoxication, 3) the sample was obtained less than 8 hours or more than 30 hours after last oral drug intake, 4) both intramuscular and oral formulation of the drug was used at the same time, or 5) there was concomitant use of a known interacting drug (i.e., an interaction that, based upon information from an interaction database,[36] was described as having a major or moderate pharmacokinetic effect on the antipsychotic agent). If the requisition form lacked information on drug dose the authors contacted the responsible physician, who attempted to obtain this information from the medical record. If we were unable to retrieve this information, the measurement was excluded. The final dataset consisted of 201 serum drug concentrations from 103 women (**Figure 1**). The individual drugs available are listed in **Table 1**.

Control samples

Having identified the pregnant women and their individual pregnancy periods in the extracted data file, we used the original TDM databases to retrieve serum concentration measurements before and after pregnancy from the same women, to serve as baseline observations. Identical inclusion and exclusion criteria as presented above were used, and 512 measurements were identified (**Table 1**). Thirty-six of these were from the first 12 weeks following delivery (i.e., in the "returning to baseline" phase). These measurements were not used in the statistical model, but are included in **Figure 2** and **Figure S1**. The remaining 476 measurements were used for the statistical comparisons. Drugs with less than five observations in total during pregnancy or with no baseline observations for any of the subjects were excluded from further analysis. These drugs are categorized as "other antipsychotics" in **Table 1**.

In order to provide an estimate of expected antipsychotic drug concentrations in a female reference population, we extracted antipsychotic serum concentration data from all women aged 18–45 from the St. Olav University Hospital TDM database, using identical inclusion and exclusion criteria as presented above. These data were not included in the statistical analyses, but the 10, 25, 50, 75, and 90 percentile values derived from these data are shown in **Figure 2** and **Figure S1** for comparison purposes. The numbers of measurements upon which these calculations were based were 1,563 for quetiapine, 4,317 for olanzapine, 569 for aripiprazole, 521 for oral perphenazine, 600 for perphenazine intramuscular depot injections, 3,810 for clozapine, 804 for ziprasidone, 1,071 for risperidone, and 241 for haloperidol.

Determination of antipsychotic concentrations in serum

Quantification of the antipsychotic and metabolite concentrations was performed with liquid chromatography-mass spectrometry/tandem mass spectrometry. The analytical methods have been described in more detail previously.[37,38] During the timespan of the study, some assays had been improved and adjusted, but all modifications were cross-validated.

Data analysis

Serum concentrations in ng/mL were divided by the daily dose used by the woman at the time of sampling, providing a serum concentration/dose ratio, and then multiplied by the defined daily dose (DDD), which is the assumed average maintenance dose per day for that drug used for its main indication in adults.[35] This procedure assumes that pharmacokinetics of the drugs are dose-proportional over the typical dosing ranges, and provides an intra- and interindividually comparable concentration for each drug. All concentrations presented and discussed in this article, including tables and figures, are dose-adjusted to the DDD of the drug. The DDDs for the various drugs are given in **Table 2**.

As the concentration distributions were found to be heavily right-skewed, the logarithm of the concentrations was employed as the outcome variable in the statistical model, to achieve near normality. Since multiple measurements were available from the same patient, a linear mixed model was used. The model assumes that each individual patient possesses a random intercept (i.e., an individual "offset") in addition to being affected by the gestational week at the time of sampling. Baseline measurements were set to gestational week 0 in the model, as shown in **Figure 2** and **Figure S1**. This way, the effect of gestational week on concentration compared to baseline is estimated for each drug. The model assumes that changes in drug concentrations on the logarithmic scale are linear throughout pregnancy.

For drugs where both the parent drug and the metabolite were measured, parent drug/metabolite concentration ratios during pregnancy were compared to baseline values as described above; ratios were log transformed and fitted into a linear mixed model, estimating the baseline ratios and effect of each gestational week.

All model parameters, including variance components, were estimated by the method of maximum likelihood using STATA 13 (Statsoft, Tulsa, OK) command "mixed." Data are presented as means with 95% confidence intervals. $P < 0.05$ was considered statistically significant, if derived from observations from more than 10 pregnancies.

Additional Supporting Information may be found in the online version of this article.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

A.A.W., E.M., and O.S. designed the research; A.A.W., M.B., and I.C. performed the research; A.A.W., E.S., and O.S. analyzed the data, A.A.W. wrote the first manuscript draft, and all authors revised it critically, and approved the final manuscript.

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SUPPLEMENTARY TABLES

Table S1. The model parameter estimates for log_e-transformed serum antipsychotic concentrations

	Number of pregnancies	Dose	Log_e serum drug concentration (in ng/mL)							
			Intercept				Change per gestational week			
Measure	N	mg/day	Estimate	95% CI low	95% CI high	p	Estimate	95% CI low	95% CI high	p
Quetiapine	35	400	4.326	4.121	4.531	<0.001	-0.042	-0.053	-0.032	<0.001
Olanzapine	29	10	3.059	2.856	3.262	<0.001	-0.003	-0.010	0.004	0.40
Aripiprazole[a]	14	15	5.449	5.320	5.577	<0.001	-0.022	-0.029	-0.014	<0.001
Perphenazine IM	8	7[b]	0.743	0.574	0.913	-	-0.026	-0.036	-0.016	-
Perphenazine PO	7	30	0.933	0.599	1.266	-	-0.032	-0.056	-0.009	-
Clozapine	4	300	6.037	5.800	6.274	-	-0.008	-0.018	0.003	-
Ziprasidone	3	80	4.038	3.494	4.582	-	-0.021	-0.043	0.002	-
Risperidone[a]	4	5	3.196	2.633	3.760	-	-0.008	-0.030	0.013	-
Haloperidol	2	8	1.607	1.188	2.025	-	-0.022	-0.040	-0.003	-

The "Intercept" columns show the model estimates for the log_e-transformed serum antipsychotic concentrations (dose-adjusted) at day 0 (in the column "estimate") and the corresponding confidence limits for each drug estimated. The "Change per gestational week" columns provide an estimate for the change in the log_e-transformed concentration for each gestational week, with corresponding confidence limits for each drug. The estimated concentration in gestational week *t* is thus calculated by the following equation: Serum concentration (week *t*) = $e^{\text{the intercept estimate} + (t \cdot \text{change per gestational week estimate})}$. **Table 2** provides an overview of the estimated concentrations for each trimester.

P-values are not given for drugs with observations from less than 10 pregnancies.

PO = oral. IM = intramuscular depot injections. CI = confidence interval.

[a] For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e aripiprazole plus dehydroaripiprazole and risperidone plus 9-hydroxyrisperidone).

[b] For perphenazine intramuscular depot injections the 7 mg dose corresponds to approximately 100 mg perphenazine decanoate given every 14 days.

Table S2. The study population and parameter estimates for $\log_e$ parent compound/metabolite ratios across pregnancy

	Number of serum drug concentration measurements		Number of pregnancies	Log_e parent drug/metabolite ratio							
	During pregnancy	At baseline		Intercept				Change per gestational week			
Ratio	N	N	N	estimate	95% CI low	95% CI high	p	estimate	95% CI low	95% CI high	p
Quetiapine / norquetiapine	27	68	12	-0.812	-1.178	-0.446	<0.001	-0.008	-0.020	0.004	0.16
Olanzapine / N-demethylolanzapine	9	6	8	1.928	1.273	2.582	-	0.027	-0.014	0.067	-
Aripiprazole / dehydroaripiprazole	31	44	14	1.163	0.943	1.382	<0.001	-0.011	-0.017	-0.005	<0.001
Clozapine / norclozapine	6	65	2	0.268	0.176	0.359	-	0.004	-0.008	0.016	0.56
Risperidone / 9-hydroxyrisperidone	5	9	4	-2.448	-3.438	-1.458	-	-0.014	-0.044	0.016	-

Only measurements with available metabolite data are included. The "intercept" columns shows the model estimates for the $\log_e$-transformed parent compound / metabolite ratio at day 0 (in the column "estimate") and the corresponding confidence limits for each drug estimated. The "Change per gestational week"-columns provide an estimate for the change in the $\log_e$-transformed ratio for each week of pregnancy, with corresponding confidence limits for each drug estimated. The estimated ratio in gestational week *t* is thus calculated by the following equation: Ratio (week *t*) $=e^{\text{the intercept estimate} + (t \cdot \text{week estimate})}$. **Table 3** provides an overview of the estimated ratios for each trimester.

P-values are not given for drugs with observations from less than 10 pregnancies.
CI = confidence interval.

Table S3. Post-dose time intervals for serum concentration measurements

	Phase	Measurements with available information on post dose time	Post dose time (hours, mean ± SD)
Quetiapine	Pregnancy Baseline	46 of 66 (70%) 96 of 144 (67%)	12.3 ± 2.0 12.6 ± 2.3
Olanzapine	Pregnancy Baseline	32 of 47 (68%) 62 of 84 (74%)	13.8 ± 2.6 13.4 ± 2.2
Aripiprazole	Pregnancy Baseline	12 of 31 (39%) 28 of 44 (64%)	16.8 ± 4.9 21.3 ± 4.4
Perphenazine	Pregnancy Baseline	3 of 7 (43%) 9 of 17 (53%)	12.7 ± 0.9 12.2 ± 1.5
Clozapine	Pregnancy Baseline	8 of 10 (80%) 95 of 114 (83%)	13.4 ± 1.7 13.8 ± 2.5
Ziprasidone	Pregnancy Baseline	5 of 7 (71%) 11 of 14 (79%)	17.0 ± 2.1 17.9 ± 6.2
Risperidone	Pregnancy Baseline	5 of 5 (100%) 9 of 9 (100%)	13.8 ± 1.6 13.3 ± 1.5
Haloperidol	Pregnancy Baseline	1 of 5 (20%) 2 of 2 (100%)	11.0 ± 0.0 12.0 ± 0.0

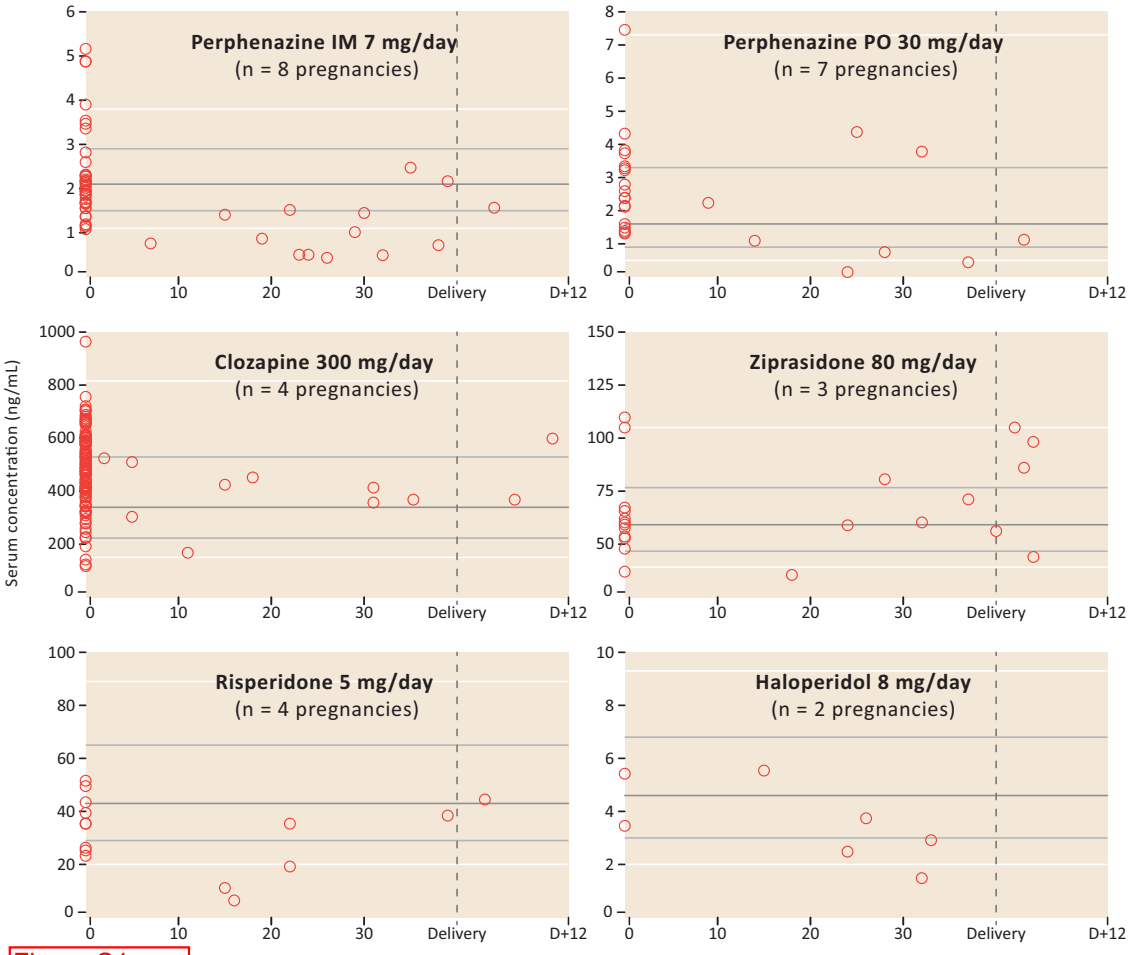
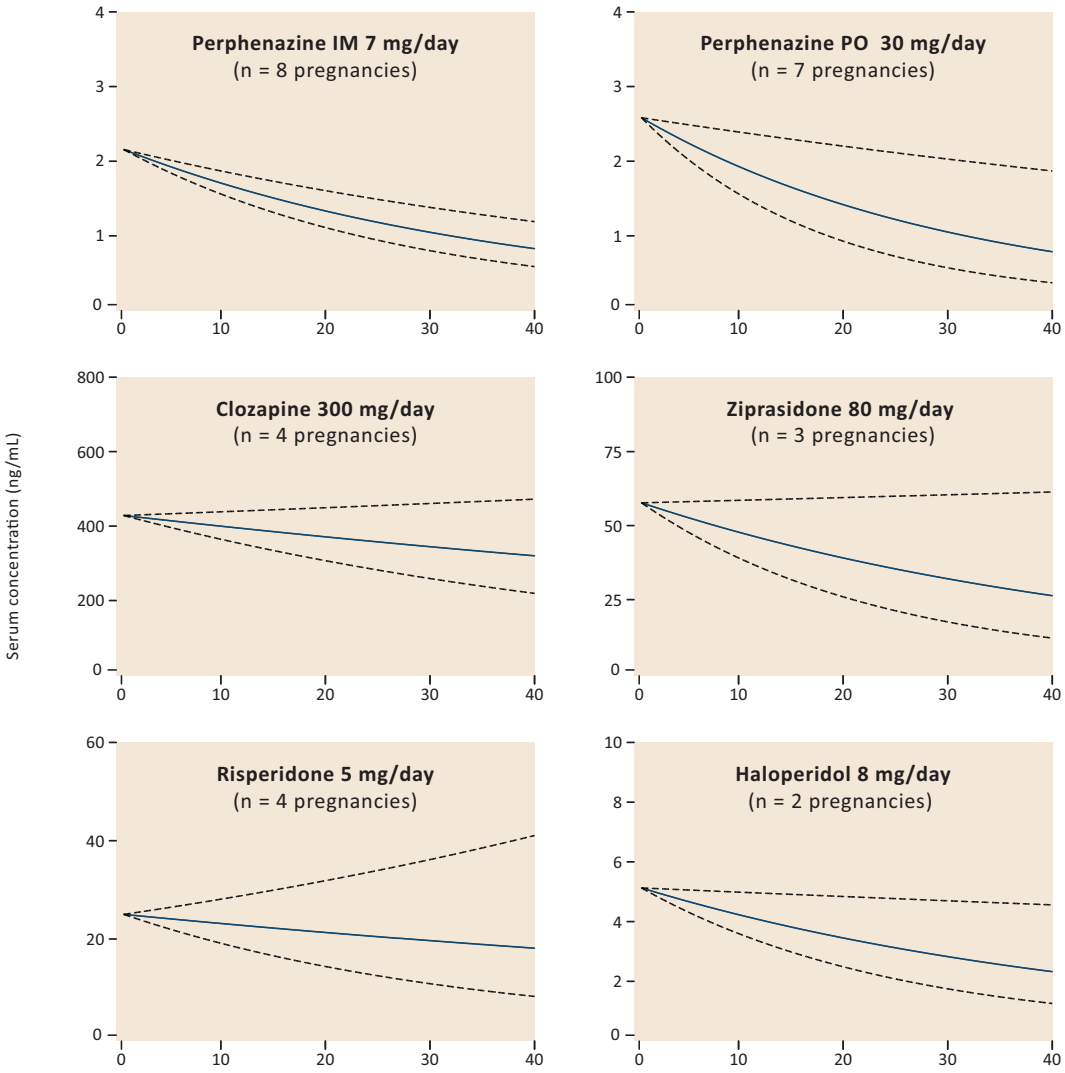

Perphenazine IM 7 mg/day
(n = 8 pregnancies)
Perphenazine PO 30 mg/day
(n = 7 pregnancies)
Clozapine 300 mg/day
(n = 4 pregnancies)
Ziprasidone 80 mg/day
(n = 3 pregnancies)
Risperidone 5 mg/day
(n = 4 pregnancies)
Haloperidol 8 mg/day
(n = 2 pregnancies)
Delivery
D+12
Serum concentration (ng/mL)
Duration of pregnancy (weeks)

Figure S1


Perphenazine IM 7 mg/day
(n = 8 pregnancies)
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(n = 4 pregnancies)
Ziprasidone 80 mg/day
(n = 3 pregnancies)
Risperidone 5 mg/day
(n = 4 pregnancies)
Haloperidol 8 mg/day
(n = 2 pregnancies)
Serum concentration (ng/mL)
Duration of pregnancy (weeks)

Figure S2

PAPER IV

PLOS ONE

RESEARCH ARTICLE

Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: Changes in drug disposition

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Abstract

Background

Pregnancy may cause changes in drug disposition. The clinical consequences may be profound and even counterintuitive; in some cases pregnant women may need more than twice their usual drug dose in order to maintain therapeutic drug levels. For antidepressants, evidence on drug disposition in pregnancy is scarce. The aim of this study was to determine the effects of pregnancy on serum levels of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine in a large and naturalistic patient material, in order to provide tentative dose recommendations for pregnant women.

Methods

Using patient data from two routine therapeutic drug monitoring (TDM) services in Norway with linkage to the national birth registry, dose-adjusted serum drug concentrations of SSRIs and venlafaxine during pregnancy were compared to the women's own baseline (non-pregnant) values, using a linear mixed model.

Findings

Overall, the TDM databases contained 196,726 serum concentration measurements from 54,393 women. After data linkage and drug selection (SSRIs or venlafaxine only), we identified 367 analyses obtained from a total of 290 pregnancies in 281 women, and 420 baseline observations from the same women. Serum concentrations in the third trimester were significantly lower than baseline for paroxetine (–51%; 95% confidence interval [CI], –66%, –30%; p<0.001), fluvoxamine (–56%; CI, –75%, –23%; p = 0.004) and citalopram (–24%; CI, –38%, –7%; p = 0,007), and higher than baseline for sertraline (+68%;

CI, +37%, +106%; p<0.001). For escitalopram, fluoxetine and venlafaxine concentrations did not change significantly.

Conclusions

For paroxetine and fluvoxamine the pronounced decline in maternal drug serum concentrations in pregnancy may necessitate a dose increase of about 100% during the third trimester in order to maintain stable concentrations. For fluoxetine, venlafaxine, citalopram, escitalopram and sertraline, the present study indicates that dose adjustments are generally not necessary during pregnancy.

Introduction

Depression in pregnancy is a serious and often overlooked condition. It is estimated to impact 14–23% of pregnant women, which makes it more prevalent in pregnancy than conditions like gestational diabetes (18%) and preeclampsia (3–5%) [1]. Maternal depression may cause a vast range of consequences for the mother and fetus, such as substance abuse, preterm delivery, neonatal intensive care unit admissions, poor bonding between mother and baby, adverse effects on the growth and neurodevelopment of the offspring, and even increased risk of maternal suicide [1, 2]. Therefore, in cases of severe or relapsing depression, the use antidepressants is considered favorable compared to exposing mother and child to untreated depressive illness [1–3].

Choosing the appropriate drug dose for a pregnant woman is a difficult balancing act between optimum maternal treatment and minimal fetal exposure, and is further complicated by the physiological changes that occur during pregnancy. Alterations in maternal body weight, plasma volume, hepatic metabolic capacity and renal function may cause changes in drug disposition [4–7]; thus the right drug dose for a woman prior to conception or for the patient group in general is not necessarily the right dose during pregnancy. For antidepressants, evidence on changes in drug disposition in pregnancy is rather scarce and generally consists of a few studies with 10–20 patients or less for each drug [7–25]. The aim of this study was to elucidate to which extent pregnancy affects serum concentrations of selective serotonin reuptake inhibitors (SSRIs) and venlafaxine in a large target population in a naturalistic setting, in order to provide tentative dose recommendations for pregnant women.

Methods

Serum concentration data

After obtaining approval from the Regional Committee for Medical and Health Research Ethics in Mid Norway, the Norwegian Centre for Research Data (Data Protection Official), the Norwegian Directorate of Health and the Medical Birth Registry of Norway (MBRN) publication council, serum concentration data for antidepressants were collected from the two largest TDM services for psychotropic drugs in Norway (i.e. Department of Clinical Pharmacology at St. Olav University Hospital in Trondheim, and Center for Psychopharmacology at Diakonhjemmet Hospital in Oslo). As the Norwegian health care system has a tradition for routine therapeutic drug monitoring (TDM) of psychotropic drugs [26], a considerable amount of TDM data could be retrieved from these databases. The antidepressant TDM data contain serum concentration measurements taken in a naturalistic setting from psychiatry inpatients

and outpatients. In addition to measured serum concentrations, the databases contain information obtained from the requisition forms, such as the prescribed antidepressant dose, time of last drug intake, time of blood sampling, and types and doses of concomitant drugs.

The Medical Birth Registry of Norway (MBRN)

The Medical Birth Registry of Norway (MBRN) is a population based registry containing information on all births in Norway since 1967 [27]. The registry is based on compulsory notification of every birth or late abortion from 12 completed weeks of gestation onwards. The report form includes date of delivery and length of pregnancy as well as other information regarding the mother and infant.

Data linkage and identification of cases

First, a combined laboratory TDM file was created, containing all serum concentration measurements (for any drug) in the period October 1999 –December 2011 for all women of reproductive age (i.e. born 1950–2000). The file consisted of a total of 196,726 analyses from 54,393 women (Fig 1). Using the unique 11-digit identification number assigned to all individuals living in Norway, the MBRN could identify all pregnant women in the TDM data set. By applying this procedure, 3206 analyses from 1,226 pregnant women were identified (Fig 1). For the current study we retrieved the following information: the personal identification number, the drug analysed, the measured drug serum concentration, time of last dose, time of sampling, drug dose, concomitant drug use, other clinical information, name of the responsible physician, gestational week at the time of sampling (calculated from the sampling date and the pregnancy onset date as determined by obstetric ultrasound if available, or by last menstruation), and date of delivery.

Inclusion criteria

The basis of the present study is all samples analyzed for an SSRI (defined as a drug classified in the World Health Organization Anatomical Therapeutic Chemical group N05AB [28]), plus venlafaxine. Then, 436 analyses from 339 pregnant women were available (Fig 1). Analyses

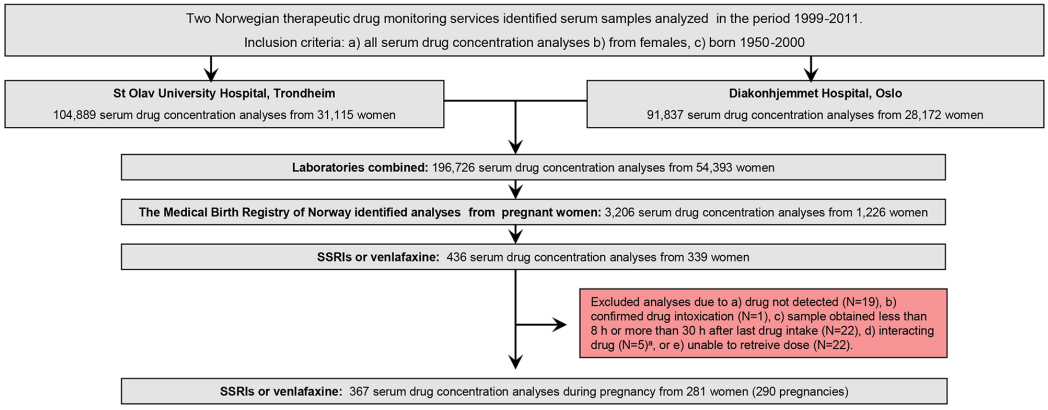

Fig 1. Inclusion flow chart. Sample identification and inclusion of therapeutic drug monitoring samples of selective serotonin reuptake inhibitors and venlafaxine obtained during pregnancy.

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Table 1. The study population.

	Number of serum drug concentration analyses			Number of pregnancies	Number of women
	During pregnancy	First twelve weeks following delivery	At baseline		
Escitalopram	110	3	161	97	95
Citalopram	78	3	80	58	58
Fluoxetine	53	2	49	43[a]	41
Sertraline	56	5	52	37	34
Venlafaxine	36	1	44	33[a]	33
Paroxetine	29	6	31	20	19
Fluvoxamine	5	2	3	3	3
Total	367	22	420	290[a]	281[a,b,c]

[a] In one pregnancy both fluoxetine and venlafaxine were analyzed (at different times) due to change in medication.

[b] One woman used paroxetine in one pregnancy and fluoxetine in another.

[c] Nine women were pregnant twice.

https://doi.org/10.1371/journal.pone.0181082.t001

were excluded if a) no drug was detected, b) the sample was obtained as a result of drug intoxication, c) the sample was obtained less than 8 hours or more than 30 hours after last drug intake, or d) there was concomitant use of a known interacting drug (i.e. a drug listed in a national drug interaction database as having a major or moderate effect on the plasma concentration on the antidepressant in question [29]). If the requisition form lacked information on drug dose the authors contacted the responsible physician, who attempted to obtain this information from the medical record. If we were unable to retrieve this information, the analysis was excluded. The final data set consisted of 367 serum drug concentrations from 281 women (290 pregnancies) (Fig 1). The individual drugs available are listed in Table 1.

Identification of observations from non-pregnant state in the same subjects

Having identified the pregnant women and their individual pregnancy periods in the extracted data file, we used the original TDM databases to retrieve serum concentration measurements before and after pregnancy from the same women, to serve as baseline observations for each of the included subjects. Identical inclusion and exclusion criteria as presented above were applied, and 442 analyses were identified (Table 1). Twenty-two of these were from the first twelve weeks following delivery (i.e. in the "returning to baseline" phase) [19, 22]. These analyses were not used in the statistical model, only for visual comparison. The remaining 420 analyses were used for the statistical comparisons.

Reference population

In order to provide an estimate of expected antidepressant concentrations in a female reference population, we extracted antidepressant serum concentration data from the same time period for all women aged 18–45 from the St. Olav University Hospital TDM database, using identical inclusion and exclusion criteria as presented above. These data were not included in the statistical analyses, but the 10, 25, 50, 75 and 90 percentile values derived from these data are used for visual comparison purposes. The numbers of analyses upon which these calculations were based were 3265 for escitalopram, 1975 for citalopram, 410 fluoxetine, 1552 for sertraline, 1453 for venlafaxine, 557 for paroxetine and 59 for fluvoxamine.

Determination of antidepressant concentrations in serum

Quantification of the drug concentrations was performed with liquid chromatography-mass spectrometry/tandem mass spectrometry (LC-MS/LC-MS/MS). The analytical methods have been described in more detail previously [30, 31]. In brief, the drugs were extracted from serum by liquid-liquid extraction, using a mixture of hexane, acetonitrile and/or butanol, or dichloromethane and isopropanol. Thereafter, the analytes were separated on C18 columns using methanol, acetonitrile, formic acid or ammonium acetate as mobile phases, and quantified on LC-MS or LC-MS-MS systems. Calibration curves were constructed for each assay with drug-free human serum by the addition of varying concentrations of the antidepressants and their respective metabolites. All methods were linear in the therapeutic range of the various drugs, and the limits of quantification were generally well below the lower limits of the reference intervals. The inter-day coefficients of variability were in most cases below 10%. During the timespan of the study, some assays had been improved and adjusted, but all modifications were cross-validated with the previous method used for the same drug.

Data analysis

Serum concentrations in ng/mL were divided by the daily dose used by the woman at the time of sampling, providing a serum concentration/dose ratio, and then multiplied by the defined daily dose (DDD), which is the assumed average maintenance dose per day for that drug used for its main indication in adults [28]. This procedure provides an intra- and interindividually comparable concentration for each drug. All concentrations presented and discussed in this article, including tables and figures, are dose-adjusted to the DDD of the drug. The DDDs for the various drugs are given in Table 2.

Table 2. Serum antidepressant concentrations across pregnancy.

	Dose[a]	Estimated serum concentrations												CF[b]
		Base-line	1st trimester		2nd trimester		3rd trimester							
Measure	mg/ day	conc	conc	change	conc	change	conc	CI low	CI high	change	CI low	CI high	p[c]	
		ng/mL	ng/mL	%	ng/mL	%	ng/mL	ng/mL	ng/mL	%	%	%		
Escitalopram	10	9.3	9.4	+1	9.7	+4	9.9	8.0	12.3	+7	-14	+32	0.55	3.08
Citalopram	20	30.4	28.9	-5	25.8	-15	23.0	18.7	28.2	-24	-38	-7	0.007	3.08
Fluoxetine[d]	20	167.1	163.2	-2	154.4	-8	146.1	107.4	198.8	-13	-36	+19	0.39	3.23/3.39[e]
Sertraline	50	9.0	9.8	+10	12.2	+36	15.1	12.3	18.5	+68	+37	+106	<0.001	3.27
Venlafaxine[d]	100	141.8	135.8	-4	122.9	-13	111.2	79.6	155.4	-22	-44	+10	0.16	3.61/3.80[f]
Paroxetine	20	33.5	29.6	-12	22.1	-34	16.5	11.5	23.6	-51	-66	-30	<0.001	3.04
Fluvoxamine	100	117.9	101.9	-14	72.5	-38	51.6	29.3	91.1	-56	-75	-23	0.004	3.14

The column "baseline" provides the model estimates for the serum antidepressant concentrations at day 0 (non-pregnant). The first, second and third trimester columns provide the model estimates for the concentrations in the middle of these trimesters (gestational weeks 6, 20 and 34), respectively. The columns "change" provide the change from baseline concentration, in percent. Conc = concentration. CI = 95% confidence interval limits.

[a] Dose = defined daily dose [28].

[b] Serum concentrations in mass units can be converted to molar units by multiplication with the conversion factor (CF). Nanomol/L = ng/mL x CF

[c] p-value for the regression line in the statistical model.

[d] For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e. fluoxetine plus norfluoxetine, and venlafaxine plus O-desmethylvenlafaxine).

[e] for fluoxetine and norfluoxetine, respectively.

[f] for venlafaxine and O-desmethylvenlafaxine, respectively.

https://doi.org/10.1371/journal.pone.0181082.t002

As the concentration distributions were found to be heavily right-skewed, the $\log_e$ of the concentrations was employed as the outcome variable in the statistical model to achieve near normality. Since multiple measurements were available from the same patient a linear mixed model was used. The model assumes that each individual patient possesses a random intercept (i.e. an individual "offset") in addition to being affected by the gestational week at the time of sampling. Baseline measurements were set to gestational week 0 in the model. Then, the effect of gestational week on concentration compared to baseline could be estimated for each drug.

For drugs where both the parent drug and the metabolite were measured, parent drug/metabolite concentration ratios during pregnancy were compared to baseline values as described above; ratios were $\log_e$-transformed and fitted into a linear mixed model, estimating the baseline ratios and the effect of each gestational week.

All model parameters, including variance components, were estimated by the method of maximum likelihood using STATA 13 command "mixed". Data are presented as means with 95% confidence intervals. P values less than 0.05 were considered statistically significant.

Results

Table 1 and Fig 1 provide an overview of all analyses and pregnancies included in the study. The model estimates for the $\log_e$-transformed serum concentrations across pregnancy are given in the S1 Table. Table 2 shows the estimated serum concentrations at baseline and by trimester during pregnancy, as well as the relative changes from baseline in percent. For paroxetine, fluvoxamine and citalopram concentrations in mid third trimester (gestational week 34) were 51%, 56% and 24% lower than baseline values, respectively. For venlafaxine, fluoxetine and escitalopram the concentration declines were smaller and not statistically significant. For sertraline, there was a 68% increase in mid third trimester concentrations compared to baseline (Table 2).

Individual concentrations related to gestational week, as well as when the women were not pregnant, are shown in Fig 2, together with the percentile values derived from the concentrations in the general female reference population. The measured concentrations in the time period from delivery to 12 weeks after delivery (i.e. in the "returning to baseline" phase) are also shown in Fig 2. The regression lines with 95% confidence limits showing the expected serum concentrations for each antidepressant drug during pregnancy are shown in Fig 3.

For escitalopram, citalopram, fluoxetine, sertraline and venlafaxine, metabolites had been measured in all or some samples, allowing us to study the parent compound / metabolite ratios. The original $\log_e$-transformed values (S2 Table) are converted to actual ratios in Table 3. For escitalopram, the parent compound / metabolite ratio in mid third trimester was 40% higher than baseline, whereas for fluoxetine and sertraline the mid third trimester ratios were 36% and 20% lower than baseline, respectively. There was also a trend towards a similar decline in parent compound / metabolite ratio for venlafaxine and citalopram, although the difference did not reach statistical significance (Table 3).

Discussion

The present study, including SSRI and venlafaxine serum concentration data from 290 pregnancies, is by far the largest study to date investigating the disposition of antidepressants during pregnancy. The main finding is that the serum concentrations of paroxetine and fluvoxamine drop to about 50% of pre-pregnancy levels, whereas sertraline concentrations increase by approximately 60–70% (Table 2). Venlafaxine, fluoxetine, citalopram and escitalopram concentrations remain largely unchanged.

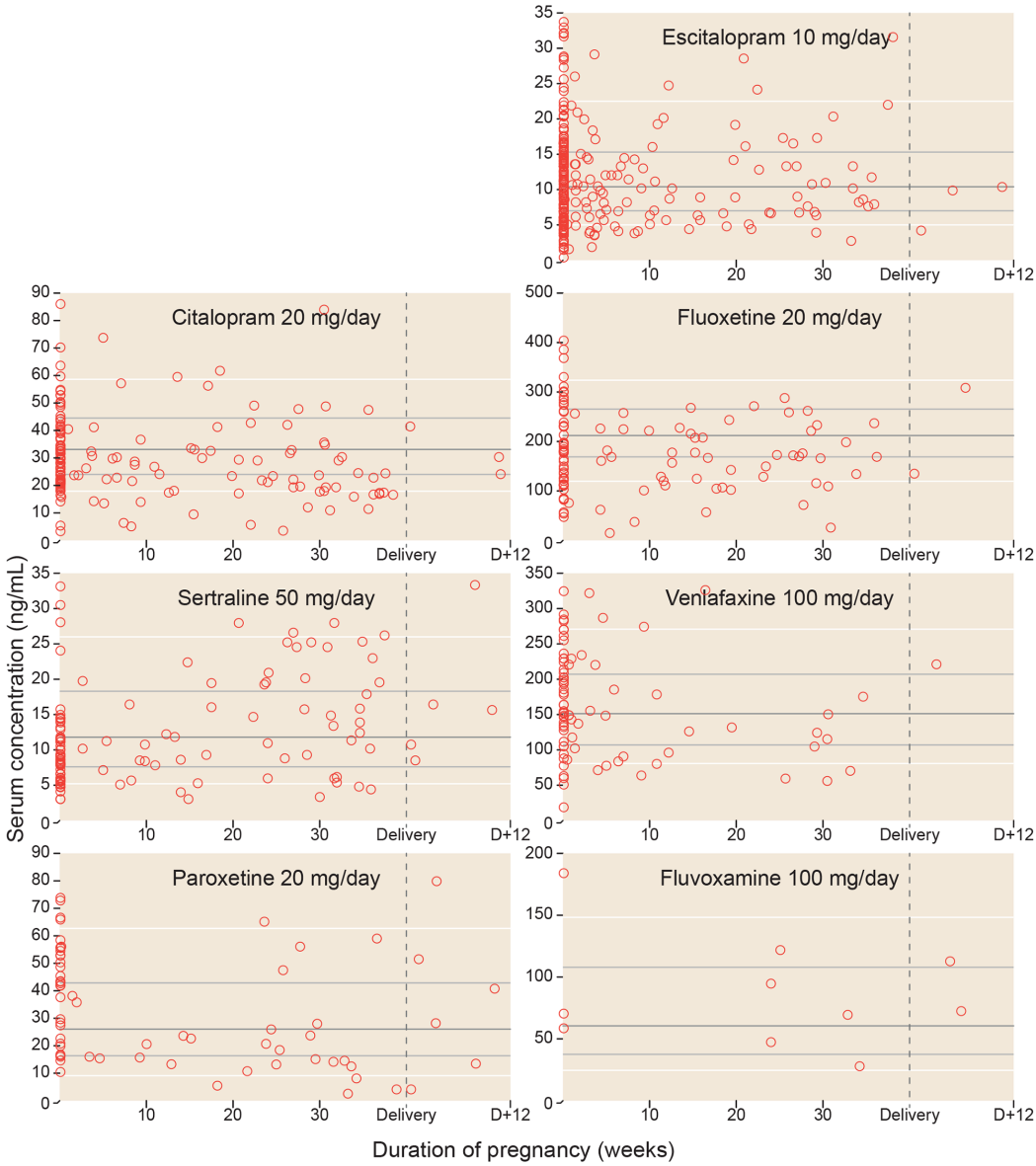

Fig 2. The serum antidepressant concentrations across pregnancy. The figure shows each of the observed serum concentrations in the study, adjusted to the doses presented in Table 2. Observations from the same women in non-pregnant state (baseline values) are shown as pregnancy week 0. Delivery is set to pregnancy week 40. Thus, for a woman who gave birth in week 38, a sample drawn x weeks after delivery would be shown x weeks to the right of the vertical delivery line. For fluoxetine and venlafaxine the concentrations shown represent the active moiety (parent drug + metabolite). Three outliers for escitalopram are not shown in the figure. These are one analysis in week 0 (concentration 36 ng/mL), one analysis in week 4 (concentration 36 ng/mL) and one analysis in week 5 (concentration 40 ng/mL). However, these concentrations are included in the statistical analyses. The horizontal lines represent the median (dark grey), 25 and 75 percentiles (light grey) and 10 and 90 percentiles (white) for dose-adjusted serum concentration measurements for all women aged 18–45 years from the St. Olav University Hospital TDM database. For further details, see Methods section.

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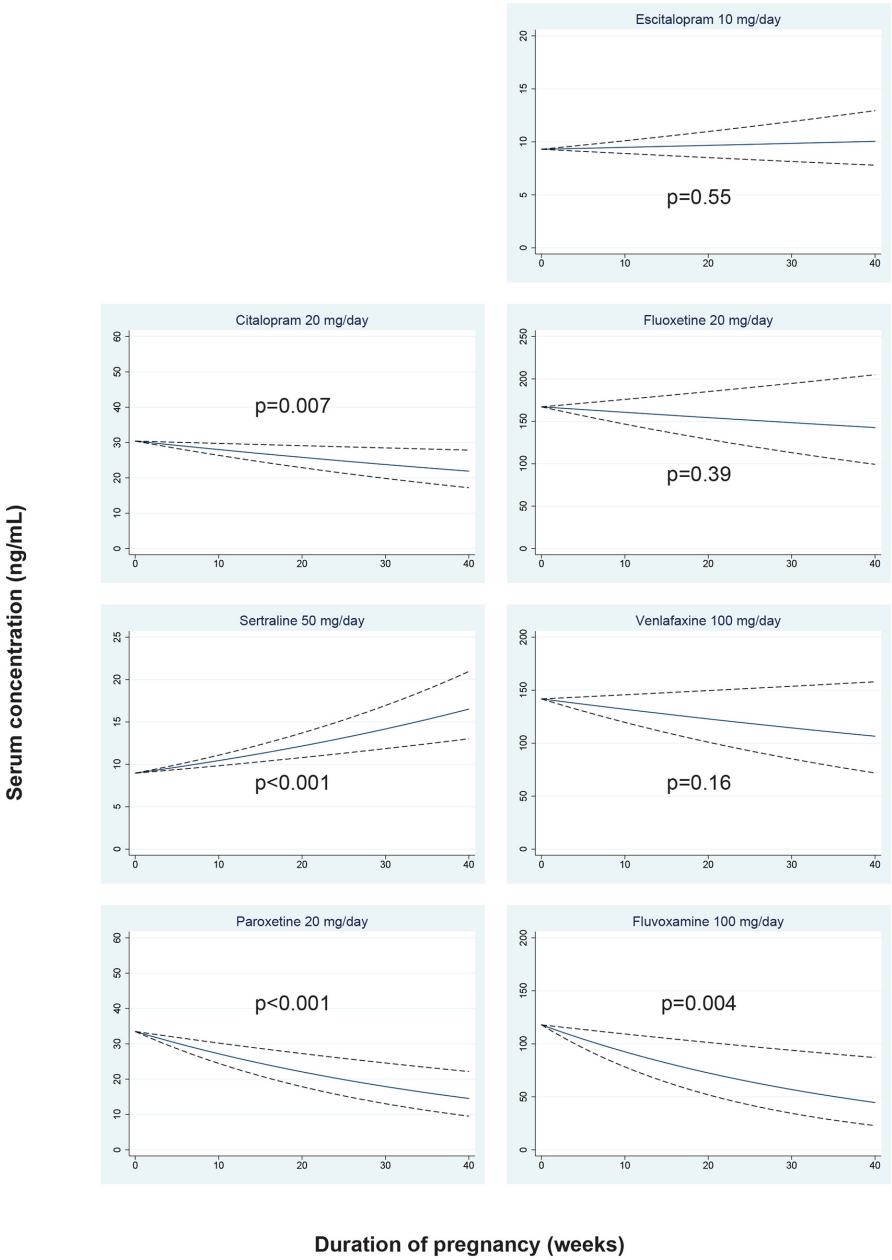

Fig 3. Regression lines for serum antidepressant concentrations across pregnancy. The figure shows the expected serum concentrations across pregnancy for women using the antidepressant doses presented in Table 2. The regression lines are shown in blue, and the 95% confidence limits with dashed black lines. For fluoxetine and venlafaxine the concentrations shown represent the active moiety (i.e. parent drug plus metabolite).

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Table 3. Serum metabolite concentrations and parent compound/metabolite ratios at baseline and in the third trimester.

	Number of serum drug concentration analyses		Number of pregnancies (number of women)	Dose[a] (mg/day)	Baseline conc.	Third trimester conc. (ng/mL)			Change from baseline conc.(%)			p[b]
	During pregnancy	At baseline			Estimate	Estimate	CI low	CI high	Estimate	CI low	CI high	
Escitalopram	63	98	61 (59)	10	8.4	10.5	7.5	14.6	+24	-11	+73	0.20
Desmethylescitalopram					4.7	4.1	3.2	5.2	-14	-32	+9	0.21
PMR					1.8	2.5	1.9	3.3	+40	+8	+82	0.012
Citalopram	50	26	37 (37)	20	32.3	19.7	14.5	26.7	-39	-55	-17	0.001
Desmethylcitalopram					12.6	8.5	6.6	11.0	-33	-48	-13	0.002
PMR					2.6	2.3	1.9	2.8	-13	-28	+5	0.16
Fluoxetine	53	49	43 (41)	20	77.7	53.3	34.5	82.3	-31	-56	+6	0.089
Norfluoxetine					83.7	83.7	61.6	112.8	0	-26	+35	0.98
PMR					1.0	0.6	0.4	0.9	-36	-55	-10	0.01
Sertraline	37	40	24 (21)	50	8.6	15.6	12.2	20.0	+83	+43	+133	<0.001
Desmethylsertraline					18.4	40.6	32.7	50.4	+120	+78	+173	<0.001
PMR					0.5	0.4	0.3	0.4	-20	-32	-5	0.009
Venlafaxine	36	44	33 (33)	100	35.8	21.4	12.6	36.1	-40	-65	+1	0.054
O-desmethylvenlafaxine					91.5	79.4	54.7	115.1	-13	-40	+26	0.45
PMR					0.4	0.3	0.2	0.5	-31	-59	+16	0.16

Only analyses with available metabolite data are included. The column "baseline conc." provides the model estimates for the serum concentration of each parent compound, its metabolite, and the parent compound / metabolite ratio (PMR) at day 0 (non-pregnant), with 95% confidence interval limits. The "third trimester conc." columns provide the model estimates for the same parameters in gestational week 34. The "change from baseline conc." columns provide the change from baseline concentrations to third trimester concentrations, in percent. Conc = concentration. CI = 95% confidence interval limits.

[a] Dose = defined daily dose.

[b] p-value for the regression line in the statistical model.

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Although a myriad of physiological changes that may alter drug disposition occur during pregnancy [4–7], total clearance is the primary determinant of the serum concentration at steady state. Since all drugs of our study are primarily eliminated by various hepatic cytochrome P450 (CYP) enzymes [32], we consider the activity of these enzymes to be the crucial explanatory factor for changes (or lack thereof) in the observed drug concentrations in our study.

Escitalopram disposition in pregnancy has previously been explored in five pregnancies in a study by Sit et al. [19]. They found only minor declines or no change in escitalopram concentrations throughout pregnancy. Our observations from 97 escitalopram pregnancies support those of Sit et al.; the concentration change estimate in our study was close to zero, with narrow confidence intervals. The clinical implication of our escitalopram findings is that dose adjustments is not expected to be necessary in pregnancy.

Citalopram is a chiral compound, consisting of S-citalopram (escitalopram, as described above) and the pharmacologically inactive R-citalopram [19]. The disposition of citalopram in pregnancy has previously been explored in two studies; Heikkinen et al. [13] found third trimester citalopram concentrations to be 42% lower than baseline values in 11 pregnancies, whereas Sit et al. [19] found third trimester concentrations to be 26% lower than baseline in two pregnancies. We found similar results; in our 58 citalopram pregnancies, there was a 24% reduction in third trimester concentrations compared to baseline. Interestingly, citalopram undergoes stereoselective metabolism; the pharmacologically active S-enantiomer

(escitalopram) is metabolized primarily by CYP2C19 [33, 34], whose activity may *decrease* in pregnancy [6, 7], whereas the inactive R-enantiomer is metabolized primarily by CYP2D6 [35], whose activity *increases* in pregnancy [4–6]. Thus, it seems likely that the decline in citalopram concentrations during pregnancy was caused primarily by a decline in the inactive R-citalopram concentrations. On the basis of these findings, we recommend that citalopram doses—as for escitalopram—as a rule of thumb should be kept stable throughout pregnancy, even though the serum concentrations may decline throughout pregnancy.

Paroxetine is metabolized mainly by CYP2D6 and CYP3A4 [36]. Its disposition in pregnancy has previously been explored in two studies [17, 20]; Brogtrop et al. included 12 pregnancies and found lower concentrations in the third trimester compared to postpartum, although no numbers were provided [17]. Ververs et al. included 74 pregnancies and estimated the effect of gestational week on paroxetine plasma concentrations, in a statistical model similar to ours. Interestingly, by including genotype data, they found that changes in paroxetine disposition in pregnancy depended not only on gestational week, but also on CYP2D6 genotype. For ultrarapid or extensive CYP2D6 metabolizers maternal paroxetine plasma concentrations declined by 0.3 ng/mL per gestational week (which translates to a 30% reduction in week 34 for our data). For intermediate and poor CYP2D6 metabolizers concentrations *increased* by 0.6 ng/mL per gestational week [20], suggesting that other mechanisms dominate when CYP2D6 activity is low. In our study, with data from 20 pregnancies, there was a 51% reduction in third trimester concentrations compared to baseline. Genotyping was not available in our material, but we assume that our population consisted mainly of extensive CYP2D6 metabolisers, which is the most prevalent genotype in a Caucasian population [37]. Thus, as a general recommendation for paroxetine use during pregnancy, physicians should be aware that concentrations are most likely to decline throughout pregnancy, and that increased dose requirement (roughly 100% in the third trimester) might ensue for most, but not all patients. Close clinical monitoring in pregnancy is thus warranted, preferentially supported by serum concentration measurements and possibly also CYP2D6 genotyping if available.

Fluvoxamine pharmacokinetics in pregnancy has not been investigated previously. Fluvoxamine is predominantly metabolized by CYP2D6 and CYP1A2 [38]. Since CYP2D6 activity increases in pregnancy [4–6] while CYP1A2 activity decreases [6, 39], it has been hypothesized that these effects might counterbalance each other with regards to net fluvoxamine concentrations in pregnancy [38]. However, the results from our three pregnancies do not indicate that this is the case. We found concentrations in third trimester to be 56% lower than baseline, suggesting CYP2D6 induction to be the dominating effect in pregnancy. Thus, the clinical advice regarding follow-up and testing for pregnant women would be the same as for paroxetine above.

For fluoxetine, both the parent compound and its primary active metabolite norfluoxetine are chiral compounds [22]. The enzymatic conversion of fluoxetine to norfluoxetine is stereoselective; the S-enantiomer is demethylated mainly by CYP2D6, and the equipotent R-enantiomer mainly by CYP2C9 [40]. Heikkinen et al. reported plasma concentration measurements from 11 pregnancies and found that third trimester concentrations of the active moiety (fluoxetine plus norfluoxetine) were 32% lower than baseline. They also found that the decline affected mainly the parent drug and to a lesser degree the metabolite. Similar observations were made in a study of nine pregnancies by Kim et al. [15], and 17 pregnancies by Sit et al. [22], who both also performed chiral analysis and found that S-fluoxetine concentrations declined more than R-fluoxetine in pregnancy. In our study chiral analyses were not undertaken, but our large sample size (43 pregnancies) supports the findings from previous studies in that fluoxetine concentrations decline in pregnancy, whereas norfluoxetine concentrations remain largely unchanged (Table 3). For the sum of the active moiety no major decline was observed in our

study (Table 2). The stereoselective fluoxetine disposition in pregnancy reported from previous studies [15, 22] (i.e. increased CYP2D6-induced bioconversion from S-fluoxetine to S-norfluoxetine, who are both pharmacologically active) may explain why antidepressant response did not deteriorate during pregnancy in previous studies [14, 22]. We therefore suggest, as a rule of thumb, that fluoxetine doses could be kept stable throughout pregnancy.

Venlafaxine is metabolized by CYP2D6 to its equipotent metabolite O-desmethylvenlafaxine (ODVM) [24]. In a case report by Klier et al., a more than 50% reduction in venlafaxine plasma levels was observed in pregnancy compared to baseline [16]. However, in a prospective study of seven pregnancies by ter Horst et al., only a 13% reduction in venlafaxine levels in pregnancy was found, with no change in ODMV levels [24]. Our study, with 33 pregnancies, confirms the latter observation; we found a trend towards a statistically significant decline in venlafaxine concentrations, but the metabolite concentrations did not change (Table 3), and the changes in total active moiety levels were not statistically significant (Table 2). These results may reflect increased CYP2D6-induced bioconversion from venlafaxine to ODMV in pregnancy. This shift is expected to be of minor or no clinical relevance, since parent drug and metabolite share equal antidepressant potency [24]. We therefore suggest venlafaxine doses could be kept stable throughout pregnancy.

For sertraline, in contrast to the other antidepressants, we found a statistically significant *increase* in serum concentrations in pregnancy compared to baseline (Table 2). Sertraline is metabolized by multiple enzymes, including CYP2B6, CYP2C19, CYP2C9, CYP2D6, monoamine oxidases, and several UGT enzymes [34, 41]. The effect of pregnancy on these enzymes is divergent and to some extent unknown [6]. However, since we found increasing levels of both sertraline and the metabolite desmethylsertraline in pregnancy (Table 3), we suspect CYP2C19 inhibition [41] to play a crucial role. Previous studies on sertraline disposition in pregnancy have been limited by small sample sizes (eight and six pregnancies, respectively [18, 19]) and variable/non-significant observations; some women had decreasing sertraline concentrations in pregnancy, some remained stable, and a few had increasing concentrations [18, 19]. The authors of one of these studies [18] suggested that genetic factors might explain the observed heterogeneity. However, in our study the changes did not appear very heterogeneous. The increasing concentrations were a general trend in the population and were not caused by outlier observations (S1 Fig) or by differences in sampling time (S3 Table). Still, due to the relatively wide reference range and low toxicity of sertraline [34], increasing concentrations do not necesarily imply a need for dose reduction. We therefore recommend that patients as a rule of thumb remain on their usual sertraline dose in pregnancy, and that dose adjustments should be made on the basis of clinical follow-up, if available combined with therapeutic drug monitoring.

For all therapeutic drugs used in pregnancy, it is also important to explore when and how maternal serum concentrations return back to normal following delivery. Some researchers have provided evidence of a postpartum drop in metabolic capacity that could result in briefly elevated concentrations (i.e. higher than baseline) of some antidepressants during the first 6–8 weeks following delivery [10, 13, 19, 22, 42]. Due to relatively few postpartum observations our study can neither conclusively confirm nor rule out that such a refractory period occurs, although our results indicate that serum concentrations return back to baseline values within the first weeks after delivery (Fig 2).

Our study has some limitations that need to be addressed. First, as we did not have access to any clinical data we do not know whether the reduced concentrations for some of the antidepressants actually caused clinical deterioration. Although it is reasonable to assume that this could occur, and some studies have provided evidence for a correlation between declining antidepressant concentrations and clinical deterioration in pregnancy [8, 9, 16, 19, 20, 22], others have failed to detect such a relationship [13, 14, 17, 25]. Thus, we need future studies to

address and explore the clinical consequences of the changing pharmacokinetics of antidepressants in pregnancy.

Second, it is unknown to which degree patients were adherent to the prescribed medication; a particular challenge during pregnancy [43]. However, all analyses with a serum concentration of zero (n = 19, Fig 1) were excluded from the study, and even though an increased degree of non-adherence during pregnancy would cause lower concentrations, we consider it being unlikely that such a situation should be confined to paroxetine, fluvoxamine and citalopram, and not for instance sertraline or escitalopram.

Third, the reason for why each serum concentration measurement was undertaken was in most cases unknown. Thus, due to the naturalistic nature of the study there is a possibility for selection bias in observations, e.g. an overrepresentation of pregnancy samples taken from patients with treatment failure. However, our impression is that serum concentration measurements in pregnancy are conducted in the same way as in non-pregnant patients, and that most samples are taken as routine follow-up. Also, we consider it being unlikely that such a selection bias should be confined to some drugs only.

Forth, there is a variability of the time interval from last dose to sampling. Ideally, this interval should have been standardized to 12 hours, and all values calculated to such using drug-specific elimination half-lives, as in a previous publication from our group [44]. However, the information needed for calculating the time interval was often missing on the requisition form, and excluding all such analyses would result in loss of precious data. We believe that some of the variability in our results (Fig 2) derives from variations in these time intervals, an inevitable factor given the retrospective nature of our study, but we found no systematical differences in the post-dose time interval for serum concentration measurements between pregnant and non-pregnant women (S3 Table).

On the other hand, this study also has some strengths, the most obvious being the very large sample size. Due to the ethical issues involved in clinical drug trials during pregnancy [45, 46], retrospective studies of samples taken in a naturalistic setting is one the very few available tools to obtain information on drug disposition in pregnancy. Due to the variability often seen in observational studies a large sample size is crucial, such as our use of data from two large routine TDM services over a time span of 12 years. It is also a strength that we could link the TDM data a national birth registry, thereby allowing precise identification of pregnant women in the data set, and making misclassification of gestational week highly unlikely.

In conclusion, our results show that in order to maintain stable serum drug concentrations in pregnancy, paroxetine and fluvoxamine doses may need to be roughly doubled in the third trimester. For escitalopram, citalopram, fluoxetine, venlafaxine and sertraline, dose adjustments are generally not necessary in pregnancy. If available, therapeutic drug monitoring could be a useful supplement to the individual clinical evaluation in pregnancy, in order to determine optimum dose for each patient. This applies to all drugs of the study, although most important for the drugs that seem to undergo the greatest changes (paroxetine, fluvoxamine and sertraline). Therapeutic drug monitoring should preferentially begin when the woman is well prior to or in an early stage of pregnancy. The measured drug level could be used as that woman's target concentration across pregnancy, in a similar approach as is already used for lamotrigine and other anticonvulsants [47].

Supporting information

S1 Table. The model parameter estimates for $\log_e$ serum antidepressant concentrations. The "Intercept" columns show the model estimates for $\log_e$ serum concentrations (dose-

adjusted) at day 0 in the column "Estimate", and the corresponding confidence limits and p-values for each drug estimated. The "Change per gestational week" columns provide an estimate for the change in the $\log_e$ serum concentration for each gestational week, with corresponding confidence limits and p-values for each drug. The estimated concentration in gestational week t is thus calculated by the following equation: Serum concentration (week t) = $e^{\text{the intercept estimate} + (t \cdot \text{change per gestational week estimate})}$. Table 2 provides an overview of the estimated concentrations for each trimester.
CI = confidence interval
[a] For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e fluoxetine plus norfluoxetine, and venlafaxine plus O-desmethylvenlafaxine).
(DOCX)

S2 Table. The model parameter estimates for $\log_e$ serum concentrations of parent compounds and their metabolites. Only analyses with available metabolite data (see Table 3) are included. The model estimates for the $\log_e$ serum concentrations (adjusted to the doses presented in Table 3) for each antidepressant and their metabolites, and the $\log_e$-transformed ratio between parent compound and metabolite (PMR). The "intercept" columns provide the baseline estimate (i.e. day 0 of pregnancy), and the corresponding confidence interval (CI) limits and p-values for each drug estimated. The "Change per gestational week" columns provide an estimate for the change in $\log_e$ concentration or $\log_e$ PMR for each week of pregnancy, with corresponding confidence limits and p-values for each drug estimated. The estimated serum concentration (or PMR) in gestational week t is thus calculated by the following equation: Serum concentration (week t) = $e^{\text{the intercept estimate} + (t \cdot \text{change per gestational week estimate})}$. Table 3 provides an overview of calculated serum concentrations and PMR for each trimester.
(DOCX)

S3 Table. Mean post-dose time intervals for serum concentration measurements.
(DOCX)

S1 Fig. Individual sertraline concentrations in pregnancy (n = 56). The figure displays the same sertraline serum concentrations as in Fig 2, but with separate symbols/colours for each subject.
(DOCX)

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S1 Table. The model parameter estimates for $\log_e$ serum antidepressant concentrations

		$\log_e$ serum drug concentration (in ng/mL)							
	Dose	Intercept				Change per gestational week			
Measure	mg/day	Estimate	95% CI low	95% CI high	p	Estimate	95% CI low	95% CI high	p
Escitalopram	10	2.230	2.101	2.360	<0.001	0.002	-0.004	0.008	0.55
Citalopram	20	3.415	3.270	3.559	<0.001	-0.008	-0.014	-0.002	0.007
Fluoxetine[a]	20	5.119	4.960	5.277	<0.001	-0.004	-0.013	0.005	0.39
Sertraline	50	2.193	1.990	2.396	<0.001	0.015	0.009	0.021	<0.001
Venlafaxine[a]	100	4.954	4.777	5.131	<0.001	-0.007	-0.017	0.003	0.16
Paroxetine	20	3.512	3.245	3.778	<0.001	-0.021	-0.031	-0.010	<0.001
Fluvoxamine	100	4.770	4.179	5.361	<0.001	-0.024	-0.041	-0.008	0.004

The "Intercept" columns show the model estimates for $\log_e$ serum concentrations (dose-adjusted) at day 0 in the column "Estimate", and the corresponding confidence limits and p-values for each drug estimated. The "Change per gestational week" columns provide an estimate for the change in the $\log_e$ serum concentration for each gestational week, with corresponding confidence limits and p-values for each drug. The estimated concentration in gestational week *t* is thus calculated by the following equation: Serum concentration (week *t*) = $e^{\text{the intercept estimate} + (t \cdot \text{change per gestational week estimate})}$. Table 2 provides an overview of the estimated concentrations for each trimester.

CI = confidence interval

[a] For drugs with clinically significant pharmacologically active metabolites the total active moiety concentrations were used for calculations (i.e fluoxetine plus norfluoxetine, and venlafaxine plus O-desmethylvenlafaxine).

S2 Table. The model parameter estimates for $\log_e$ serum concentrations of parent compounds and their metabolites

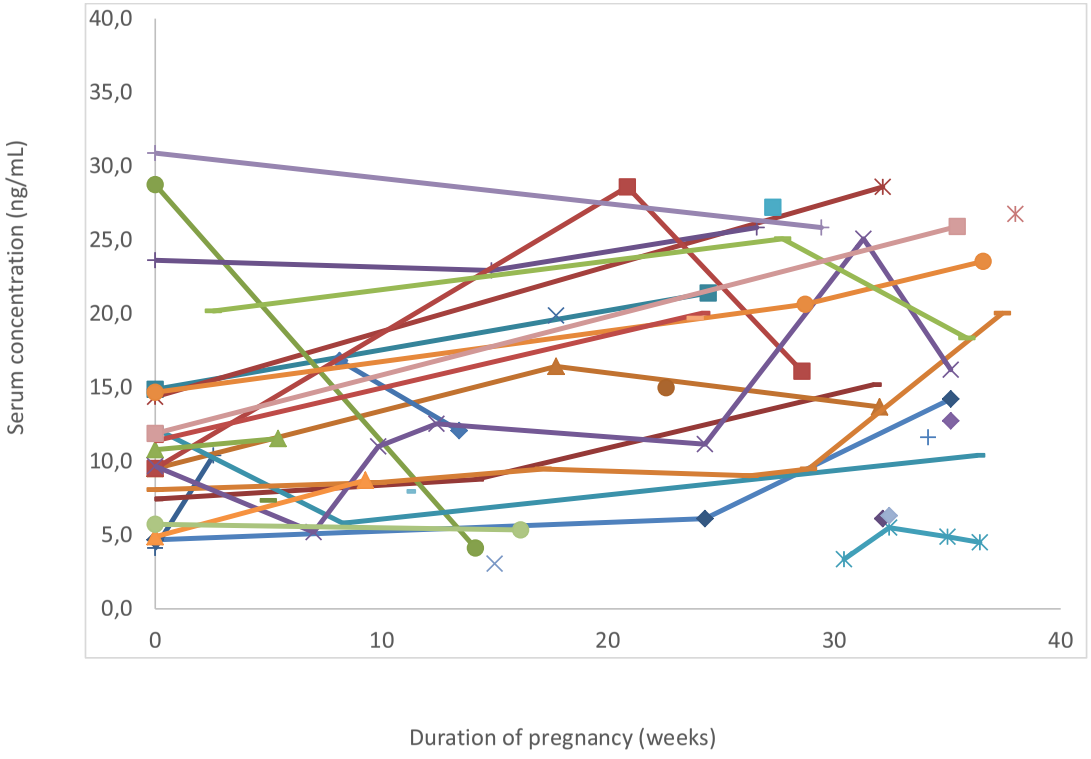
	Log_e serum concentration, or $\log_e$ PMR							
	Intercept				Change per gestational week			
	estimate	95% CI low	95% CI high	p	estimate	95% CI low	95% CI high	p
Escitalopram	2.129	1.964	2.295	<0.001	0.006	-0.003	0.016	0.20
Desmethylescitalopram	1.557	1.405	1.710	<0.001	-0.004	-0.011	0.002	0.21
PMR	0.581	0.417	0.745	<0.001	0.010	0.002	0.018	0.012
Citalopram	3.475	3.275	3.676	<0.001	-0.015	-0.024	-0.006	0.001
Desmethylcitalopram	2.534	2.363	2.706	<0.001	-0.012	-0.019	-0.004	0.002
PMR	0.973	0.826	1.119	<0.001	-0.004	-0.010	0.002	0.16
Fluoxetine	4.353	4.141	4.565	<0.001	-0.011	-0.024	0.002	0.089
Norfluoxetine	4.427	4.237	4.617	<0.001	0.000	-0.009	0.009	0.98
PMR	-0.045	-0.262	0.173	<0.001	-0.013	-0.023	-0.003	0.01
Sertraline	2.147	1.893	2.400	<0.001	0.018	0.010	0.025	<0.001
Desmethylsertraline	2.914	2.720	3.108	<0.001	0.023	0.017	0.030	<0.001
PMR	-0.764	-0.896	-0.631	<0.001	-0.006	-0.011	-0.002	0.009
Venlafaxine	3.577	3.239	3.914	<0.001	-0.015	-0.031	0.000	0.054
O-desmethylvenlafaxine	4.516	4.336	4.697	<0.001	-0.004	-0.015	0.007	0.45
PMR	-0.927	-1.287	-0.566	<0.001	-0.011	-0.026	0.004	0.16

Only analyses with available metabolite data (see Table 3) are included. The model estimates for the $\log_e$ serum concentrations (adjusted to the doses presented in Table 3) for each antidepressant and their metabolites, and the $\log_e$-transformed ratio between parent compound and metabolite (PMR). The "intercept" columns provide the baseline estimate (i.e. day 0 of pregnancy), and the corresponding confidence interval (CI) limits and p-values for each drug estimated. The "Change per gestational week" columns provide an estimate for the change in $\log_e$ concentration or $\log_e$ PMR for each week of pregnancy, with corresponding confidence limits and p-values for each drug estimated. The estimated serum concentration (or PMR) in gestational week t is thus calculated by the following equation: Serum concentration (week t) $= e^{\text{the intercept estimate} + (t \cdot \text{change per gestational week estimate})}$. Table 3 provides an overview of calculated serum concentrations and PMR for each trimester.

S3 Table. Mean post-dose time intervals for serum concentration measurements

	Phase	Post dose time (hours, mean ± SD)
Escitalopram	Pregnancy Baseline	20.1 ± 5.7 20.9 ± 6.0
Citalopram	Pregnancy Baseline	19.7 ± 5.7 20.1 ± 5.9
Fluoxetine	Pregnancy Baseline	20.2 ± 6.0 19.5 ± 6.6
Sertraline	Pregnancy Baseline	18.3 ± 6.4 19.6 ± 5.4
Venlafaxine	Pregnancy Baseline	19.1 ± 5.9 18.4 ± 6.3
Paroxetine	Pregnancy Baseline	20.9 ± 5.4 22.4 ± 5.2
Fluvoxamine	Pregnancy Baseline	13.0 ± 0.8 12.4 ± 0.4

S1 Fig. Individual sertraline concentrations in pregnancy (n = 56)



The figure displays the same sertraline serum concentrations as in Figure 2, but with separate symbols/colours for each subject.

PLOS ONE

CORRECTION

Correction: Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: Changes in drug disposition

Andreas Austgulen Westin, Malin Brekke, Espen Molden, Eirik Skogvoll, Olav Spigset

The affiliation for the 1st author is incomplete. Andreas Austgulen Westin is affiliated with #1 and #6.

There is an error in the caption for Fig 1, "Inclusion flow chart." Please see the complete, correct Fig 1 caption here.

Citation: Westin AA, Brekke M, Molden E, Skogvoll E, Spigset O (2018) Correction: Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: Changes in drug disposition. PLoS ONE 13(1): e0191508. https://doi.org/10.1371/journal.pone.0191508

Published: January 16, 2018

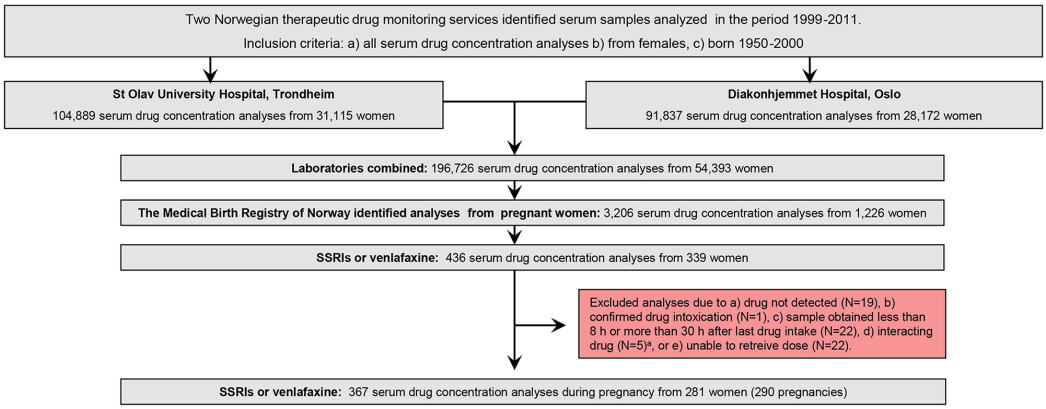


Fig 1. Inclusion flow chart. Sample identification and inclusion of therapeutic drug monitoring samples of selective serotonin reuptake inhibitors and venlafaxine obtained during pregnancy. [a] Five analyses were excluded due to the following drug interactions: sertraline + carbamazepine (n = 1), venlafaxine + bupropion (n = 4).

https://doi.org/10.1371/journal.pone.0191508.g001

Reference

1. Westin AA, Brekke M, Molden E, Skogvoll E, Spigset O (2017) Selective serotonin reuptake inhibitors and venlafaxine in pregnancy: Changes in drug disposition. PLoS ONE 12(7): e0181082. https://doi.org/10.1371/journal.pone.0181082 PMID: 28708853

Appendix 1-6

Appendix 1

REKVISISJON
Avdeling for klinisk farmakologi

ST. OLAVS HOSPITAL
UNIVERSITETSSYKEHUSET I TRONDHEIM

Rekvirentkode/HPR-nr.	Fødselsnr.: (11 siffer)
Rekvirent:	Navn:
Adr./Post:	Adr.:
Postnr.:	Postnr./sted:
Tlf.nr.:	☐ Institusjon/inneliggende ☐ Poliklinikk ☐ Allmenn-/spesialistpraksis
Kopi av svar til:	

Diagnose/kliniske opplysninger:

☐ Kvinne ☐ Mann

☐ Akuttforgiftning ☐ Bivirkninger ☐ Doseendring

☐ Misbruksdiagnostikk ☐ Rutinekontroll ☐ Terapisvikt

☐ Redusert nyrefunksjon: GFR: ____ ☐ Hjertesvikt ☐ Leversvikt ☐ Gravid

☐ **Øyeblikkelig hjelp**
Ring alltid vakthavende lege på tlf. 917 06 522

LEGEMIDDELANALYSER SERUM/BLOD

0 0 1

Ønskes analysert (sett x)		LEGEMIDLER Se baksiden for analyserepertoar Ved lite serum prioriteres analyser iht. rekkefølge	DOSERING Eksempel 200 mg/døgn eller 100 + 0 +100 mg	SISTE DOSE Dato og klokkeslett
	1			
	2			
	3			
	4			
	5			

Legg ved liste dersom pasienten bruker mange medisiner

RUSMIDDELANALYSER

Denne blanketten skal leses maskinelt. Bruk blå eller svart kulepenn. Kryss slik ☒ ikke slik ☓ ✓

URIN (10 ml) Kryss av for ønsket analyse eller analysepakke

☐ **Basispakke urin** (alle analysene nedenfor)
- ☐ Alkohol (etanol)
- ☐ Cannabis
- ☐ Benzodiazepiner (alprazolam, diazepam, flunitrazepam, klonazepam, nitrazepam, oksazepam)
- ☐ Z-hypnotika (zolpidem, zopiklon)
- ☐ Opioider (morfin, kodein, heroin, oksykodon, etylmorfin, buprenorfin, metadon, fentanyl, tramadol, petidin)
- ☐ Sentralstimulerende midler (amfetamin, metamfetamin, efedrin, ecstasy, kokain, metylfenidat, PMMA, PMA)
- ☐ Ketamin
- ☐ Pregabalin

Øvrige rusmiddelanalyser
- ☐ Etanolmetabolitter (EtG og EtS)
- ☐ GHB
- ☐ Barbiturater
- ☐ Syntetiske cannabinoider
- ☐ Annet:
- ☐ LSD
- ☐ Khat
- ☐ Psilocin (fleinsopp) (prøven må kjøles)

Toksiske alkoholer
- ☐ Metanol, isopropanol, aceton
- ☐ Etylenglykol (frostvæske)

SERUM minimum 1,5 ml serum pr. kryss

- ☐ Alkoholer (etanol, metanol, isopropanol, aceton)
- ☐ Cannabis
- ☐ Benzodiazepiner (alprazolam, diazepam, flunitrazepam, klonazepam, midazolam, nitrazepam, oksazepam)
- ☐ Zolpidem
- ☐ Zopiklon
- ☐ Morfin, heroin, kodein, etylmorfin, oksykodon
- ☐ Buprenorfin
- ☐ Metadon
- ☐ Amfetamin, metamfetamin, ecstasy (MDMA)
- ☐ Kokain
- ☐ Metylfenidat
- ☐ GHB
- ☐ Annet (se også bakside):

HÅR Kryss av for ønsket analysepakke. Ta kontakt med avdelingen for prøvetakingsutstyr

☐ **Basispakke hår** (alle analysene nedenfor)
- ☐ Benzodiazepiner (alprazolam, diazepam, flunitrazepam, klonazepam, nitrazepam, oksazepam) og zopiklon
- ☐ Opioider (morfin, kodein, etylmorfin, heroin, oksykodon, metadon, buprenorfin)
- ☐ Sentralstimulerende midler (amfetamin, metamfetamin, efedrin, ecstasy, kokain, metylfenidat)

OBS: Cannabis og etanol analyseres ikke i hår

☐ **Sanksjonære prøver etter IS-2231**

Prøvetaker bekrefter herved at prøvetakingen er gjennomført i henhold til gjeldende retningslinjer.

Sted/dato .....

Singatur/prøvegiver: .....

Signatur prøvetaker: .....

For prøvetaker:

Innsendt materiale: ☐ Serum/blod ☐ Urin ☐ Hår

Antall glass: ....

Kommentar vedrørende prøvetaking: .....

Dato for prøvetaking ..... Kl.slett:..... Sign.: .....

For laboratoriet:

Etikett sanksjonære prøver IS-2231 festes her

☐ Det ønskes svar kun på bestilte analyser

St. Olavs hospital, Avdeling for klinisk farmakologi
Postboks 3250 Sluppen, 7006 Trondheim.
Besøksadresse: Teknostallen, Professor Brochs gate 6
Telefon: 72 82 91 00 • www.stolav.no/farma

Rekvisisjon versjon 001, gyldig fra 04.2015. Godkjent av TAa

Legemiddelanalyser i serum/blod

Tidspunkt for prøvetaking:
Som hovedregel bør blodprøver tas 12-24 timer etter siste dose. Unntatt er depot-injeksjoner, der prøver bør tas i slutten av doseringsintervallet, kort tid før neste injeksjon. Unntatt er også analyser merket med 1, se tabell til høyre for detaljer.

Prøveglass:
Som hovedregel brukes serumglass (med eller uten gel). Prøven koaguleres i minst 30 minutter, og sentrifugeres og avpipetteres innen 2 timer. Unntak: Prøver merket med 2 må tas på EDTA-glass.

Prøvevolum:
Beregn minimum 1,5 ml avpippetert serum pr analyse.

Lysbeskyttelse:
Prøver merket med 3 må lysbeskyttes med aluminiumsfolie.

Legemiddel	**Tid fra siste dose til prøvetaking**
Atomoksetin	4-8 timer
Buprenorfin	24 timer
Ciklosporin	12 timer
Litium	12 timer
Metadon	24 timer
Metylfenidat	4-8 timer
Moklobemid	12 timer
Smertestillende midler (morfin, paracetamol, kodein, ketobemidon, oksykodon, etc)	4-6 timer (12t ved depot-tbl)
Takrolimus tabletter Takrolimus depot-tabletter	12 timer 24 timer
Quetiapin tabletter Quetiapin depot-tabletter	12 timer 24 timer

Analyserepertoar i serum/blod: Generisk navn (eksempler på handelsnavn)

Antidepressiva
Amitriptylin (Sarotex)
Bupropion (Wellbutrin, Zyban)
Citalopram (Cipramil)
Doksepin (Sinequan)
Duloksetin (Cymbalta)
Escitalopram (Cipralex)
Fluoksetin (Fontex)
Fluvoksamin (Fevarin)
Klomipramin (Anafranil)
1 Litium (Lithionit)
Mianserin (Tolvon)
Mirtazapin (Remeron)
1 Moklobemid (Aurorix)
Nortriptylin (Noritren)
Paroksetin (Seroxat)
Reboksetin (Edronax)
Sertralin (Zoloft)
Trimipramin (Surmontil)
Venlafaksin (Efexor, Venlix)

Midler ved ADHD
Amfetamin
Deksamfetamin (Dexedrine, Metamina)
1 Atomoksetin (Strattera)
1 Metylfenidat (Concerta, Equasym, Medikinet, Ritalin)

Benzodiazepiner og z-hypnotika
Alprazolam (Xanor)
Diazepam (Stesolid, Valium, Vival)
Flunitrazepam (Flunipam)
Klonazepam (Rivotril)
Midazolam (Dormicum)
Nitrazepam (Apodorm, Mogadon)
Oksazepam (Alopam, Sobril)
Zopiklon (Imovane)
Zolpidem (Stilnoct)

Antipsykotika og førstegenerasjons antihistaminer
Alimemazin (Vallergan)
Amisulprid (Solian)
Aripiprazol (Abilify)
Flupentiksol (Fluanxol)
Haloperidol (Haldol)
Klorpromazin (Largactil)
Klorprotiksen (Truxal)
Klozapin (Leponex)
Levomepromazin (Nozinan)
3 Olanzapin (Zyprexa, Zypadhera)
Paliperidon (Xeplion)
Perfenazin (Trilafon)
Pimozid (Orap)
Proklorperazin (Stemetil)
Prometazin (Phenergan)
1 Quetiapin (Seroquel)
Risperidon (Risperdal, Rispolept)
Sertindol (Serdolect)
Ziprasidon (Zeldox)
Zuklopentiksol (Cisordinol)

Antiepileptika
Eslikarbazepin (Zebinix)
Fenobarbital (Fenemal)
Fenytoin (Epinat)
Gabapentin (Neurontin)
Karbamazepin (Tegretol, Trimonil)
Lamotrigin (Lamictal)
Levetiracetam (Keppra)
Okskarbazepin (Trileptal)
Pregabalin (Lyrica)
Topiramat (Topimax)
Valproat (Orfiril)
Zonisamid (Zonegran)

Analgetika og anestesimidler
1 Buprenorfin (Norspan, Suboxone, Subutex, Temgesic)
Etylmorfin (Cosylan, Solvipect Comp)
Fentanyl (Durogesic)
Ibuprofen (Brufen, Ibumetin, Ibux)
Ketamin (Ketalar)
1 Ketobemidon (Ketogan, Ketorax)
1 Kodein (Paralgin Forte, Pinex Forte)
1 Metadon
1 Morfin (Dolcontin, Oramorph)
1 Oksykodon (OxyContin, OxyNorm)
1 Paracetamol (Pamol, Panodil, Paracet, Pinex)
1 Petidin
1 Salisylsyre (Aspirin, Globoid)
Tiopental (Pentothal - Natrium)
1 Tramadol (Nobligan, Tramagetic)

Immunsuppressiva og midler ved hjerte-, kar- og lungesykdom
Atenolol (Tenormin, Uniloc)
1,2 Ciklosporin (Sandimmun)
Digitoksin (Digimerck)
Digoksin (Lanoxin)
Flekainid (Tambocor)
Metoprolol (Seloken, Selo-Zok)
Propranolol (Inderal, Pranolol)
Teofyllin (Nuelin Depot, Theo-Dur)
1,2 Takrolimus (Advagraf, Prograf)
Warfarin (Marevan)

Rusmiddelanalyser i serum
Se rekvisisjonens forside. Vær oppmerksom på at urin er bedre egnet enn serum for å påvise rusmiddelinntak (på grunn av lengre påvisningstid og større prøvevolum).

Referanseområder og oversikt over akkrediterte analyser finnes på www. stolav.no/farma. Oversikt over analytisk usikkerhet kan fås på forespørsel. Ta kontakt med avdelingen ved ønske om andre analyser.
Prøvesvar må ikke brukes til forskning/publikasjoner uten avtale med laboratoriet.

Appendix 2

Oslo universitetssykehus
Avdeling for farmakologi
Telefon 67 50 11 70
Avdeling for kompleks epilepsi - SSE
GF Henriksens vei 23, 1337 Sandvika
Postadresse: Postboks 853, 1306 Sandvika

01502115 1

Legemiddelanalyser
Avd. for kompleks epilepsi - SSE

Rekvirent
Legenavn
HPR-nr.
Enhet/Legekontor
LEGE
Adresse
Telefon
ENHET
Postnr. Poststed
Kortkode/ Rekv.kode

Pasient
Fødselsdato Personnr.
Kvinne Mann
Etternavn - fornavn
Adresse
Poliklinisk
Inneliggende
Postnr. Poststed
Rom-seng -

Kopi av svar sendes til
Legenavn
HPR-nr.
Avdeling/Legekontor
Adresse
Postnr./sted

Prøve tatt av:
☐ Rekvirent
☐ Laboratoriet

Prøvetakingstidspunkt
D D M M Å Å
T T M M

Prøvetakers signatur

Kliniske opplysninger fylles ut av rekvirent

VEKT: kg

Andre faste medikamenter	Døgndose	Startet dato

Indikasjon for analyse:
Rutinekontroll ☐
Doseendring ☐
Bivirkninger ☐
Forgiftning ☐
Terapisvikt ☐
Mistenkt misbruk ☐

Kryss av om:
Hjertesvikt: ☐
Leversvikt: ☐
Nyresvikt: ☐
Smitte: ☐

For laboratoriet:
Mottatt

	Gelrør
	Avpip.serum
	Usentrifugert rør

Sign. mottak

Info til prøvetaker:
Avpipettert serum uten gel
Sentrifugert gelrør

Informasjon til rekvirent:
Påfør indikasjon for målingen og **preparatnavn** og **døgndose** for ønsket analyse. Oppgi andre legemidler som er i bruk. Som ledd i terapikontroll tas prøven vanligvis medikamentfastende om morgenen.
Se baksiden for et utvalg andre aktuelle analyser som utføres på enhet for farmakologiske analyser,Ullevål.
* utføres på farmakologisk avd. Ullevål ☐ Prøver bestilt på baksiden Kontakttelefon SSE, se baksiden

Informasjon til prøvetaker:
Påfør prøvetakingsdato og kl. Bruk korrekt type rør og sentrifuger innen 2 timer. Påfør dato og kl for siste dose
Medikamentfastende: JA ☐ NEI ☐

		Preparatnavn	Døgndose	Siste dose dato og kl.
☐ Eslikarbazepin	0,5 ml			
☐ Etosuksimid	0,5 ml			
☐ Felbamat	0,5 ml			
☐ Fenobarbital	0,5 ml			
☐ Fenytoin	0,5 ml			
☐ Gabapentin	0,5 ml			
☐ Karbamazepin	0,5 ml			
☐ **Klobazam**	0,5 ml			
☐ **Klonazepam**	**2,0 ml**			
☐ Lakosamid	0,5 ml			
☐ Lamotrigin	0,5 ml			
☐ Levetiracetam	0,5 ml			
☐ Okskarbazepin	0,5 ml			
☐ Pregabalin	0,5 ml			
☐ Rufinamid *	0,5 ml			
☐ Topiratmat	0,5 ml			
☐ Valproat	0,5 ml			
☐ Zonisamid	0,5 ml			

Informasjon til rekvirent:
Ved spesielle kliniske tilstander kan det være viktig å analysere fritt valproat eller fritt fenytoin.

Kryss samtidig av for total-konsentrasjon og oppgi preparatnavn og døgndose.

OBS: Analysene blir ikke analysert uten at klinisk årsak er beskrevet.

Klinisk årsak:

Analyse som ønskes analysert:
☐ Fritt fenytoin 2,0 ml
☐ Fritt valproat 2,0 ml

Avdeling for farmakologi, SSE

OUS Blankettnr. 202558. 09.15. Opplag W&J 837147.

Informasjon om preparatnavn og analysebestilling.

PREPARATNAVN	Analysebestilling
Apydan	Okskarbazepin
Depakote	Valproat
Deprakine, Deprakine Retard	Valproat
Divalproex	Valproat
Epanutin	Fenytoin
Epinat	Fenytoin
Fenemal	Fenobarbital
Fenobarbital-Na	Fenobarbital
Frisium	Klobazam
Inovelon	Rufinamid
Keppra	Levetiracetam
Kevesy	Levetiracetam
Lamictal	Lamotrigin
Liskantin	Fenobarbital
Lyrica	Pregabalin
Mysoline	Fenobarbital
Neurontin	Gabapentin

PREPARATNAVN	Analysebestilling
Orfiril, Orfiril Retard, Orfiril Long	Valproat
Petnidan	Etosuksimid
Phenhydan	Fenytoin
Primidon	Fenobarbital
Pro-Epanutin	Fenytoin
Rivotril	Klonazepam
Suxinutin	Etosuksimid
Taloxa	Felbamat
Tegretol, Tegretol Retard	Karbamazepin
Topimax	Topiramat
Trileptal	Okskarbazepin
Trimonil Retard	Karbamazepin
Vimpat	Lakosamid
Zarondan	Etosuksimid
Zarontin	Etosuksimid
Zebinix	Eslikarbazapin
Zonegran	Zonisamid

Kontakttelefon på SSE
Laboratoriet: 67 50 11 70 (kl 8-15:00 mandag- fredag)
Spørsmål om tolkning av legemiddel og farmakogenetiske analyser rettes til medisinsk faglig tlf: 48 01 62 74 (kl 8:00-15:00 mandag- fredag).

Vår rekvisisjon kan skrives ut fra www.oslo-universitetssykehus.no, under FAG fane eller kontakt laboratoriet for forsendelse av rekvisisjoner eller forsendelseskonvolutter.

ANALYSER TIL AVD. FOR FARMAKOLOGI, ULLEVÅL

Et utvalg av legemidler og farmakogenetiske analyser utføres på enhet for farmakologiske analyser, Ullevål:
Ved rekvirering av disse sendes prøven fra SSE med intern budbil til Ullevål.
Ønskes kun analyser til Ullevål, må rekvisisjonen OUS Blankettnr. 322 Farmakologi benyttes og prøven sendes direkte.

Farmakogenetiske analyser

- ☐ CYP2C9 — Tot. 0,5 mL EDTA
- ☐ CYP2C19
- ☐ CYP2D6
- ☐ CYP3A5
- ☐ CYP1A2
- ☐ CYP2B6

Oppgi aktuelle legemidler og indikasjon

- ☐ TPMT (tiopuriner)
- ☐ UGT1A1 (irinotekan)
- ☐ DPYD (5-fluorouracil)
- ☐ VKORC1 (warfarin)

Antidepressiva

- ☐ Litium — 0,2 mL
- ☐ Citalopram — Tot. 2 mL
- ☐ Escitalopram
- ☐ Amitriptylin
- ☐ Nortriptylin
- ☐ Klomipramin
- ☐ Mianserin
- ☐ Mirtazapin

Antipsykotika

- ☐ Levomepromazin — 2 mL

Benzodiazepiner

- ☐ Alle — Tot. 2 mL
- ☐ Diazepam
- ☐ Desmetyldiazepam
- ☐ Oxazepam
- ☐ Klonazepam
- ☐ Flunitrazepam
- ☐ Nitrazepam
- ☐ Alprazolam

Appendix 3

Senter for Psykofarmakologi — Diakonhjemmet Sykehus

Legemidler og farmakogenetikk

Rekvirent

ID:

Rekvirent navn:

Postadr.:

Postnr./-sted:

Ekstra svarbrev ønskes sendt til:

Pasient

Fødselsnr. (11 siffer): ☐ Kvinne ☐ Mann

Etternavn: Fornavn:

Postnr./-sted:

Betales av:
☐ Helfo (poliklinisk) ☐ Institusjon (innlagt)
☐ Bedriftshelsetjeneste ☐ Annet:

Prøvetaking (Dato/Kl./Sign.)

Kliniske opplysninger. Spesifiser problemstilling.

Vekt ____kg
Røyker Ja ☐ Nei ☐
Red. nyrefunksjon Ja ☐ Nei ☐

Indikasjon for analyse:
☐ Bivirkninger ☐ Oppstart
☐ Mangelfull effekt
☐ Annet:

Legemidler (evt. vedlegg)	Oppstart/doseendring (dato)	Morgen (mg)	Middag (mg)	Kveld (mg)	Dato siste dose	Tidspunkt (kl.)

LEGEMIDDELANALYSER

3 mL serum (ikke gel)

Antidepressiva
- ☐ Amitriptylin (Sarotex)
- ☐ Bupropion (Wellbutrin)
- ☐ Citalopram (Cipramil)
- ☐ Escitalopram (Cipralex)
- ☐ Duloksetin (Cymbalta)
- ☐ Fluoksetin (Fontex)
- ☐ Fluvoksamin (Fevarin)
- ☐ Klomipramin (Anafranil)
- ☐ Mianserin (Tolvon)
- ☐ Mirtazapin (Remeron)
- ☐ Nortriptylin (Noritren)
- ☐ Paroksetin (Seroxat)
- ☐ Sertralin (Zoloft)
- ☐ Trimipramin (Surmontil)
- ☐ Venlafaksin (Efexor)
- ☐ Vortioksetin (Brintellix)

Antipsykotika
- ☐ Amisulprid (Solian)
- ☐ Aripiprazol (Abilify)
- ☐ Asenapin (Sycrest)
- ☐ Flupentiksol (Fluanxol)
- ☐ Haloperidol (Haldol)
- ☐ Klorprotiksen (Truxal)
- ☐ Klozapin (Leponex)
- ☐ Kvetiapin (Seroquel)
- ☐ Levomepromazin (Nozinan)
- ☐ Lurasidon (Latuda)
- ☐ Olanzapin (Zyprexa)
- ☐ Paliperidon (Xeplion)
- ☐ Perfenazin (Trilafon)
- ☐ Risperidon (Risperdal)
- ☐ Sertindol (Serdolect)
- ☐ Ziprasidon (Zeldox)
- ☐ Zuklopentiksol (Cisordinol)

Antiepileptika
- ☐ Eslikarbazepin (Zebinix)
- ☐ Fenobarbital (Fenemal)
- ☐ Fenytoin
- ☐ Gabapentin (Neurontin)
- ☐ Karbamazepin (Tegretol, Trimonil)
- ☐ Klonazepam (Rivotril)
- ☐ Lamotrigin (Lamictal)
- ☐ Levetiracetam (Keppra)
- ☐ Okskarbazepin (Trileptal)
- ☐ Pregabalin (Lyrica)
- ☐ Topiramat (Topimax)
- ☐ Valproat (Orfiril)

Opioider
- ☐ Kodein (Paralgin forte, Pinex forte)
- ☐ Tramadol (Nobligan)
- ☐ Metadon
- ☐ Buprenorfin (Subutex, Temgesic)

Antikoagulantia
- ☐ Apiksaban (Eliquis)
- ☐ Dabigatran (Pradaxa)
- ☐ Rivaroksaban (Xarelto)

Benzodiazepiner
- ☐ *Benzodiazepiner screening*
- ☐ Alprazolam (Xanor)
- ☐ Diazapam (Stesolid, Valium, Vival)
- ☐ Flunitrazepam (Flunipam, Rohypnol)
- ☐ Nitrazapam (Apodorm, Mogadon)
- ☐ Oksazepam (Sobril)
- ☐ Zolpidem (Stilnoct)
- ☐ Zopiklon (Imovane)

Andre legemidler
- ☐ Atomoksetin (Strattera)
- ☐ Litium (Lithionit)
- ☐ Ritalinsyre (Ritalin, Equasym, Concerta)
- ☐

FARMAKOGENETISKE ANALYSER

1 EDTA/Citrat rør

		Gener som analyseres
CYP-analyse	☐ **CYP-screening (CYP2C9, CYP2C19, CYP2D6)** ☐ Enkelt(e) analyse(r):	
Depresjon	☐ **SSRI-panel** (citalopram (Cipramil), escitalopram (Cipralex), fluoksetin (Fontex), fluvoksamin (Fevarin), paroksetin (Seroxat), sertralin (Zoloft)) ☐ Venlafaksin (Efexor) ☐ Bupropion (Wellbutrin) ☐ TCA (amitriptylin (Sarotex) og øvrige TCA) ☐ Andre (duloksetin (Cymbalta), mirtazapin (Remeron), mianserin (Tolvon), vortioksetin (Brintellix))	SLC6A4, CYP2D6, CYP2C19 CYP2D6 CYP2B6 CYP2D6, CYP2C19 CYP2D6
Psykose	☐ Aripiprazol (Abilify), flupentiksol (Fluanxol), haloperidol (Haldol), perfenazin (Trilafon), risperidon (Risperdal), sertindol (Serdolect), zuklopentiksol (Cisordinol)	CYP2D6
Epilepsi	☐ Fenytoin ☐ Lamotrigin (Lamictal)	CYP2C9 UGT1A4
ADHD	☐ Atomoksetin (Strattera)	CYP2D6
Smerte	☐ **Opioid-panel** (kodein (Paralgin/Pinex forte), tramadol (Nobligan), morfin (Dolcontin) og øvrige opioider)	CYP2D6, OPRM1
Hjerte/kar	☐ **Marevan-panel** (warfarin) ☐ **Statin-panel** (atorvastatin (Lipitor), lovastatin, pravastatin (Pravachol), rosuvastatin (Crestor), simvastatin (Zocor)) ☐ Klopidogrel (Plavix) ☐ Metoprolol (Selo-Zok)	CYP2C9, VKORC1 CYP3A4, CYP3A5, SLCO1B1 CYP2C19 CYP2D6
Diabetes	☐ Sulfonylurea (glimepirid (Amaryl), glibenklamid)	CYP2C9
Andre	☐ Allopurinol (Zyloric) ☐ Metadon ☐ Tamoksifen	HLA-B*58:01 CYP2B6, CYP3A5 CYP2D6

Versjon: 02/2017

Informasjon til prøvetaker

Farmakogenetiske analyser: Ett EDTA- eller Citrat-rør. Røret vendes forsiktig 6 ganger. Påfør pasientens fulle navn og personnummer på prøverøret. Ved vanskelig prøvetaking er 0,5 ml tilstrekkelig.

Legemiddelanalyse: Prøven tas på glassrør uten tilsetning. Det trengs minimum 1 ml per analyse, ved flere analyser er 3 ml tilstrekkelig. Prøven må koagulere i minimum 30 minutter, og sentrifugeres og avpipetteres innen 2 timer. Prøvetakingstidspunkt og tidspunkt for siste dose må fylles ut på skjema. Påfør pasientens fulle navn og personnummer på prøverørene.

Blodprøve til de fleste serumanalysene bør tas legemiddelfastende, dvs. 12-24 timer etter siste doseinntak.
Unntak:

Legemiddel:	*Preparatnavn:*	*Anbefalt tidsintervall mellom siste doseinntak og prøvetaking:*
Atomoksetin	*Strattera*	*4-8 timer*
Dabigatran	*Pradaxa*	*12-16 timer*
Kodein	*Paralgin/Pinex forte*	*4-6 timer*
Kvetiapin	*Seroquel (tabletter)*	*12 timer ± 1 time*
	Seroquel (depottabletter)	*18-24 timer*
Levetiracetam	*Keppra*	*12 timer ± 1 time*
Litium	*Lithionit*	*12 timer ± 30min*
Ritalinsyre	*Ritalin/Equasym/Concerta*	*4-8 timer*
Rivaroksaban	*Xarelto*	*24 timer*

Ved depotmedikasjon bør prøven tas 0-2 dager før neste depotinjeksjon

Kontaktinformasjon:

Postadresse: Senter for Psykofarmakologi
Diakonhjemmet Sykehus
Postboks 23, Vinderen
0319 Oslo
Tlf. 22 02 99 40

Informasjon om analysene

Ved avkryssing for flere legemidler/paneler og/eller CYP-enzymer som genererer samme farmakogenetiske analyse, kjøres analysen kun én gang.

Informasjon om de farmakogenetiske analysene/panelene, samt oversikt over legemiddelanalyser, referanseområder, forsendelse, oppbevaring og etterrekvirering finnes på www.psykofarmakologi.no. For analyse av CYP1A2, vennligst ta kontakt med oss.

Svar/tolkning av analysene

Farmakogentiske analyser: Påviste mutasjoner tolkes i forhold til kliniske opplysninger og oppgitte legemidler/avkryssede legemidler. Farmakogenetisk analyse er bare nødvendig å utføre en gang. Ny tolkning av analysesvaret kan imidlertid være aktuelt hvis pasientens legemiddelbehandling endres. Ta kontakt med Senter for Psykofarmakologi for rådgiving, tlf: 22 02 98 99 (lege/farmasøyt).

Legemiddelanalyser: Analysesvar tolkes i forhold til dose og referanseområde, samt kliniske opplysninger gitt på rekvisisjonen. Det forutsettes at prøven er tatt ved standardbetingelser (se «Informasjon til prøvetaker»).

Informasjon til pasienten

Innsendt prøvemateriale (blod eller serum) kan i noen tilfeller bli brukt til forskningsformål. Dersom pasienter ønsker å reservere seg mot dette, kan man registrere seg i databasen Biologisk forskningsreservasjon via Folkehelseinstituttets nettside (www.fhi.no/div/personvern/biologisk-forskningsreservasjon/).

Blodprøvetaking

Rekvisisjonen medbringes ved prøvetaking ved Senter for Psykofarmakologi.
Åpent: kl. 08.00 – 14.00 (ingen timebestilling)
Besøksadresse: Senter for Psykofarmakologi
Psykisk Helsevern Vinderen
Forskningsveien 7, inngang C1
0319 Oslo

Versjon: 02/2017

Appendix 4

ANTIEPILEPTIC DRUGS AND PREGNANCY REGISTRY
International concerted Action on the Teratogenesis of Anti-epileptic Drugs

EURAP

Subform A-B-C-D-E

(**C**ase **R**ecord **F**orms)

Sub-form A: Registration (to be completed as early as possible)

Sub-form B: Follow-up at the end of 1st trimester
(includes 1st trimester)

Sub-form C: Follow-up at the end of 2nd trimester
(includes 2nd trimester)

Sub-form D: Follow-up at birth
(includes 3rd trimester and neonatal period)
NB: To be completed within three months after birth.

Sub-form E: Follow-up at the age of one year

Sub-form A: Registration *(to be completed as early as possible)* Side 1/3

Questionnaire (codes' names refer to data dictionary)

Pregn_num	Number of pregnancy of the centre (5 digits)	
Date_I	Date of reporting form A (ddmmyyyy)	
date_first	Date of notification of pregnancy to investigator (and assignement of identification number; ddmmyyyy)	
LMP	First day of last menstruation (ddmmyyyy)	
Country	Identification number country	**19**
Centre	Identification number centre	
rep_phys	Reporting physician	

reas_AED	Is epilepsy reason for prescribing AED? 0 = no 1 = yes	
reasAED_sp	If previous question is 0, specify other reason	
gender_p	Father has epilepsy? 0 = no 1 = yes 8 = not ascertained 9 = unknown	
fam_name	Family name (first 3 letters)	
fir_name	First name (first 3 letters)	
bir_moth	Birth date mother (ddmmyyyy)	
soc_moth	Eductional level mother 1 = tertiary (fullført universitet/høyskole) 2 = secondary (fullført videregående skole/yrkesutdanning) 3 = primary (fullført ungdomsskole) 4 = illiteracy (minimal/ingen skolegang) 8 = not ascertained 9 = unknown	
soc_fath	Eductional level father (see soc_moth)	
eth_moth	Ethnic background of the mother 1 = Caucasian 2 = North African 3 = Negro 4 = Asiatic 5 = Aborigenal 6 = Pacific Islands 7 = Mixed 8 = other 88 = not ascertained 99 = unknown	
X-ray	Ionising radiation exposure 3 months <u>before</u> pregnancy? 0 = no 1 = yes (enter specification in comment field) 8 = not ascertained 9 = unknown	

Gravida	Number of this pregnancy (inkl. alle påbegynte svangerskap) 01 = first pregnancy 02 = second pregnancy 03 = third pregnancy etc.... 88 = not ascertained 99 = unknown	
Parity	Number of previous deliveries 00 = none 01 = once 02 = twice etc.... 88 = not ascertained 99 = unknown	
Stillborn	Number of stillborn offspring (*dødfødsel*) (see parity)	
Death	Number of neonatal deaths (see parity)	
Normal	Number of **not** malformed offspring and **not** with chromosomal abnormalities) (see parity)	
Malformed	Number of malformed offspring (see parity)	
malform_sp	Specify malformations or chromosomal abnormalities	
Abortion	Number of spontaneous abortions	
Maternal_a	Number of induced abortions **not** due to foetal malformations and **not** due to chromosomal abnormalities	
Fetal_a	Number of induced abortion due to foetal malformation	
fetal_sp	Specify malformations or chromosomal abnormalities	

Epilepsy	Type of maternal epilepsy 1 = generalised 2 = localisation related 3 = undetermined 8 = not ascertained 9 = unknown	
Etiology	Aetiology of epilepsy 1 = idiopathic 2 = symptomatic 3 = cryptogenic 8 = not ascertained 9 = unknown	
ILAE	Epilepsy syndrome	

malf_fam	Proband's (**fosterets**) family history of congenital malformations 00 = none 01 = proband's mother (enter specification in comment field) 02 = proband's father (enter specification in comment field) 03 = proband's sister 04 = proband's brother 05 = proband's sibling (when sex is unknown) 06 = proband's twin 88 = not ascertained 99 = unknown	
treatPrevPreg	Was patient on AED in previous pregnancies? **Complete only in case of abnormal outcome** 1 = yes (with same AED treatment) 2 = yes (with different AED treatment) 3 = no 8 = not ascertained 9 = unknown	
epil_fam	Proband's (**fosterets**) family history of epilepsy 00 = none 02 = proband's father (enter specification in comment field) 03 = proband's sister 04 = proband's brother 88 = not ascertained 99 = unknown	
commentsA	Comments	

Sub-form B: Follow-up at the end of 1st trimester *(at 14-24 weeks of pregnancy)*

Questionnaire (codes' names refer to data dictionary)

Pregn_num	Number of pregnancy of the centre (5 digits)	
date_B	Date of reporting sub-form B (ddmmyyyy)	
Country	Identification number country	**19**
Centre	Identification number centre	

Spont_ab	Spontaneous abortion? 0 = no 1 = yes 8 = not ascertained 9 = unknown	
Spont_abdate	Spontaneous or induced abortion <u>date</u> (ddmmyyyy):	
term_pregn	Induced termination of pregnancy? 0 = no 1 = foetal abnormality (enter specification in "Specify results" field) 2 = maternal medical 3 = maternal social 4 = other (enter specification in comment field) 8 = not ascertained 9 = unknown	
Chrom/malf	Post mortem examination? 0 = not performed 1 = chromosome abnormalities 2 = malformations 3 = chromosome abnormalities and malformations 4 = no abnormalities 5 = other abnormalities 8 = not ascertained 9 = unknown	
Specresult	Specify results (post mortem examination)	
Aterm	Calculated term date (ddmmyyyy)	

OAC_preg	Oral contraceptive use during pregnancy? 0 = no 1 = yes 8 = not ascertained 9 = unknown	
fert_ass	Assisted fertilisation? 0 = no 1 = yes 8 = not ascertained 9 = unknown	

smoke_tr1	Cigarette smoking in 1st trimester? 0 = no 1 = 1-10/day 2 = 11-20/day 3 = >20/day 8 = not ascertained 9 = unknown	
alcoh_tr1	Alcohol intake in 1st trimester? 0 = no 1 = <1 drinks/day 2 = <3 drinks/day 3 = 3-6 drinks/day 4 = >6 drinks/day 8 = not ascertained 9 = unknown	
Xray_tr1	Ionising radiation exposure in 1st trimester? 0 = no 1 = yes (enter specification in comment field) 8 = not ascertained 9 = unknown	

othdis_tr1	Specify other maternal diseases (including relevant infections) in 1st trimester of pregnancy	
Othmed_tr1	Specify other drugs used in 1st trimester	

suppl_fa	Folic acid use; dose in µg (Please include folic acid content also in multivitamin tablets) 0000 = none 0100 = 100 µg = 0,1 mg 0400 = 400 µg = 0,4 mg 0500 = 500 µg = 0,5 mg 1000 = 1000 µg = 1,0 mg 4000 = 4000 µg = 4,0 mg 5000 = 5000 µg = 5,0 mg etc. 7777 = dose unknown 8888 = not ascertained 9999 = unknown	
start_fa	Start date of folic acid use (ddmmyyyy)	
end_fa	End date of folic acid use (ddmmyyyy)	

AED_tr1	AED use in 1st trimester? 0 = no 1 = yes 8 = not ascertained 9 = unknown	

sort1_tr1	Generic name in full of AED used in 1st trimester	1. 2. 3. 4. 5.
dose1_tr1	Total daily dose of AED in mg in 1st trimester	
peak1_tr1	Largest single dose of AED in mg per day	
gift1_tr1	Number of administrations per day of AED in 1st trimester	
star1_tr1	Start date of AED (ddmmyyyy)	
end1_tr1	End date of AED (ddmmyyyy)	
AEDmodtr1	Was AED dosage changed in 1st trimester? 0 = no 1 = yes (hvis ja, - hvilke endringer er gjort og når?) 8 = not ascertained 9 = unknown	

GTCS_tr1	Frequency of generalised tonic-clonic seizures in 1st trimester 0 = none 1 = < 1/month 2 = monthly 3 = weekly 4 = > weekly 5 = daily 6 = other 8 = not ascertained 9 = unknown	
OTH_tr1	Frequency of other seizures in 1st trimester **(EPA, KPA, absenser o.a.) (bruk samme skala som for GTK)**	

Statustr1	Status epilepticus in 1st trimester? 0 = no 1 = non-convulsive 2 = convulsive 8 = not ascertained 9 = unknown	
commentsB	Comments	

Appendix 5

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon:
- ☐ Hjemme, planlagt
- ☐ Hjemme, ikke planlagt
- ☐ Under transport
- ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus: ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja — Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn

Mors fødselsnr:

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte: Levendefødte | Dødfødte (24. uke og over) | Spontanabort/Dødfødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja — UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet:
- ☐ Intet spesielt
- ☐ Astma
- ☐ Allergi
- ☐ Tidligere sectio
- ☐ Res. urinveisinfeksjon
- ☐ Kronisk nyresykdom
- ☐ Kronisk hypertensjon
- ☐ Reumatoid artritt
- ☐ Hjertesykom
- ☐ Epilepsi
- ☐ Diabetes type 1
- ☐ Diabetes type 2
- ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei

	Før sv.sk.	I sv.sk.
Multivitaminer	☐	☐
Folat/Folsyre	☐	☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet:
- ☐ Intet spesielt
- ☐ Blødning < 13 uke
- ☐ Blødning 13–28 uke
- ☐ Blødning > 28 uke
- ☐ Glukosuri
- ☐ Svangerskapsdiabetes
- ☐ Hypertensjon alene
- ☐ Preeklampsi lett
- ☐ Preeklampsi alvorlig
- ☐ Preeklampsi før 34. uke
- ☐ HELLP syndrom
- ☐ Eklampsi
- ☐ Hb < 9.0 g/dl
- ☐ Hb > 13.5 g/dl
- ☐ Trombose, beh.
- ☐ Infeksjon, spes. i «B»
- ☐ Annet, spesifiser i «B»

Legemidler i svangerskapet:
- ☐ Nei
- ☐ Ja – spesifiser i «B»

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden

- ☐ Skriftlig orientering gitt til mor
- ☐ Samtykker ikke for røykeoppl.

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til — Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til — Ant. sig. dagl.:

Mors yrke
- ☐ Samtykker ikke for yrkesoppl.
- ☐ Ikke yrkesaktiv
- ☐ Yrkesaktiv heltid
- ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon:
- ☐ Normal bakhode
- ☐ Sete
- ☐ Tverrleie
- ☐ Avvikende hodefødsel
- ☐ Annet, spesifiser i «C»

Fødselstart:
- ☐ Spontan
- ☐ Indusert
- ☐ Sectio

Ev. induksjonsmetode:
- ☐ Prostaglandin
- ☐ Oxytocin
- ☐ Amniotomi
- ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon
- ☐ Komplikasjoner som beskrevet nedenfor
- ☐ Fostermisdannelser
- ☐ Overtid
- ☐ Annet, spesifiser i «C»

Inngrep/tiltak
- ☐ Ingen
- ☐ Utskj. tang, hodeleie
- ☐ Annen tang, hodeleie
- ☐ Vakuumekstraktor
- ☐ Episitomi

Fremhj. ved setefødsel:
- ☐ Vanlig fremhjelp
- ☐ Uttrekning
- ☐ Tang på etterk. hode

Sectio:
Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
- ☐ Utført som elektiv sectio
- ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner
- ☐ Ingen
- ☐ Vannavg. 12–24 timer
- ☐ Vannavg. > 24 timer
- ☐ Mekaniske misforhold
- ☐ Vanskelig skulderforløsning
- ☐ Placenta previa
- ☐ Abruptio placentae
- ☐ Perinealruptur (grad 1-2)
- ☐ Sphincterruptur (gr. 3-4)
- ☐ Blødn.> 1500 ml, transf.
- ☐ Blødning 500–1500 ml
- ☐ Eklampsi under fødsel
- ☐ Navlesnorfremfall
- ☐ Truende intrauterin asfyksi
- ☐ Risvekkelse, stimulert
- ☐ Langsom fremgang
- ☐ Uterus atoni
- ☐ Annet:

Anestesi/analgesi:
- ☐ Ingen
- ☐ Lystgass
- ☐ Petidin
- ☐ Epidural
- ☐ Spinal
- ☐ Pudendal
- ☐ Infiltrasjon
- ☐ Paracervical blokk
- ☐ Narkose
- ☐ Annet:

Placenta:
- ☐ Normal
- ☐ Hinnerester
- ☐ Ufullstendig
- ☐ Infarkter
- ☐ Koagler
- ☐ Utskrapning
- ☐ Manuell uthenting

Placenta-vekt

Navlesnor
- ☐ Normal
- ☐ Velamentøst feste
- ☐ Marginalt feste
- ☐ Karanomalier
- ☐ Omslyng rundt hals
- ☐ Annet omslyng
- ☐ Ekte knute

Navlesnor-lengde:

Fostervann
- ☐ Normal
- ☐ Polyhydramnion
- ☐ Oligohydramnion
- ☐ Misfarget
- ☐ Stinkende, infisert
- ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel
- ☐ Intet spesielt
- ☐ Feber > 38.5°
- ☐ Trombose
- ☐ Eklampsi post partum
- ☐ Mor overflyttet
- ☐ Mor intensivbeh.
- ☐ Sepsis
- ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet:
- ☐ Enkeltfødsel
- ☐ Flerfødsel

For flerfødsel: Nr. | Av totalt

Kjønn: ☐ Gutt ☐ Pike

Ved tvil spesifiser i «D»

For dødfødte: ☐ Usikkert kjønn

Barnets vekt | Hode-omkrets:

Total lengde: | Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var:
- ☐ Levendefødt
- ☐ Dødfødt/sp.abort — Oppgi dødsårsak i «D»

For dødfødte:
- ☐ Død før fødsel
- ☐ Død under fødselen
- ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også
- ☐ Død før innkomst
- ☐ Død etter innkomst

Levendefødt, død innen 24 timer — Livet varte: Timer | Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja — Dato:

Overfl. til

Indikasjon for overflytting:
- ☐ Respirasjonsproblem
- ☐ Prematur
- ☐ Medfødte misd.
- ☐ Perinatale infeksjoner
- ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater)
- ☐ Intet spesielt
- ☐ Hypoglyk. (< 2 mmol/l)
- ☐ Medf. anemi (Hb < 13.5 g/dl)
- ☐ Hofteleddsdyspl. beh. m/pute
- ☐ Transit. tachypnoe
- ☐ Resp. distress syndr.
- ☐ Aspirasjonssyndrom
- ☐ Intrakraniell blødning
- ☐ Cerebral irritasjon
- ☐ Cerebral depresjon
- ☐ Abstinens
- ☐ Neonatale kramper
- ☐ Konjunktivitt beh.
- ☐ Navle./hudinf. beh.
- ☐ Perinat. inf. bakterielle
- ☐ Perinat. inf. andre
- ☐ Fract. claviculae
- ☐ Annen fraktur
- ☐ Facialisparese
- ☐ Plexusskade

Behandlingskodar:
- ☐ Systemisk antibiotika
- ☐ Respiratorbeh.
- ☐ CPAP beh.

Icterus behandlet:
- ☐ Lysbehandlet
- ☐ Utskifting

Årsak:
- ☐ AB0 uforlik.
- ☐ RH immunisering
- ☐ Fysiologisk
- ☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D — Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Lege:

Lege barsel/barneavd:

Utskrivningsdato — Mor: | Barn:

Protokollnr.: /

IS-1002 23011. 07.06. Andvord Grafisk.

Appendix 6

St. Olavs Hospital HF
Avdeling for klinisk farmakologi

Universitetssykehuset i Trondheim

HELSE MIDT-NORGE

Til våre rekvirenter, Vår ref: 08/7700-1/L33545/anauwe Dato: 31.10.2008

Psykofarmaka og gravide: rutiner for serumkonsentrasjonsanalyser

Mange legemidler håndteres annerledes i en gravid enn i en ikke-gravid kropp. Dette kan skyldes mange forhold, som økt kroppsvolum, endret proteinbinding, økt metabolisme og økt utskillelse. Til tross for økende bruk av psykofarmaka hos gravide, vet man lite om svangerskapsrelaterte endringer i farmakokinetikk av disse legemidlene. For de fleste legemidler forventer man at konsentrasjonen faller gradvis i løpet av graviditeten, og returnerer til vanlig nivå i løpet av de første ukene etter graviditeten. Det er imidlertid stor variasjon mellom legemidler i omfanget av disse endringene, og hvorvidt dosejusteringer behøves. For psykofarmaka anbefaler vi derfor at serumkonsentrasjonsanalyser utføres rutinemessig, både under svangerskapet og den første tiden etter fødsel.

Forslag til prøvetakingsintervall:

- Prøve 1: Før graviditeten (tas dersom graviditet planlegges)
- Prøve 2: I første trimester, for eksempel en gang i svangerskapsuke 6-8 (eventuelt så raskt som mulig etter at pasienten kontakter lege pga. graviditet hvis det skjer etter dette)
- Prøve 3: Ca. midt i annet trimester, for eksempel en gang i svangerskapsuke 18-22
- Prøve 4: Ca. midt i tredje trimester, for eksempel en gang i svangerskapsuke 32-36
- Prøve 5: Ca. en uke etter fødsel
- Prøve 6: Ca. to uker etter fødsel
- Prøve 7: Ca. fire uker etter fødsel

NB! Husk å merke rekvisisjonen med: *Gravid* og *dato for siste mens* og evt *dato for fødsel* (for prøver tatt etter nedkomst) i feltet for "diagnose/kliniske opplysninger". Prøver tas på vanlig måte (12-24 timer etter inntak av siste dose, dvs. at en eventuell morgendose må utsettes til etter at prøven er tatt), og vanlig rekvisisjonsskjema benyttes (se vedlegg). Det må gjerne tas hyppigere prøver enn det vi her skisserer, dersom den kliniske situasjonen tilsier det, eller ved uventede prøvesvar.

Ta gjerne kontakt med assistentlege Andreas Austgulen Westin på tlf 73 59 87 20 eller e-post andreas.westin@legemidler.no ved spørsmål.

Med vennlig hilsen,

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