Fetal effects of maternal drug treatment. Risk assessment and communication.

Nörby, Ulrika

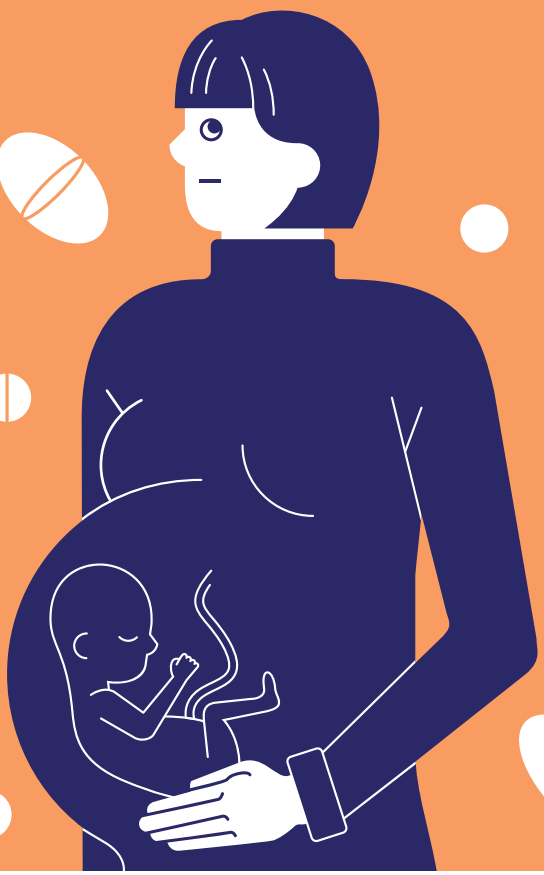
2017

Document Version:
Publisher's PDF, also known as Version of record

Fetal effects of maternal drug treatment

Risk assessment and communication

ULRIKA NÖRBY
DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY | LUND UNIVERSITY



Printed by Media-Tryck, Lund 2017 NORDIC ECOLABEL, 3041 0903

"I am still not sure what to do during this pregnancy; to continue the antidepressant treatment since it works fine or do everything I can to avoid that my child will be damaged. Last pregnancy, I stopped using the medicine on my own and I ended up with a severe depression."

Study participant describing her situation

Drug treatment during pregnancy is often challenging. The fear of harming the unborn child is frequently unrealistically high which might prevent essential therapy. At the same time, it is crucial not to expose the fetus to avoidable hazards. This thesis deals with how to assess fetal risks of medicines and how to reach out with relevant information to both health care professionals and the public. It is especially important to reach pregnant women since they to an increasing extent participate in decisions concerning their medical care.

Ulrika Nörby

LUND UNIVERSITY
Faculty of Medicine

Department of Obstetrics and Gynaecology

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2017:100
ISBN 978-91-7619-480-5
ISSN 1652-8220

Fetal effects of maternal drug treatment

Risk assessment and communication

Ulrika Nörby

LUND
UNIVERSITY

Cover illustration by Erik Kirtley
Photo on the back cover by Ella Nörby

Faculty of Medicine
Department of Obstetrics and Gynaecology

ISBN 978-91-7619-480-5
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University, Lund 2017

"The owl of Minerva takes its flight
only when the shades of night are gathering"
Hegel

Content

Abstract

Drug treatment during pregnancy is a delicate and often emotional issue. To deal with these situations in an optimal way, it is crucial to have access to reliable information concerning the fetal safety of the drugs. This thesis originates from the work with the scientific knowledge database *Drugs and Birth Defects,* which provides assessments of fetal risks for around 1300 medicinal drug substances.

In the first study, we describe the concept behind *Drugs and Birth Defects*. This includes the model for fetal risk assessment where the Swedish Medical Birth Register constitutes a main resource. In the second study, the perceived value and utility of the database were estimated among 712 healthcare professionals and 275 pregnant women via electronic questionnaires. The results demonstrate that *Drugs and Birth Defects* is an appreciated and valuable tool for both target groups, even though the contents are not intended for lay people.

In the last two studies, we investigated neonatal morbidity after exposure in utero to antidepressant drugs and medications for treatment of ADHD (Attention deficit hyperactivity disorder). Data from the Swedish Medical Birth Register, the Prescribed Drug Register and two neonatal quality registers were combined to obtain detailed information on maternal and neonatal health on a population level. The studies included 741 040 and 964 734 singleton births respectively, whereas 22 507 (3.1%) were exposed to antidepressant drugs and 1591 (0.2%) to ADHD medication.

We found an increased risk for admission to neonatal care units linked to both drug groups, adjusted ORs 1.7 (95% CI 1.6–1.9) for use of antidepressant drugs during late vs early pregnancy and 1.4 (95% CI 1.2–1.6), for use of ADHD medication during pregnancy vs no use of these drugs. Selective serotonin reuptake inhibitors (SSRIs), that were analyzed in more detail than the other antidepressants, increased the risk for mild respiratory symptoms, persistent pulmonary hypertension, CNS-disorders, feeding difficulties and hypoglycemia. Exposure to ADHD drugs was associated with moderate prematurity and CNS-disorders. The absolute risk for severe disease was low and there was no increased risk for birth defects or perinatal death.

Our analyses indicate a causal effect of exposure to antidepressant drugs and ADHD medication and the neonatal symptoms, but there might still be residual confounding from maternal conditions. The results will be used to improve the assessments for these drugs in the knowledge database *Drugs and Birth Defects.*

Svensk sammanfattning

Läkemedelsanvändning i samband med graviditet är en komplex situation, där nytta och risker med behandlingen måste bedömas för både kvinnan och det ofödda barnet. Ofta finns det en överdriven oro för att fostret ska ta skada av läkemedlet. Bedömningarna kompliceras av att det kan vara svårt att hitta tillförlitlig information inom området, särskilt för allmänheten. Den här avhandlingen utgår från kunskapsstödet *Läkemedel och fosterpåverkan* som är avsett för sjukvårdspersonal (numera namnändrat till *Janusmed fosterpåverkan)*. Tjänsten tillhandahåller riskbedömningar för fostret av cirka 1300 läkemedel och är fritt tillgänglig på internet.

Avhandlingens första studie beskriver arbetet med kunskapsstödet vars innehåll i stor utsträckning bygger på analyser av data från det svenska medicinska födelseregistret. Registret ger unika möjligheter att studera effekter på foster av läkemedelsanvändning under graviditet. I den andra studien utvärderades nytta och risker med *Läkemedel och fosterpåverkan* bland 712 läkare och barnmorskor och 275 gravida kvinnor. Resultaten visade att både sjukvårdspersonal och gravida ansåg att informationen var värdefull och lättillgänglig, trots att den inte är anpassad för allmänheten.

I de två sista studierna undersökte vi mer utförligt hur behandling med antidepressiva läkemedel respektive läkemedel vid ADHD under graviditeten, påverkar sjukligheten hos nyfödda barn. Bakgrunden är att allt fler gravida använder preparaten och att säkerheten för fostret ofta har ifrågasatts. Vi analyserade data från flera nationella hälsodata- och kvalitetsregister. Totalt ingick 741 040 respektive 964 734 barn i studierna, av vilka 22 507 (3.1%) var exponerade för antidepressiva och 1591 (0.2%) för ADHD-läkemedel. Båda läkemedelsgrupperna ökade risken för att barnen behövde vård på neonatalavdelning. För de vanligaste antidepressiva preparaten, SSRI (selektiva serotoninåterupptagshämmare), kan resultaten beskrivas som att om 17 gravida kvinnor behandlas i sen graviditet, så orsakar detta ett ytterligare vårdtillfälle. Riskökningen var ungefär lika stor för ADHD-läkemedel.

Barn vars mammor hade använt SSRI under graviditeten hade bland annat oftare milda andningsproblem, lågt blodsocker och symtom från centrala nervsystemet. Även ADHD-läkemedel var kopplade till centralnervös påverkan. Risken att barnen blev svårt sjuka var dock mycket liten. I likhet med andra registerstudier, går det inte att säkert fastslå att problemen berodde på läkemedelsbehandlingen. Mycket tyder dock på att den ökade sjukligheten hänger ihop med medicineringen.

List of papers

I. **Nörby U,** Källén K, Eiermann B, Korkmaz S, Winbladh B, Gustafsson LL. *Drugs and Birth Defects:* a knowledge database providing risk assessments based on national health registers. *Eur J Clin Pharmacol.* 2013;69(4):889–99.

II. **Nörby U,** Källén K, Shemeikka T, Korkmaz S, Winbladh B. Pregnant women's view on the Swedish internet resource *Drugs and Birth Defects* intended for health care professionals. *Acta Obstet Gynecol Scand.* 2015;94(9):960–8.

III. **Nörby U**, Forsberg L, Wide K, Sjörs G, Winbladh B, Källén K. Neonatal Morbidity After Maternal Use of Antidepressant Drugs During Pregnancy. *Pediatrics.* 2016;138(5):e20160181.

IV. **Nörby U**, Winbladh B, Källén K. Perinatal outcomes after treatment with ADHD medication during pregnancy. *Manuscript* 2017 (invited to resubmit).

Abbreviations

ACE	Angiotensin-converting enzyme
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorders
ATC	Anatomical therapeutic chemical classification
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
CPAP	Continuous positive airway pressure
ENTIS	European Network of Teratology Information Services
EUROCAT	The European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
GA	Gestational age
5-HT	5-hydroxytryptamine (serotonin)
ICD	International Classification of Diseases
IgG	Immunoglobulin G
ICBDSR	The International Clearinghouse for Birth Defects Surveillance and Research
LGA	Large for gestational age
MAS	Meconium aspiration syndrome
NA	Noradrenaline
MBR	Swedish Medical Birth Register
NCU	Neonatal care unit
NNH	Number needed to harm

NPR	National Patient Register
NRI	Noradrenaline reuptake inhibitor
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OTC	Over the counter
OTIS	Organization of Teratology Information Specialists
PDA	Patent ductus arteriosus
PDR	Prescribed Drug Register
PRS	Perinatal Revision South Register
PIL	Patient information leaflet
PIN	Personal identification number
PPHN	Persistent pulmonary hypertension of the newborn
RDS	Respiratory distress syndrome
SGA	Small for gestational age
SNQ	Swedish Neonatal Quality Register
SNRI	Serotonin noradrenaline reuptake inhibitor
SPC	Summary of product characteristics
SSRI	Selective serotonin reuptake inhibitor
TIS	Teratology information services
TCA	Tricyclic antidepressant

Introduction

The clear majority of pregnant women use medications at some point during their pregnancies [1-7]. Consequently, questions and worries concerning fetal effects of drug exposure are common. These situations are delicate since benefits and risks must be considered for both the woman and her unborn child [8]. The risk assessments are often complicated since available data concerning fetal effects are limited for many drugs [9, 10].

Further, it is often difficult to find reliable and consistent information concerning fetal impact of drugs, even when data do exist. This is especially problematic when it comes to information intended for lay people who often must settle with untrusted reports from the internet.

This thesis deals with risk assessment of drug treatment during pregnancy and how to communicate the findings to health care professionals and pregnant women. Special focus is on antidepressant drugs and ADHD medication that are increasingly used by pregnant women and where more knowledge concerning their fetal safety is desirable.

Fetal impact of drug exposure

Almost all drugs cross the placenta to reach the fetus to some extent [11, 12]. The most common way of transfer is via passive diffusion. The rate of diffusion depends on the physicochemical properties of the drug. Lipophilic drugs with a molecular weight <500 Da can readily cross the placenta. The diffusion also depends on the degree of ionization and protein binding of the drug since only the non-ionized and non-protein bound fractions are able to cross. Some drugs are transferred from the maternal to the fetal side of the placental membrane or vice versa, via active transporters, like p-glycoprotein and multidrug resistance proteins [11, 13]. Antibodies of IgG-type which constitute the active parts in many modern drugs are like other proteins too large to diffuse across the placenta. They are however transported by pinocytosis from the maternal to the fetal circulation, mainly in the third trimester. This is the same way as other IgG antibodies are transferred from the pregnant woman to the fetus to provide passive immunity in the first few months of life [14].

Whether the drug exposure might subsequently harm the offspring depends on the fetal stage of development, properties of the drug substance, in most cases dose and duration of exposure as well as the genetic susceptibility of the embryo [15-17].

A drug or another external agent with a potentially harmful effect on the developing fetus is often referred to as a teratogen [18]. Earlier, teratogenesis was mainly associated with structural birth defects (congenital malformations). Lately, the term regularly includes other negative impact on the fetus, like intrauterine growth restriction and impaired long term neurodevelopment [8, 19] but the exact definition varies in the scientific literature.

Apart from a direct fetal impact, drugs could also affect the fetus via pharmacological effects on the pregnant woman, such as causing drug-induced hypotension or uterus contractions [15]. Substances can also have mutagenic effects on the maternal or paternal germ cells and thereby influence the offspring [15, 20].

Early pregnancy

During the first two weeks after fertilization, exposure to a teratogen will most often result in either death of the embryo or a complete recovery without defects [16]. The embryo is most sensitive to structural birth defects when the organs are developing which occurs during the first trimester, primarily in pregnancy week 4-8 [8, 16, 21].

There is a quite specific risk period for each organ system. For example, the potent teratogen thalidomide might cause severe limb defects if exposure takes place between day 24-36 after conception, which is the critical period for limb development [16].

Figure 1. Kindergartner injured by drug thalidomide writing with aid of pencil-holding device.(Photo by Leonard Mccombe/The LIFE Picture Collection/Getty Images).

The mechanisms by which drugs may cause birth defects are not fully understood. Some processes have though been identified, i.e. folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and damage caused via acting on specific receptor or enzyme sites [22].

The background rate of major, quality of life-affecting birth defects among infants is 2-4% [17]. In most cases, the etiology is unknown but drugs have been estimated to cause less than 1% of structural birth defects [21].

Mid and late pregnancy

During the second and third trimester, all major structures in the fetus are formed but they continue to grow and mature. Exposure to drugs during this time cause mainly physiological and functional disturbances. Most organs are less vulnerable than in early gestation [8, 16]. The brain is however highly susceptible to environmental factors throughout the entire pregnancy, since it differentiates and growths rapidly until birth and beyond [10, 16]. Teeth, the skeletal and genital systems also have prolonged developmental periods [16]. It is further known that disturbances of the blood circulation after the first trimester might cause structural anomalies in organs initially formed normally [22]. Abnormal blood pressure is for example believed to be associated with increased risk of some congenital heart malformations, like septal defects [23].

Fetal exposure at later stages of the pregnancy is otherwise mainly associated with for example intrauterine growth restriction, impaired renal function, early closure of ductus arteriosus, intellectual disability, or behavioral effects during childhood [15, 16, 24]. Neonatal toxicity or withdrawal symptoms, usually predictable from the pharmacological profile of the drugs, are other effects usually connected with exposure near term [8, 24]. The delivery is an especially strenuous situation [25] where drug exposure might cause problems with adaption to extrauterine life.

Established or suspected teratogens

Since most drugs reach the fetus, many are associated with birth defects or suspected of entailing a risk. However, only a few are considered as established teratogens [13, 16, 18].

Generally, drugs that are proven teratogens have high odds ratios for fetal harm. Other drugs have weaker associations and the link from exposure to defect is likely more dependent upon other factors. In most cases, the cause of birth defects is multifactorial where drug treatment might constitute one of the risk factors [18].

An important aspect in the fetal response to a teratogen seems to be the genotype of the embryo [16, 26]. For example, only a small fraction of embryos exposed to phenytoin

develop the so called fetal hydantoin syndrome, while some have only a fraction of the birth defects associated with the syndrome and the majority of exposed fetuses are unaffected [16].

In Table 1, some drugs that are known to or strongly believed to have the potential to cause fetal harm, are listed.

Table 1. Examples of established teratogens or drugs that are highly associated with negative embryofetal effects.

Drug substance	Fetal effects (not comprehensive)
ACE-inhibitors	Oligohydramnios, anuria, IUGR (intrauterine growth restriction) and secondary pulmonary hypoplasia [15, 16]
Androgens and progestogens	Masculinization of the female external genitalia, progestogens can cause hypospadias and/or ambiguous genitals in the male fetus and cardiovascular defects [15, 16]
Antiepileptics, especially valproate and combination therapy	Congenital malformations: e.g. NTD (neural tube defects), orofacial clefts, microcephaly and cardiovascular defects, growth restriction, impaired neurodevelopment and intellectual disability [15, 27].
Methotrexate and other folic acid antagonists	Major birth defects: decrease in ossification of the skull; hypoplastic supraorbital ridges; small, low-set ears; micrognathia; limb abnormalities [15, 16]
Mycophenolate	Spontaneous abortions and major birth defects involving the external ear, facial anomalies, cleft lip/palate, and defects of the distal limbs, heart, esophagus, and kidney [15]
Opioids	Respiratory depression and withdrawal symptoms in the newborn [15]
NSAIDs	Constriction of ductus arteriosus which might result in pulmonary hypertension and death in severe cases, impaired renal function and oligohydramnios [15]
Retinoids	Retinoic acid embryopathy: CNS, craniofacial, cardiovascular and thymic anomalies [15, 16]
Thalidomide	Phocomelia (absence of or shortened part of a limb), heart defects, anomalies of the urinary and alimentary systems, absence of the external and internal ears, hemangioma of the face [15, 16]
Thyroid drugs: methimazole and propylthiouracil	Fetal goiter and scalp defects [15, 16]
Warfarin and other coumarine derivatives	Fetal warfarin syndrome: hypoplasia of the nasal cartilage and the extremities, various CNS defects and intellectual disability [15, 16]

The most infamous substance is the sedative thalidomide (Neurosedyn, Contergan), whose teratogenic effects were first described in scientific literature by McBride and Lenz in 1961 [28, 29]. It has been estimated that almost 12 000 children were born with thalidomide induced malformations worldwide in the end of the 1950s and beginning of the 1960s before the drug was withdrawn from the market [16].

Thalidomide was later reintroduced in several countries, mainly for treatment of leprosy [30]. In Brazil, this has caused additional infants to be born with thalidomide specific malformations since regulations and information concerning the risks associated with the drug has been inadequate [30, 31]. Nowadays, thalidomide and closely related substances are authorized in many countries around the world for treatment of multiple myeloma and leprosy. The use is strictly regulated and a risk management plan must be followed to avoid pregnancy during treatment [32].

Risk assessment

For ethical reasons, pregnant women are normally excluded from clinical trials [10, 33, 34]. Consequently, when a new drug enters the market, there are in most cases no human data on teratologic risks at all [10]. To establish fetal safety of a drug, postmarketing surveillance is therefore crucial and different surveillance systems were initiated world-wide after the thalidomide tragedy [35].

Shepherd suggested criteria for proof of teratogenicity in 1994 [36]. For example, it must be evidenced that exposure to the substance took place at a critical time in prenatal development and the teratogenic findings must be consistent in two or more epidemiologic studies of high quality. The latter is crucial. To establish a finding of a negative fetal effect in an epidemiological study, it should be confirmed in an independent data set.

Animal studies

For modern drugs, extensive animal studies investigating the reproductive and embryofetal toxicity are normally mandatory before authorization. Several species, of which one should be a non-rodent, are used, in most cases rats and rabbits. [24]. These studies might provide important information since the majority of established teratogens in humans, show similar effects in animal research [37]. However, there are sometimes essential differences between species [38]. For example thalidomide causes serious malformations in humans but not in rats and mice [8, 37]. Another example is acetylsalicylic acid that has induced malformations in animals but this seems not to be the case when used by pregnant women [8, 37]. Thus, animal studies are not trustworthy for assessments of fetal risks. Negative animal studies are no guarantee that a substance is free from reproductive effects in humans [39].

Observational studies

Researchers have instead to rely on different observational methods that all have their limitations [34]. It is therefore wise to consider information from different postmarketing surveillance sources to optimize detection and characterization of the reproductive effects of prenatal drug exposure [10].

Case reports from health care professionals or from affected families can generate important signals that a drug might have a negative fetal impact. To detect an association via case reports, it is usually necessary that the drug is a strong teratogen and that the outcome is unusual which is a quite rare situation [40]. Even so, it is important that clinicians report suspected negative outcomes to the authorities so that they in turn can initiate more detailed investigations.

The best available methods are well-performed epidemiology studies [39, 40]. Epidemiology data can identify associations between a given drug exposure and abnormalities in the newborn, and they can quantify the strength of such associations. Further, they can provide some measure of reassurance if risks are not found, although it is impossible to demonstrate absolute safety. The degree of reassurance depends on the sample size (power) of the study [10].

In cohort studies, a group of individuals who used for example a drug is followed. Birth and neonatal outcomes are thereafter analyzed and compared to a control group [10, 41]. Cohort studies are useful for studying many different, quite common fetal outcomes associated with a specific exposure [41, 42]. The challenges are mainly to define the cohort and to ascertain the outcomes. It might also be difficult to find a proper control group.

In case-control studies, the analyses start with the identification of cases, for example a congenital malformation. Thereafter, exposure to external agents is compared between cases and controls without this defect [10, 41]. This methodology provides the possibility to study the association between different exposures and a selected outcome. Case-control studies are especially suitable if the drug is a major cause of the teratogenic effect [42]. The problem is often to ascertain the exposure data [41]. In many studies, information on drug intake is collected after the birth outcome is known, for example via interviews with affected families. The drawback is that parents to children born with birth defects are more likely to report use of drugs than the control groups. This so called recall bias might result in an over-estimation of the fetal risk [42].

An advantageous situation is when exposure and outcome data are available for a whole population. In this case many different exposures and different fetal outcomes can be analyzed at the same time [42]. It is though important to be aware that when large number of drugs and fetal outcomes are studied, associations can arise by chance. The results must be confirmed in independent studies – either in a completely unrelated study or a continuation of the study which generated the signal [41].

In all observational studies, the challenge is to elucidate whether an association is a "true" association between exposure and outcome, or caused by confounders [8, 41]. A confounder is a factor that could distort the association between exposure and outcome if it is unequally distributed between the study groups. For a variable to be considered as a confounder, the following criteria must be fulfilled [43]:

- It is associated with the exposure
- It is associated with the outcome, either as a cause or a proxy for a cause, but not as an effect of the outcome
- It should not be in the causal pathway between exposure and outcome

Common confounders in research of fetal effects of drug exposure are maternal age, smoking, alcohol intake and use of other drugs [8, 41]. Dependent on the data sources, some confounders are quite simple to adjust for. However, confounding by indication – a negative outcome that is linked to the maternal disease being treated – is very difficult to deal with. A classic example is diabetes that per se is associated with an increased risk of malformations, making it complicated to study the fetal impact of anti-diabetic drugs [41].

Data resources

Some epidemiology data resources are used regularly within research regarding prenatal drug effects. Below is a brief overview of some categories of resources that have generated publications concerning fetal effects of drug exposure.

Total population databases

The Scandinavian countries hold several national health data registers on a population level that can be used for studying the association between drug exposure and birth defects [8, 41, 44]. The most important ones are birth registers, congenital malformation registers, drug prescription registers and hospital discharge registers (patient registers) [44]. The registries can be cross-linked via personal identification numbers and offers the possibility to adjust for many confounders [44]. Since whole populations are covered, the data are representative for pregnant women in the countries, something that might be difficult to achieve in smaller cohort studies. Another advantage is prospective collection of exposure data in relation to pregnancy outcome and high statistical power since no sampling is undertaken [41].

Pregnancy registries

Pregnancy registries are observational prospective cohorts of women receiving biopharmaceutical products, often maintained by drug companies [45]. A couple of examples are NTPR (National Transplantation Register) [46] and EURAP

(International Registry of Antiepileptic Drugs and Pregnancy) [47]. In the US, pregnancy registries are obliged by the FDA (Food and Drug Administration) for newly approved drugs [45]. In the analyses of fetal effects, pregnancy outcome in exposed women are compared either to control groups also included in the registries (non-exposed or exposed to other drugs) or to controls outside the register, usually based on population data. Pregnancy registries mostly contain reliable and detailed information on exposure but information on outcome data are sometimes week [41]. In general, pregnancy registries have not been very efficacious in generating useful information [48]. According to an evaluation carried out by FDA, data from such registries contributed to changes in the pregnancy labeling for only 12% (7/59) of the products surveyed [48].

Teratology Information Service Data

Teratology information services (TIS) counsel newly pregnant women regarding safety of medication use. The services are organized in two large networks: the European Network of Teratology Information Services (ENTIS) and the Organization of Teratology Information Specialists (OTIS) in North America [49, 50]. Based on data collected for women who contact a TIS, cohort studies are undertaken. Women exposed to a certain drug are compared to non-exposed or to women who used substances considered safe [50]. Like data from pregnancy registers – in fact information collected by TIS can be defined as pregnancy registries – exposure data are usually well described in these studies but power is often low. The external validity can also be a problem, since women who consult a TIS might differ from other women [8, 50].

Congenital malformation registers

Malformation registers were set up based on the thought that exposure to a new teratogen would lead to an unusual frequency and cluster of malformations [10, 35]. Until now, the registers have though not been very successful in identifying teratogens [35]. However, malformation registers might be used for identifying cases of malformations for further analysis in case-control studies [10]. Some malformation registers in Latin America and Spain include controls from the beginning (often the next non-malformed baby of the same sex born in the same hospital) [51, 52]. In the US, the National Birth Defects Prevention Study (NBDP) that covers around 10% of the births in the country includes controls without major birth defects from the same areas as the cases [53]. The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) and the European Surveillance of Congenital Anomalies (EUROCAT) are two large international networks of malformation registers [54, 55]. In Euromedicat, which is a project built on EUROCAT, information on maternal drug exposure is continuously collected for a subset of the malformation registers [8, 54]. In case control studies from Euromedicat and ICBDSR, the researchers used other malformed infants as controls, often infants with chromosomal anomalies [54-56]. This

makes the interpretation of the results somewhat different from that in standard case-control studies. Since healthy controls are not included, the odds ratios cannot be considered a direct estimate of the risks in the true population. It is however possible to detect signals of potential teratogens with this methodology [57].

Administrative databases

Information from administrative databases like health insurance programs are sometimes used to find associations between drugs and negative fetal outcome. The data are then linked to birth outcomes, often from other sources [34, 41]. Administrative databases frequently include large samples but they are not set up for pharmacoepidemiologic research and important data might thereby be missing [34]. The Medicaid and the Kaiser Permanente systems in the US are examples of administrative claims databases that have been used in research concerning teratogenicity [44].

Risk communication

Breaking news

Several studies show that both pregnant women and health care professionals believe that the teratogenic risk of drug exposure is much higher than the true risk [58-64]. The thalidomide tragedy is probably a main reason for this fear of fetal harm. However, in a recent survey, 70% of women – the majority younger than 40 years old – had actually not heard about thalidomide [65]. Still, they were quite skeptical concerning the safety of drugs in connection with pregnancy. Thus, the beliefs that drugs in general are potentially dangerous to the unborn child seem to prevail [65].

This opinion is possibly strengthened by numerous media reports describing how different medical drugs might harm the baby. These breaking news articles are often based on studies with major limitations that are far from conclusive. There is evidence that negative information from the internet or other media can have an adverse impact on the decision-making regarding drug treatment [66-68]. Compliance to drug treatment during pregnancy is often low [69-74], which is especially true for psychotropic drugs [70, 72-74]. Recently, researchers even introduced the term Psychopharmacoteratophobia, to describe the avoidance of these drugs during pregnancy [75].

On the other hand, there might also be a risk that non-reliable information contributes to overuse of medications with uncertain safety during pregnancy. There are examples of websites publishing “safe lists” of medications during pregnancy, even though

evidence for these assessments is missing [76]. Dependent on the definition of risk categories and study design, it has been reported that up to 5% of pregnant women use drugs considered contraindicated during pregnancy and that as many as 60% use drugs with some evidence of potential fetal harm [5, 77].

The informed patient

An important aspect when it comes to risk communication is that pregnant women to an increasing extent participate in decisions regarding their maternal health care and search for relevant information on their own [78-80]. In general, patients can nowadays often access complex medical information that previously was only obtainable for health care workers, for example medical records [81-83]. However, studies of the effects when lay people use this kind of information are still sparse [83].

To facilitate the understanding of scientific information regarding fetal safety of drugs, it is essential to describe basics like the background rate of birth defects and to put the results from studies into the right context. A 100% risk increase for an abnormality might sound deterrent. In reality, the absolute risk is generally still low. Explaining the risk increase in terms of number needed to harm (NNH) often simplifies the risk benefit assessments.

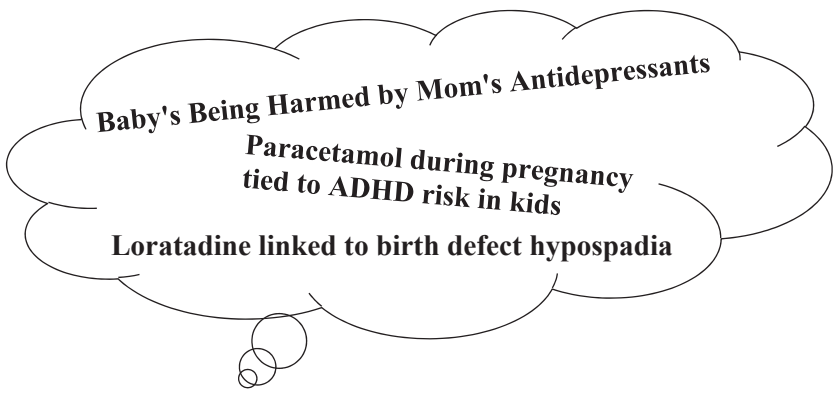


Figure 2. Examples of media headlines concerning adverse fetal impact due to drug exposure.

Available information resources

The most commonly used sources for information on fetal effects of drugs are possibly the official summaries of product characteristics (SPCs) and patient information leaflets (PILs) which describe properties and conditions for using a medicinal product. Unfortunately, this information is often conflicting [84, 85], overly cautious [86], difficult to interpret and of limited value in a busy clinical situation.

One of the problems is that information for drugs containing the same substance but produced by different manufacturers might be inconsistent, an issue that has been recognized in several countries [84, 85]. This discrepancy causes confusion. An everyday situation is when a physician convinced a pregnant woman to use a certain drug and she receives another generic brand with different information at the pharmacy. There are also examples where a pharmaceutical company provides different information concerning its own product in various countries which raises concerns about the reliability of the SPCs and PILs [87].

Commercial subscription databases or encyclopedias, nowadays also available on the internet are other ways to get information, at least for health care professionals. These resources often contain good quality information but might be costly with a tendency to be of better quality, the more expensive they are [88].

In the Nordic countries, health care professionals have the possibility to contact a drug information center for advice [89, 90]. This service is appreciated [90], but only available during office hours and can be time consuming. In Norway, the drug information centers also offer advice directly to pregnant women [91], while this service is not available in Sweden. Teratology information services (TIS) provide information to both pregnant women and health care professionals in North America and some European countries [49, 58].

To ensure easy access to reliable and consistent information on fetal risks of drugs, a national Swedish database – *Drugs and Birth Defects* – was launched in 2001. The database is part of a concept initiated within the Stockholm County Council to provide non-commercial drug information at point of care [92]. *Drugs and Birth Defects* provides assessments of potential fetal effects of all drugs on the Swedish market. The information is based on analyses of the Swedish Medical Birth Register and scientific literature. The database is freely available on the website www.janusinfo.se and can also be used as an integrated application in electronic health record systems. It was originally intended for health-care professionals but is increasingly used by the public.

Study I in this thesis describes the methodology behind the database and in study II, we investigated the perceived value of the information among different user categories.

Antidepressant drugs

The most controversial drug group in connection with pregnancy is nowadays probably antidepressant drugs. They have generated lots of media reports and belong to the most searched medications in the database *Drugs and Birth Defects*. Altogether, it is intricate to decide whether to use antidepressant drugs during pregnancy or not and it is also a common issue. Approximately 13% of pregnant women report depressive symptoms

[93].The prevalence of anxiety disorders, which is another indication for antidepressant drugs, range between 4 and 39% in the pregnant population [94]. Presently, around 4% of pregnant women in Sweden and at least 6% in the US undergo treatment with antidepressant drugs [93, 95, 96] and the use is increasing [95, 96].

Drug categories

There are several categories of antidepressant drugs, with different properties. They have however in common that they in some way affect the monoaminergic receptor sites in the brain [97]. The classical theory behind the effects of antidepressant drugs is that they enhance the transmission of the neurotransmittors serotonin (5-HT), noradrenaline (NA) or both [97, 98].

Selective serotonin reuptake inhibitors (SSRIs), block specifically the reabsorption of serotonin from the synaptic cleft into the presynaptic cell [97]. The SSRIs are first-line pharmacological treatment for depression and anxiety because of their combination of effectiveness and favorable side effect profile [98, 99].

The older tricyclic antidepressant drugs (TCAs) enhance both the serotonergic and the noradrenergic activities via blocking the reuptake mechanisms. Additionally, TCAs act on histaminic, cholinergic and alpha-1-adrenergic receptor sites which bring about unwanted side effects.

A third antidepressant category is serotonin and noradrenaline reuptake inhibitors (SNRIs) [98]. As the name implies, SNRIs have a broader effect on neurotransmittors than SSRIs, but they act on fewer receptor sites than the TCAs [97]. The SNRI-group is used as second-line therapy as an alternative to SSRIs. For treatment of severe depression, both the TCAs amitriptyline and clomipramine and the SNRI venlafaxine, have been demonstrated to be more efficient than SSRIs [98].

Mirtazapine is another second-line antidepressant drug. The substance is a presynaptic alpha-2-receptor antagonist which results in enhanced noradrenergic transmission but it also inhibits postsynaptic 5-HT2 and 5-HT3-receptors [98]. Another substance with similar mechanisms as mirtazapine is mianserin [97, 98].

The different antidepressant substances have diverse side effect profiles [98]. The SSRI substances quite often cause sexual disturbances, gastrointestinal problems and psychiatric adverse events [100]. The TCAs are associated with constipation, dry mouth, drowsiness and dizziness. Further, TCAs are toxic and can cause cardiovascular problems which is also the main cause of death due to overdose which is a special risk with these drugs [97]. The SNRI drug venlafaxine, is recognized for causing nausea and increased blood pressure [100]. Mirtazapine is linked to sedation, increased appetite and weight gain [100]. The most commonly used antidepressant drugs are all known to cause withdrawal symptoms [100].

There are more antidepressant drugs available that are not mentioned in this introduction, since they are prescribed quite rarely. The overview of fetal effects of antidepressant drugs below, regard the most frequently used drugs, primarily SSRIs.

Fetal effects

Congenital malformations

There seems to be enough evidence to rule out a significant risk of malformations after exposure to many antidepressant drugs during early pregnancy [95, 101-103] although paroxetine, fluoxetine and clomipramine have been associated with a slight increased risk for cardiac malformations [102, 104]. Paroxetine and fluoxetine have also been linked to some other malformations but the absolute risk increase was small and it is uncertain whether the association was causal [104]. For drugs where there are still few exposures during pregnancy, it is not yet possible to assess their potential to cause malformations.

Neonatal complications

Treatment with antidepressants during later stages of pregnancy is more problematic. It has been linked to neonatal complications like respiratory distress, hypoglycemia and CNS effects, as well as premature birth, low birth weight and low Apgar scores [105-121]. The neonatal symptoms seem to be transient [106, 107, 113, 114, 122] but can necessitate observation and treatment in a neonatal care unit (NCU) [105, 107, 108, 110, 116]. The neonatal problems are assumed to be withdrawal effects [109, 122, 123] as seen after discontinuation of antidepressant agents among adults [109, 124] or a serotonergic overstimulation syndrome [109, 122]. The symptoms are sometimes referred to as a poor neonatal adaptation syndrome (PNAS) [109].

It is however unclear to what extent these complications are caused by the antidepressant drugs or by the underlying disease. Several studies failed to show an effect of the drugs when adjusting for the mother's depression or when exposed infants were compared to a control group of infants to depressed but untreated mothers [125-128]. Other studies indicated that the symptoms are indeed drug-induced [110, 115, 117, 120, 129].

A serious but rare complication associated with use of SSRIs during pregnancy is persistent pulmonary hypertension (PPHN) in the newborn [130, 131]. The mortality rate of PPHN is around 10% [132] and its association with SSRI-treatment during pregnancy has caused bold headlines in the press. It is unclear whether SSRI-exposed infants with PPHN have the same symptom severity as other infants diagnosed with PPHN. In study III, we aimed at quantifying the neonatal morbidity after maternal use of antidepressants during pregnancy. One objective was to analyze the severity of symptoms in infants diagnosed with PPHN after intrauterine SSRI-exposure.

Long-term effects

Regarding the children's long term neurodevelopmental effects after intrauterine exposure to antidepressants, there are less evidence in the literature. The results are inconsistent, even though most studies didn't show a negative impact [95, 133, 134]. The studies were though quite small and included relatively young children, thus there are no data concerning for example future psychiatrics conditions in exposed individuals [95].

Lately, a discussion has been ongoing whether in utero exposure to antidepressant drugs may cause autism spectrum disorders (ASD). Again, the results from existing studies are conflicting [135-141]. Some researchers showed an association [137, 139] while others did not [135, 136, 138, 140, 141]. Children, whose mothers are treated with antidepressant drugs, probably have an increased genetic disposition for ASD, which is difficult to adjust for in observational studies. Genetic components could thereby explain the increased risk for ASD. This is supported by studies where no difference in risk for ASD was found between siblings exposed and unexposed to antidepressants during pregnancy [140, 141]. Researchers have also displayed that treatment with antidepressant drugs before pregnancy also is associated with ASD [136, 138, 141], in a couple of studies even more so than treatment during pregnancy [136, 138]. This further strengthens the theory that other factors than the antidepressants drugs are responsible for the link to ASD.

ADHD-medication

Another area that currently receives lots of attention is treatment of ADHD/ADD (Attention deficit disorder with or without hyperactivity). The prevalence of ADHD among adults is in the range of 2-5% [142]. During the last 10 years, the use of ADHD-medications has increased rapidly, especially among young women [143, 144]. In Sweden around 30 000 women between 15 and 54 years old are treated with at least one of the drugs approved for treatment of ADHD [145]. The use during pregnancy is also increasing [96, 144, 146] and there is a growing demand for information concerning the fetal safety of these drugs.

Drug categories

Centrally acting sympathomimetics (stimulants) are first line pharmacological treatment of ADHD [143, 147]. In Sweden and Denmark, methylphenidate is the most commonly used drug [143, 146] while different amphetamine preparations are more often used in the US [144]. In Sweden, dexamphetamine and the long acting prodrug lisdexamphetamine have been approved quite recently [143]. However, amphetamine

has been used in the treatment for ADHD via special permissions (licences) for many years.

The centrally stimulating drugs increase the catecholamine availability but the exact mechanism of action is not known [147]. They are classified as narcotics and are associated with drug abuse [143, 147]. Significant side effects of stimulants are loss of appetite, stomach pain, nausea, headache, increased pulse and blood pressure, tics, sleep disorders, anxiety, reduced mood and other psychiatric symptoms [143, 147]. They can also cause withdrawal symptoms after discontinuation of treatment [143, 147].

Another drug for treatment of ADHD is atomoxetine, a presynaptic inhibitor of noradrenaline reuptake (NRI). Atomoxetine is a non-stimulant, non-narcotic drug that is not associated with abuse. Otherwise, it shares many of the side effects of the stimulant drugs like loss of appetite, nausea, increased pulse and blood pressure and psychiatric symptoms [143, 147, 148]. Until now, withdrawal symptoms has not been reported for atomoxetine [143].

A newly approved drug for ADHD with a different profile is guanfacin, an alpha-receptor agonist initially developed for treating hypertension [143, 149]. Guanfacin lacks stimulating properties and its main side effect seems to be sedation [143].

Finally, the substance modafinil belongs to stimulant drugs. Modafinil is approved for treatment of narcolepsy but there are studies where the effect of modafinil for treatment of ADHD has been evaluated [150]. Modafinil is sometimes included among drugs for treatment of ADHD and there might be some off-label prescribing for this indication [87, 146].

Fetal effects

Compared to antidepressant drugs, ADHD-medications are less studied during pregnancy and data are still limited [146, 151-154], especially when it comes to neonatal effects usually associated with exposure during late pregnancy. Therefore, study IV in this thesis was undertaken to increase the knowledge within this area.

Methylphenidate has to date not been associated with an increased rate of congenital malformations in humans [151, 153, 154]. In animal studies, the substance only induced malformations in doses much larger than the recommended human dose [153, 155]. However, an increased risk for miscarriage [146] and low Apgar scores was shown after exposure to methylphenidate [152] in Danish register based studies.

Concerning amphetamine salts, it is difficult to evaluate existing data. The studies were mostly undertaken among pregnant women with illicit drug use or who used amphetamine products for weight loss [156, 157]. However, amphetamine products do not seem to increase the overall risk of structural malformations [102, 158], even though a few human reports with methodological limitations indicated a higher rate of some

birth defects [159-161]. Otherwise, an association has been found between prenatal exposure to amphetamines and low birth weight, preterm birth, smaller head circumference and problems in the newborn infant like poor feeding, tachypnea and lethargy [156, 162-167]. Some of the neonatal problems were possibly withdrawal symptoms [164, 167]. Confounding factors like misuse of alcohol and other drugs were most likely affecting the results [162, 168].

The available studies regarding long term effects on children exposed to amphetamines in utero were probably even more affected by confounding factors, than those regarding short term neonatal outcomes [162]. The results indicate an association with impaired neurodevelopment and inferior school results but it is impossible to define to what extent the problems were caused by exposure to amphetamine or other factors like the psychosocial environment [162, 169].

For the non-stimulant drug atomoxetine, there is very limited information regarding pregnancy. Since it is an NRI-drug, atomoxetine could theoretically be suspected to cause similar problems as antidepressants, for example neonatal adaption problems. For guanfacin and modafinil, data in connection with pregnancy seem to be non-existent.

Aims

The overall aim of this thesis was to explore how fetal risk assessments can be communicated via a knowledge database and to investigate the fetal safety of two selected drug groups.

Specific objectives

1. To present the concept and methods behind the scientific knowledge database *Drugs and Birth Defects*
2. To estimate the perception and value of the database among health care professionals and pregnant women
3. To quantify neonatal morbidity measured as admissions to neonatal care units, the infant's diagnoses and interventions after in utero exposure to antidepressant drugs
4. To assess the risk of negative birth and neonatal outcomes after maternal treatment with ADHD medication during pregnancy

The results regarding antidepressants and ADHD treatment were intended to fill knowledge gaps within these areas and thereby improve the risk assessments in the database *Drugs and Birth Defects.* Antidepressant drugs and ADHD medication were chosen due to the current debate concerning the appropriate use of these drugs and since there were unanswered questions regarding their fetal safety.

Methods

Study I: *Drugs and Birth Defects* – database concept

Workflow

The database *Drugs and Birth Defects* provides assessments of fetal risks for all drugs on the Swedish market. It is produced according to a concept for knowledge databases developed in the Stockholm county council [170], see Figure 3.

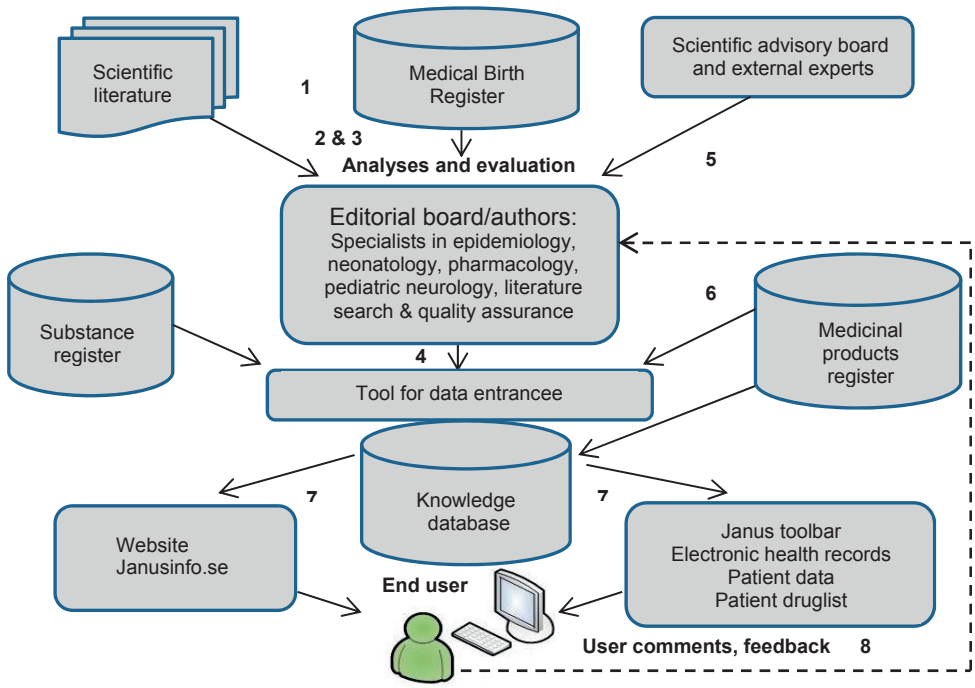


Figure 3. Work-flow for producing and maintaining the database *Drugs and Birth Defects.*
1. Epidemiological data and literature sources. 2 and 3. Assessment and classification of fetal risks based on data collected in step 1. 4. Entry of fetal assessments in structured format supported by standard expressions. 5. Reviews of advisory board members and external clinical experts. 6. Linkage to a medicinal products register followed by quality assurance. 7. Distribution through various channels; freely on the internet or integrated into electronic health records. 8. Regular evaluations among users.

Essential steps are evaluation of scientific information, medical editing and quality control, linkage to medicinal product registers to enable searches for all drugs on the market, distribution to end-users and evaluation of contents and functions during use in clinical practice. The details vary however, dependent on which therapeutic area the database is intended.

Assessment of fetal risk

For *Drugs and Birth Defects*, the corner stone is information from the Swedish Medical Birth Register (MBR) [96]. The register holds data on all pregnancies in Sweden that have resulted in deliveries, including information on the newborn infants. It is described in more detail in the methods section for study III and IV below.

To identify signals of negative fetal outcomes, MBR data on maternal drug use during pregnancy are analyzed in relation to birth outcome. The main outcome studied is "weeded malformations", which is defined as malformations excluding some common minor conditions[1]. Other outcomes studied are preterm birth, Apgar score less than 7 at 5 minutes, low birth weight, small for gestational age, multiple pregnancies, still births and perinatal deaths.

The results from the MBR are interpreted together with data on fetal impact from published epidemiological and clinical studies. For new drugs and other substances where experience is sparse or missing, the assessments are mainly based on pharmacodynamic and pharmacokinetic properties of the substance and animal data. The drugs are classified per a 3-tier system based on the estimated fetal risk level, defined in Table 2.

Selected documents are reviewed and discussed with a scientific advisory board and clinical specialists. These experts have a consultative, though very important, role.

Statistical methods

When analyzing the MBR data, the frequency of an evaluated outcome among infants exposed to a drug substance is compared with the population rate. If the number of expected cases is less than 10, the significance level is based on the exact Poisson distribution; otherwise a Chi-square test is performed. In order to estimate the power to detect a true association between drug use and birth defects, the lowest detectable risk ratio (two-sided with α=0.05 and β=0.8) for any relatively serious birth defect is estimated.

[1] Tongue tie, nevus, undescended testicles, ductus in preterm infants, single umbilical artery, hip dislocation/subluxation

Table 2. Risk classification in the database *Drugs and Birth Defects.*

Risk class	Definition
1	The drug can be used during pregnancy without any increased fetal risk.
2	Important information is available concerning this drug during pregnancy.The experience of the drug may be limited. Therefore, it should be used with caution. The drug might also be suspected of causing – or in rare cases have been demonstrated to cause – a moderate risk increase of birth defects or other negative fetal effects.
3	If used during pregnancy, the drug entails or is suspected of entailing a considerable risk to the fetus.The patient should be informed about the risk and exposure should result in a discussion regarding how to handle the pregnancy.

Study II: Evaluation of *Drugs and Birth Defects*

Study design and data collection

The database *Drugs and Birth Defects* was evaluated via electronic questionnaires in two different settings:

1. Among pregnant women and health care professionals recruited at the same maternal health care centers (thesis paper II)
2. Among the main target group – gynecologists, midwives, neonatologists and general practitioners around the country – reached via e-mail (unpublished)[2]

Data collection via questionnaires was chosen to reach enough material to be able to compare different user categories and to analyze the answers in relation to background characteristics among the respondents.

1. Pregnant women and their midwives/physicians

This study was undertaken to verify previous results from a pilot study showing that the database works well also for lay people. At first, we considered to use validated methods for assessing information technology, like TAM (Technology Assessment Model) [171], and established scales for measuring anxiety like STAI (State Trait Anxiety Inventory) [172]. However, we concluded that these tools, even when modified for our purposes,

[2] Previous evaluations among health care professionals are described in study I. The results presented here are from a more recent survey undertaken in 2013-2014.

were not specific enough. Therefore, we developed an electronic questionnaire on our own in cooperation with behavioral scientists with experience from similar projects. The questionnaire consisted of multiple choices, scaled and open-end questions and focused on benefits and risks when pregnant women use the database. It was validated via semi-structured interviews with five women who were either pregnant or recently gave birth and adjusted along with their suggestions.

Pregnant women were consecutively recruited by midwives or research staff from the Health and Medical Care Administration at the women's regular visits at 10 antenatal clinics. This method of recruitment was less biased than in the pilot study, where only persons who had already found the website took part. The women, who agreed to participate, signed an informed consent and received a leaflet with instructions how to reach the database and the electronic questionnaire. They were free to search for drugs that they were interested in and could also choose how many texts they preferred to read. The only exclusion criterion was women who did not understand Swedish.

Further, we sent a similar questionnaire via e-mail to midwives and physicians working at the same antenatal clinics as the pregnant women attended. Administrative staff or midwives at the clinics provided us with the e-mail addresses. The aim was to get the staff's opinions about lay people reading the texts. The participating physicians were specialists in gynecology/obstetrics and the majority was employed at university hospitals.

The questionnaires are available in the appendices in thesis paper II.

2. Gynecologists, midwives and general practitioners throughout Sweden

Parallel to the study among pregnant women, an evaluation was also carried out via e-mail among the main users of the database: gynecologists, midwives, neonatologists and general practitioners. This questionnaire focused mainly on utility and value of the database in the clinical work of the professionals. A couple of questions were however included regarding risk and benefits if pregnant women use the database, to get additional information on this topic besides the evaluation in setting 1. The e-mail addresses were obtained from specialist associations for the respective profession and included members from all parts of Sweden.

To set up and collect data from the electronic questionnaires, we used the survey tool Easyresearch provided by Questback.

Statistical methods

Chi-square or Fisher's exact tests were used to analyze whether pregnant women, health care staff and subgroups of pregnant women answered differently to essential questions.

To find factors associated with increased anxiety among pregnant women after they had read the texts, we conducted univariable logistic regression analysis after dichotomization of the answers. "Increased anxiety" was dependent variable and the following factors independent variables: "primipara", "continuous drug treatment", "searched for drug information from at least three different sources", "drug use during previous pregnancy", "age", "health status", "education", "medical education/ background", "the contents are difficult to understand", "the contents strengthen information from the staff", "the information is helpful in deciding whether to use drugs", "there are risks associated with pregnant women reading the texts", "I would fully recommend other pregnant women to read the texts" and "I would prefer a version of the database specially adapted for lay people".

The six variables with the strongest associations in the univariable analysis were used in multivariable logistic regression analysis. Missing values were imputed using last observation carried forward. The statistical software was IBM SPSS, ver. 22 (IBM Corp., Armonk, NY, USA).

Study III and IV: Antidepressants and ADHD medication

Sweden offers excellent possibilities for epidemiological research. Therefore, we used register based data to study perinatal effects of antidepressant drugs and ADHD medication. The National Board of Health and Welfare is responsible for six mandatory health data registers covering the whole population [173]. The information is used for statistics, quality assurance of health care services and research [173].

Additionally, there are many national and regional quality registers, covering different therapeutic areas [174]. They complement the health data registers and hold more detailed information on diseases and interventions. Most quality registers have been initiated by health care professionals with the aim to examine and improve patient care [174]. Unlike the governmental health data registers, it is optional to be recorded in a quality register.

In medical research, data from different registers are linked via the Swedish personal identification number (PIN), which is assigned to every legal resident in the country [175].

Data sources

In this thesis, the following data sources were used.

Swedish Medical Birth Register

The Swedish Medical Birth Register (MBR) was established in 1973 by an act of the parliament [176]. The purpose of the register is to compile information on antenatal and perinatal factors, and their importance for the health of the infant. It covers more than 97% of all births in Sweden [176]. The information is collected from antenatal records and records from the delivery and examination of the newborn infant [40]. Some data, for example the PIN of the newborn – are imported from the government administrative agency, Statistics Sweden (Statistiska Centralbyrån, SCB) [177].

At the pregnant woman's first visit to the antenatal clinic, she is interviewed by a specially trained midwife [40]. Information on family situation, previous pregnancies, weight, height, maternal diseases, smoking habits and medication use is collected and later stored in MBR. Since the initial visit takes place during the first trimester for 90% of the women, this information on drug use is mainly interesting for studying congenital malformations [176]. It has been estimated that around 60-70% of drug treatment for chronic diseases are reported by the women during the midwife interview [1, 176]. Information in the MBR on drug use during the rest of the pregnancy covers mostly drugs prescribed in antenatal care and not from other health care centers. Therefore, this information is often incomplete [176].

Additionally, MBR includes information on gestational length, birth weight, Apgar scores, congenital malformations and other neonatal diagnoses from delivery and neonatal records. Gestational age (GA) is in >95% of the pregnancies in Sweden, based on ultra sound estimation [178]. The diagnoses registered in MBR are coded according to the International Classification, 10th Revision (ICD-10) and the drug exposure according to the ATC (Anatomical Therapeutic Chemical) classification system.

Prescribed Drug Register

The Prescribed Drug Register (PDR) was established in Sweden in 2005. It contains information on drugs dispensed at the Swedish pharmacies [179]. Age, sex and PIN of the patient are recorded together with the dispensed item: substance, brand name, formulation, date of prescribing and dispensing at the pharmacy [179]. The coverage is almost complete for drugs prescribed and dispensed in ambulatory care. However, drugs used for inpatient care in hospitals are not registered. Extraction of data on drug exposure from both the MBR and the PDR, gives a more comprehensive picture of maternal drug use during pregnancy than each register alone [180]. The MBR covers for example OTC-drugs bought without a prescription. As in MBR, the drugs are classified using the ATC-classification system in the PDR.

Swedish Neonatal Quality Register

The Swedish Neonatal Quality Register (SNQ) was initiated in 2001 and holds information on infants that are admitted to a neonatal care unit (NCU) at birth or within 28 days afterwards [181]. Since 2012, all 37 neonatal care units in Sweden are covered. The register constitutes the basis for improvement of the neonatal care in Sweden. After ethical approval, data can also be used for research via an application to the register's steering board [181]. In SNQ, information is stored on the infant's diagnoses and treatments, for example interventions like continuous positive airway pressure (CPAP) and ventilator treatment. The diagnoses are registered as ICD-10-codes or via predefined checkboxes in the infant's medical record.

Perinatal Revision South Register

The Perinatal Revision South Register (PRS) is a quality registry that covers the southern healthcare region in Sweden. It contains information on obstetric and neonatal care in this area since 1995 [182]. The objective is to improve clinical care and the variables registered are similar to those in SNQ. Since 2012, data from PRS are also included in SNQ.

Study design

Figure 4 displays an outline of the study designs and data sources for study III and IV respectively. We identified singleton births via MBR, which was also used for maternal background characteristics, birth outcomes and neonatal conditions. Data on drug exposure were obtained both from the PDR (late and early pregnancy exposure) and from MBR (mainly early pregnancy exposure collected via midwife interview). For neonatal outcomes, we used the quality registers SNQ and PRS together with the MBR. Collecting data on neonatal outcome from these three registers provided a more complete recording of diagnoses than in previous studies, where only the MBR was used. Additionally, the quality registers provided unique information not available in MBR.

Linkage between the registers was carried out via the Swedish PIN.

A crucial problem was to distinguish between the effects of the drug exposure and the psychiatric or neuropsychiatric conditions of the women. These diagnoses are not registered in MBR. They are however recorded in the National Patient Register (NPR) [183]. We therefore considered using this register to identify pregnant women with relevant psychiatric disorders but who did not use antidepressant drugs or ADHD medication during pregnancy. However, the NPR only covers inpatient treatment in hospitals or visits at specialist outpatient clinics, and not primary care [183]. Thereby, this approach would have limited our data material. Instead, we adjusted for the underlying condition in study III by comparing infants exposed to antidepressant drugs

during late pregnancy with infants exposed during early pregnancy only, Figure 4. We believe that this approach was a better solution than using the NPR. The difference in for example disease severity is probably lesser between women who use antidepressants during different stages of the pregnancy than between women who are treated and untreated during pregnancy.

In study IV, infants of mothers who used ADHD medication during pregnancy were compared to infants of mothers who used ADHD medication anytime during the study period but not during pregnancy, Figure 4. This method is most likely more reliable than trying to identify untreated controls via the NPR.

The different control groups for antidepressant drugs and ADHD medication was due to partly different perinatal outcomes studied, se below, and fewer exposures to ADHD medication than to antidepressant drugs. It is also likely that ADHD medication more often was interrupted than antidepressant drug treatment, which would have made a comparison between late and early pregnancy exposure less precise for these drugs.

Drug exposure and perinatal outcomes

Antidepressant drug exposure was defined as drugs belonging to ATC-class N06A (antidepressants). The substances were divided into subgroups based on their pharmacologic properties: SSRI, SNRI, TCA, mirtazapine/mianserin and other antidepressants, see Table 3. The use of antidepressants was allocated into any use (self-reported use according to MBR and/or registered in PDR during pregnancy or 1 month before), late use (drugs registered in PDR during the last 90 days of the pregnancy with or without early use), and early use only (self-reported use according to MBR and/or registered in PDR during pregnancy or 1 month before and during pregnancy but not during the last 90 days of the pregnancy).

In the study of ADHD medication, information on the following drugs was obtained: methylphenidate, amphetamine, dexamphetamine, lisdexamphetamine, atomoxetine and modafinil (Table 4). We divided treatment with ADHD drugs into use during pregnancy (self-reported use according to MBR and/or registered in PDR during pregnancy or 1 month before) and use before/after pregnancy (use at any time during the study period except during the interval 1 month before pregnancy until delivery).

We also collected data on other drugs that might cause the same perinatal problems as antidepressants and ADHD medications, for example opioids and sedatives. For details, see Table 3 and 4.

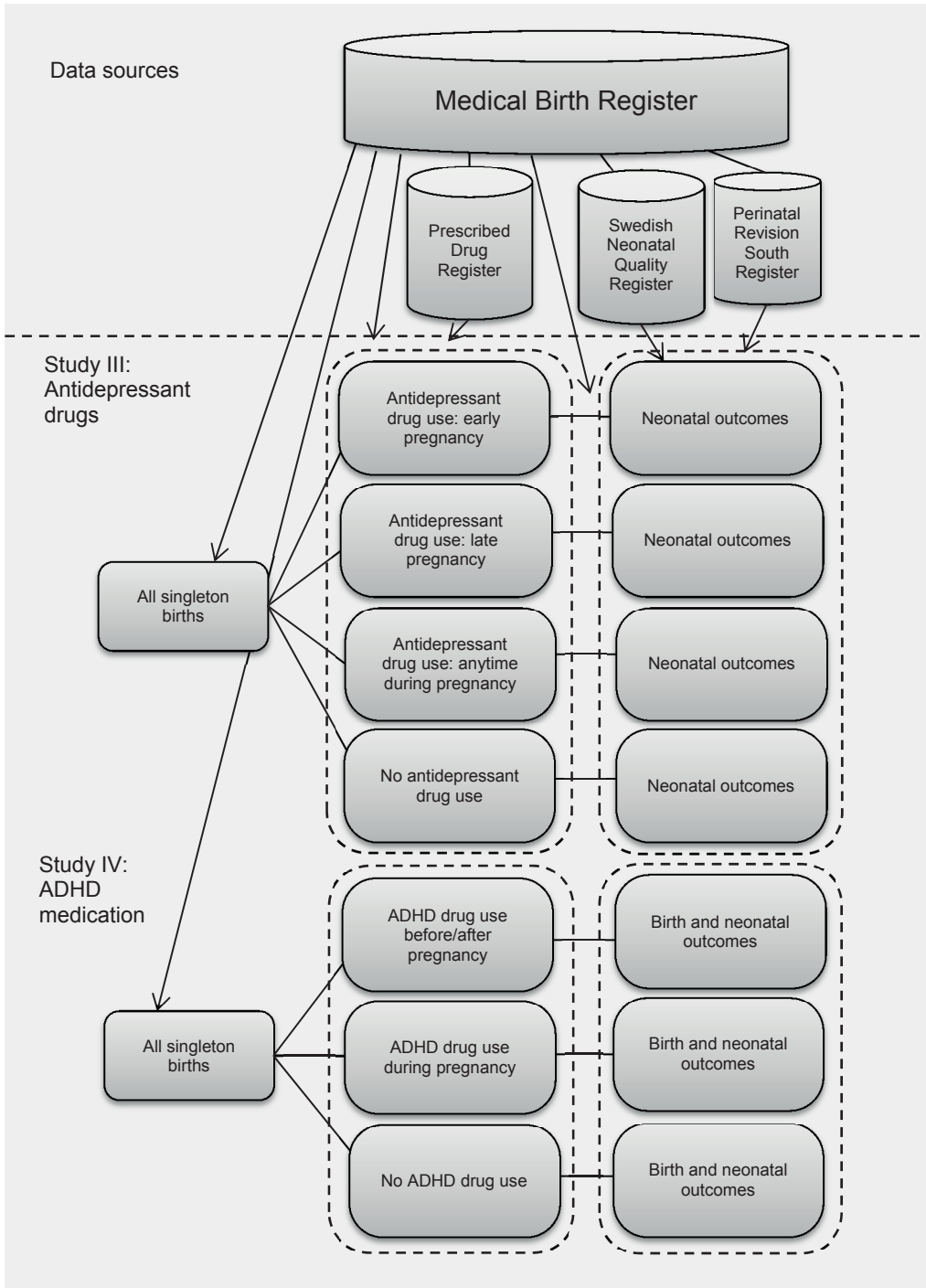


Figure 4. The register based studies: flow chart of design and data sources.

Perinatal outcomes

Study III focused on neonatal morbidity, primarily measured as admission to NCU. For SSRIs, which was by far the largest drug group, data on the main neonatal diagnoses as well as common interventions were obtained, see Table 3. The diagnoses were recorded as ICD-10 codes or via predefined checkboxes in the neonatal quality registers. A detailed list of definitions of the outcomes is available in the appendix to paper III.

Table 3. Study III. Antidepressant drugs. Overview of exposure, covariates and outcomes.

Drug exposure (ATC-code)	Covariates	Perinatal outcomes
Any antidepressant (N06A)	Maternal factors	Admission to NCU – duration of stay
SSRI (N06AB)	Age	Any respiratory disorder[C]
SNRI	Year of childbirth	RDS
Venlafaxine (N06AX16)	Primiparity	Transient tachypnea/ other respiratory disease
Duloxetine (N06AX21)	BMI	PPHN
TCA (N06AA)	Born in Sweden	MAS
Mirtazapine (N06AX11) and mianserin (N06AX03)	Smoking	CPAP – duration
Other antidepressants	Not living with father of child	Ventilator – duration
Moclobemide (N06AG02)	Cesarean delivery	Hypoglycemia[C]
Bupropion (N06AX12)	Use of mild sedatives[A]	Hyperbilirubinemia[C]
Reboxetine (N06AX18)	Use of other neurotropic drugs[B]	CNS-related disorders[C]
Agomelatine (N06AX22)	Fetal factors	Feeding difficulties[C]
Combinations/change of drug	Gestational age	Intracranial hemorrhage[C]
	Birth weight z-score	Verified infections[C]
		Treated PDA[C]

[A] Alimemazine, promethazine, propiomazine, and hydroxyzine
[B] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05) and stimulants (N06BA).
[C] Only analyzed for SSRIs
Abbreviations: RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; MAS, meconium aspiration syndrome; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus

Apart from neonatal diagnoses, study IV included other outcomes like gestational age, Apgar scores, birth weight z-score [184], and birth defects (Table 4). The reason was that previous data concerning these outcomes in connection with ADHD medication were sparse, in contrast to antidepressant drugs. Some of the diagnoses analyzed in study III had to be omitted in study IV due to low power.

Table 4. Study IV. ADHD medication. Overview of exposure, covariates and outcomes.

Drug exposure (ATC-code)	Covariates	Perinatal outcomes
Any ADHD medication (all ↓)	Maternal factors	Gestational age[B]
Stimulants	Age	Birth weight, z-score[B]
Methylphenidate (N06BA04)	Year of child birth	Apgar score at 5 minutes[B]
Amphetamine (N06BA01)	Primiparity	Birth defects (weeded)[B]
Dexamphetamine (N06BA05)	BMI	Perinatal death[B]
Modafinil (N06BA07)	Mother born outside the Nordic countries	Admission to NCU – duration of stay
Non-stimulant	Smoking	Any respiratory disorder
Atomoxetine (N06BA09)	Not living with father of child	Transient tachypnea/ other respiratory disease
	Cesarean delivery	PPHN
	Use of other neurotropic drugs[A]	RDS
		CPAP – duration
		Ventilator – duration
		Hyperbilirubinemia
		Hypoglycemia
		Feeding difficulties
		CNS-related disorders
		Withdrawal symptoms from therapeutic drugs

[A] Opioids (N02A), antiepileptics (N03A), psycholeptics (N05) and antidepressants (N06A), alimemazine (R06AD01) and promethazine (R06AD02, R06AD52)
[B] Not adjusted for cesarean delivery
Abbreviations: PPHN, persistent pulmonary hypertension of the newborn; RDS, respiratory distress syndrome; CPAP, continuous positive airway pressure

Statistical methods

Logistic regression analyses were used for dichotomous outcomes to obtain odds ratios (ORs). We compared any antidepressant use vs no use, the individual antidepressant substances vs no use, and late pregnancy use vs early pregnancy use only. In the same way, any use of ADHD medication was compared to no use and to use before/after pregnancy.

Both crude and ORs adjusted for the maternal background characteristics presented in Table 4 and 5, were calculated. The outcomes GA, birth weight, birth defects, Apgar scores and perinatal death were however not adjusted for cesarean delivery. The reason is that cesarean delivery is an effect, or a proxy of an effect, of these three outcomes. Thereby, it should not be dealt with as a confounder. In study IV, we used backwards selection procedures to obtain a final model that included maternal covariates with $p<0.2$. All maternal factors were included in the final model in study III.

In some of the analyses in study III, we also controlled for fetal factors – GA and birth weight for GA and sex. Both depression and antidepressant drug exposure during pregnancy are known to be associated with prematurity and SGA. Our adjustments yielded a measure of the effect of the antidepressant drugs on neonatal morbidity, not mediated via these factors, see Figure 5. The results should not be regarded as a final effect of the drug exposure, but as an assessment of whether the neonatal outcomes seemed to be due to prematurity or intrauterine growth restriction.

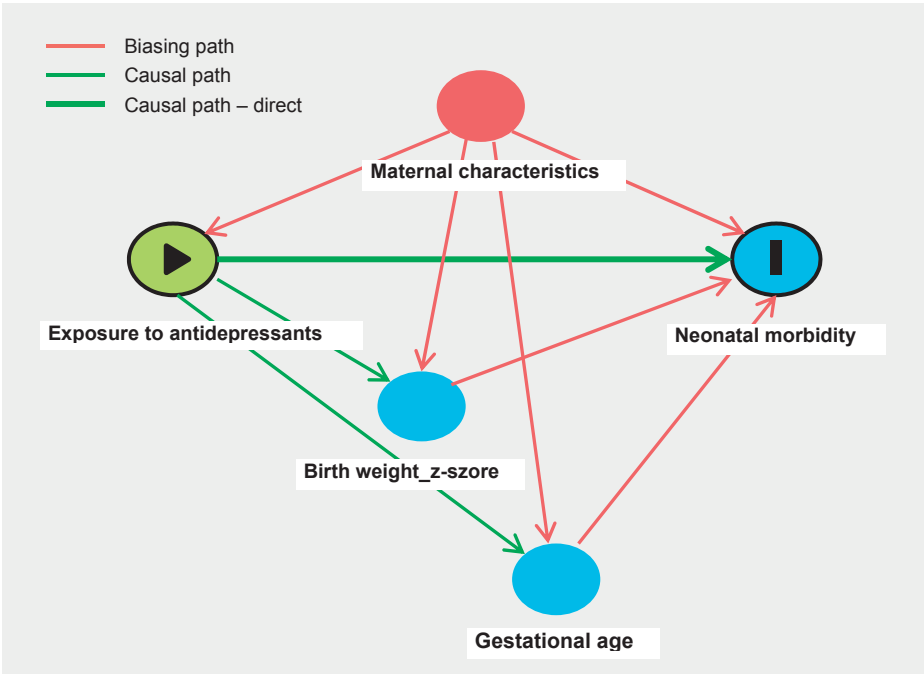


Figure 5. Simplified acyclic graph of exposure, covariates and outcomes in study III.

The differences in length of stay at NCU and number of days on a ventilator or CPAP were evaluated with Mann-Whitney U or Kruskal-Wallis tests.

Tests of homogeneity of the ORs across the antidepressant groups were based on weighted sums of the squared deviations of the stratum specific log-ORs from their weighted means.

The statistical analyses were conducted by using SPSS versions 22 and 23 (IBM SPSS Statistics, IBM Corporation, Armonk, NY) and Gauss (Aptech Systems Inc, Maple Valley, WA; http:// www.aptech.com, version 10).

Ethical considerations

In the evaluation study, the main ethical concern was that pregnant women would be anxious from reading texts concerning malformations and other negative impact on the unborn child. This could potentially have resulted in that they chose to terminate necessary treatment. When recruiting women to the study, we asked whether they were interested in reading about fetal effects of drugs and they had the possibility to decline participation. Women who entered the study were offered to contact an experienced neonatologist, in addition to their maternal health care center, if they had questions in connection with the information. Another concern was that women would find some questions too personal, even though the answers were anonymous. Therefore, we advised them to pass by questions they perceived as offensive.

Concerning the register studies, the risk for integrity problems was lesser. The material was very large, the results analyzed without PIN and only presented on a group level. There were however other ethical aspects, mainly how to interpret and present the results. Without a thorough analysis of confounders and other sources of error, there was a risk of misinterpretation of the data. This would probably result in mainly an overestimation of the negative effects of the drug exposure.

Study II was approved by the regional ethical review board in Stockholm (dnr. 2013/1188-31/5) and study III and IV by the regional ethical review board in Lund (dnr. 2013/342-31/5).

Results

The knowledge database *Drugs and Birth Defects*

Contents

The database contains close to 1450 documents providing assessments of fetal risks. Apart from covering all authorized medicinal products, slightly more than 20% of the documents deal with drugs prescribed with special permissions from the regulatory authority or drugs that have been withdrawn from the market. This is an advantage since these drugs are not covered by the Swedish PDR (Fass) and it might be difficult to find information regarding them elsewhere.

In most cases, one document in *Drugs and Birth Defects* deals with one substance. For some drugs, the database provides individual assessments for systemic and topical use and for different dosage levels. A few documents cover groups of substances, i.e. electrolytes for parenteral use, for practical reasons.

Of the documents, 70% belong to risk classification category 2 = there is important information to consider for this drug during pregnancy. Compared to Fass, fewer substances are placed in the most rigorous category (class 3 *in Drugs and Birth Defects*, category D in Fass) according to an analysis undertaken in 2012.

User and search statistics

At present, around 17 000 searches are performed monthly in the database via www.janusinfo.se. The main users are health care professionals with physicians constituting the largest group followed by midwives. Gynecology and general practice are the most common specialties among the doctors. Approximately 20% of the users were private citizens in the latest evaluation of user categories from 2012. It is likely that the amount of lay people using the database has increased, since then. Besides www.janusinfo.se, around 1500 documents are opened per month via Janus toolbar, an application integrated into electronic health records.

Over the years, the types of drugs that represent most searches *in Drugs and Birth Defects* have remained fairly constant. Sertraline, citalopram, loratadine, paracetamol, omeprazole, intranasal mometasone and codeine, have always been on the top list. The data in the MBR for these drugs are quite satisfactory and it is possible to detect a relative risk increase for weeded malformations below 1.3.

Perceived value for pregnant women

The study included 275 answers to the questionnaire from pregnant women. The response rate was 55% among women who agreed to participate and 48% among all pregnant women who were asked to take part in the study. The respondents differed from the average pregnant woman in Sweden. They were older, had to a larger degree an academic education and as many as 45% used drugs continuously during their pregnancies.

Drug treatment during pregnancy was an important topic to the study participants. Only 2% had not searched for such information at all. On average, the pregnant women had used 3.4 different information sources and 11% already knew about the database *Drugs and Birth Defects* before the study.

Almost 70% of the women stated that the contents of the database were easy to understand and there was no difference in this aspect between women with a university degree or not, see Figure 6.

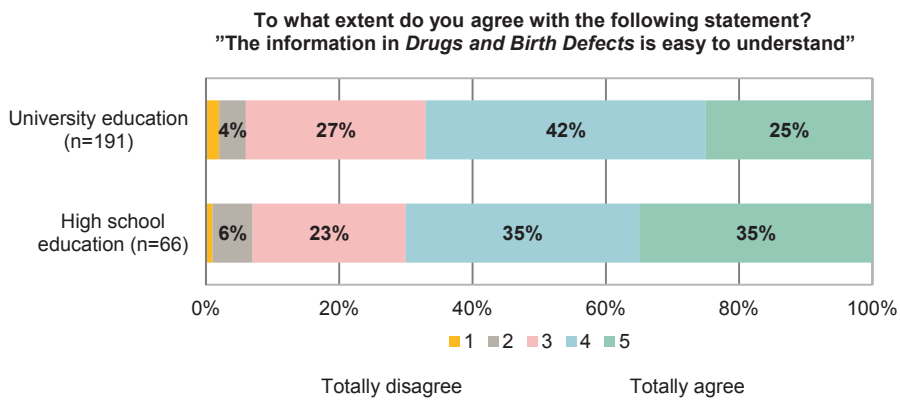


Figure 6. Pregnant women's perception of understanding the contents by different educational levels, p = 0.407, Fisher's exact test.

Further, 80% of the pregnant women replied that the database to a high extent was valuable for them, almost all women that the contents strengthened and complemented information from health care professionals and around 60% stated that the information was helpful when making decisions about drug treatment.

Differences between pregnant women and health care professionals

Apart from the pregnant women, 38 midwives (response rate 59%) and 30 physicians (response rate 55%) completed the questionnaire. For some key questions, there were important differences in the opinions between the pregnant women and their physicians and midwives, see Table 5. The health care professionals were more reluctant towards that pregnant women use the database. At the same time, they overestimated the contents ability to reduce the pregnant women's anxiety for negative fetal impact due to drug intake.

Table 5. Differences between pregnant women and health care professionals in their opinions concerning pregnant women using the database, $p<0.001$ for each question (Fisher's exact test).

Question	Response option	Pregnant women	Physicians and midwives
Do you see any risks associated with pregnant women reading the texts in *Drugs and Birth Defects*?	Yes	45 (17%)	29 (44%)
	No	155 (59%)	25 (38%)
	Don't know	63 (24%)	12 (18%)
Would you recommend *Drugs and Birth Defects* to pregnant women?	Yes, fully	169 (65%)	16 (24%)
	Yes, partly or sometimes	83 (32%)	46 (70%)
	No	8 (3%)	4 (6%)
Would you prefer if the information was specially adapted for lay people?	Yes, it would be easier to understand	104 (40%)	42 (64%)
	Doesn't matter	48 (18%)	3 (4%)
	No, it's better if everyone reads the professional version	70 (27%)	11 (16%)
	Don't know	38 (15%)	10 (15%)
How does the information in *Drugs and Births Defects* affect your/the pregnant woman's anxiety for negative fetal impact?	Anxiety decreases	118 (45%)	43 (64%)
	No impact	68 (26%)	1 (2%)
	Anxiety increases	58 (22%)	15 (22%)
	Not relevant/cannot judge	16 (6%)	8 (12%)

The logistic regression analyses revealed that the most strongly associated factor with increased anxiety among the pregnant women was the perception that there are risks associated with pregnant women reading the texts. This association was significant in

both the univariable and the multivariable analyses. Likewise, increased anxiety was linked to the opinions that the texts were difficult to understand and not helpful when deciding whether to use drugs during pregnancy. In the multivariable analysis, lower education had an increased odds ratio for anxiety. Among the women who perceived increased anxiety, 76% still found the database valuable.

The midwives and physicians answered differently to some crucial questions. The midwives did to a higher degree than physicians assess the database as highly valuable for pregnant women; they did more often read the texts together with pregnant women at the clinics and they did more often than physicians advise pregnant women to use the database.

Answers to open-ended questions

The questionnaire generated numerous comments from the pregnant women. Of 242 replies to an open-ended question regarding their general impression of the database, 72% were clearly positive, 6% were negative and 22% neither positive nor negative. Some representative quotes were:

"Good, reliable source instead of ending up at irresponsible message boards via Google."

"Good, more informative than Fass (Swedish Physicians' Desk Reference), even if you use Fass for health care professionals."

"Informative! Good that the assessments are complemented with actual statistics."

"This is exactly what pregnant women need!"

Some open comments from the health care professionals reflected that they were more uncertain about the appropriateness of the database for pregnant women:

"Let's wait and see what the study concludes. Until now, I have regarded Drugs and Birth Defects as a service for health care professionals."

"The woman herself hasn't the medical knowledge to assess the contents. She should be informed by a physician."

"I could consider recommending the database in selected cases, but not generally."

Several pregnant women and health care professionals stated that the communication between the pregnant woman and the physician/midwife was important. This was also reflected in that pregnant women, who perceived that the contents of the database to *a high extent* strengthened the information from the health care professionals, were more positive towards the database.

Perceived value for health care professionals

The study among health care professionals included 644 respondents. Among them 408 were midwives (63%), 103 general practitioners (16%), 75 gynecologists/obstetricians (12%), 45 neonatologists (7%) and 13 had other specialties (2%). The response rate was 43%.

More than 90% of the participants were familiar with *Drugs and Birth Defects.* However, the awareness was lower among general practitioners, 72%. Among gynecologists and neonatologists, all respondents knew about the database.

The users searched the database regularly: 5% daily, 26% weekly, and 37% monthly. In other words, approximately 70% used the information at least every month. At the time of the survey, *Drugs and Birth Defects* was only available as a web version and not as an integrated application in medical records. Even so, 80% answered that they used the information during the pregnant woman's visit at the clinic.

The respondents were overall content with the information: 92% replied that it to a large extent provided answers to their questions and 94% that the information was reliable. It did also have a direct impact on the clinical work, see Figure 7.

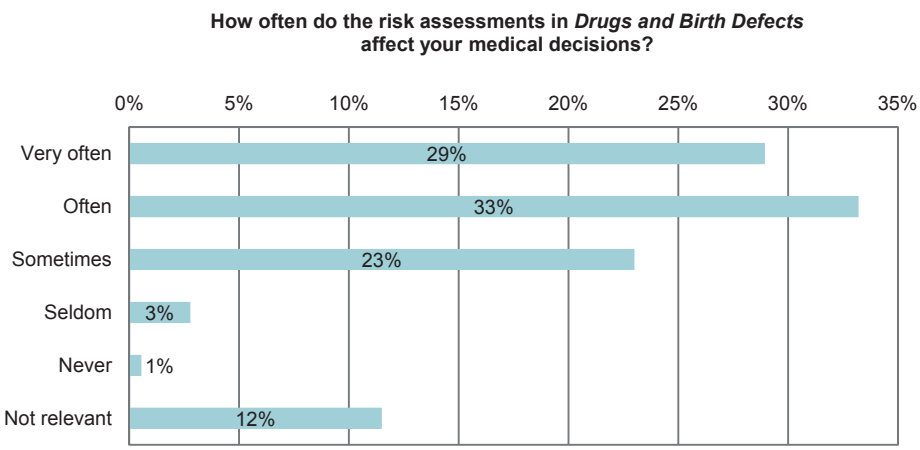


Figure 7. Health care professionals judgement on how the contents in *Drugs and Birth Defects* influence their clinical decisions.

Further, 82% of the health care professionals stated that *Drugs and Birth Defects* was time saving, compared to if this service would not be available. The respondents were also asked to estimate how much time they saved per session, Figure 8. Even a few minutes gained for each question will generate quite a substantial amount of man-hours per year.

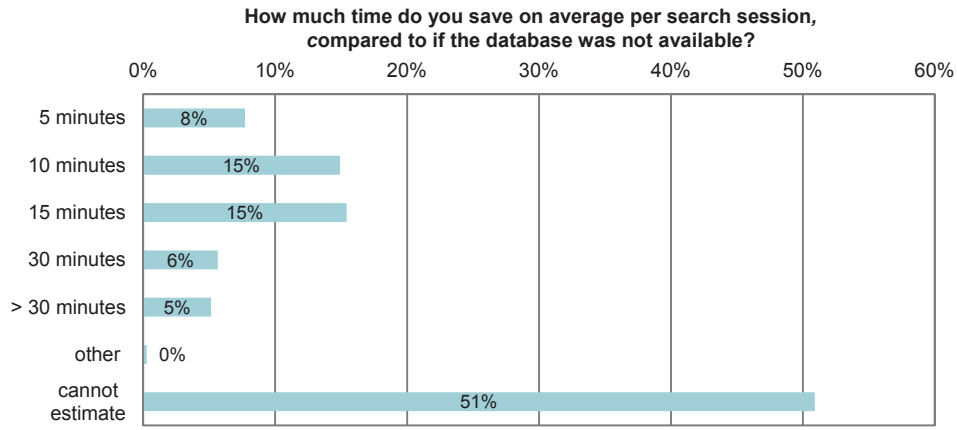


Figure 8. Estimated time saving per search session in the database *Drugs and Birth Defects*.

Moreover, the survey provided information on how the contents ought to be improved. The users requested more information regarding effects of drug exposure during late pregnancy and wished that the database also would include treatment recommendations for different diseases during pregnancy. Additionally, they requested more comprehensive lists of references and that the assessments of fetal risks were more concise.

Antidepressant drugs

Study population

Study number III comprised 741 040 singleton births, whereas 22 507 (3.1%) were exposed to antidepressant drugs. The most common drug group was SSRIs with 17 736 exposures (2.4% of the total population). It was common to interrupt the treatment during pregnancy and only around half of the treated women used antidepressant drugs during late pregnancy 10 969/22 507 (49%).

Women who used antidepressant drugs differed from the non-exposed subcohort. They were for example older, to higher extent smokers, more often obese, gave more frequently birth by cesarean delivery and used other medications to larger extent.

Exposed infants were more often born moderately preterm and with Apgar scores <7 at 5 minutes, crude ORs 1.6 (95% CI 1.5–1.7) and 2.1 (95% CI 1.9–2.3), compared to non-exposed infants. There was no increased rate of birth defects or perinatal death, after adjustment for maternal characteristics.

Admission to NCU

Infants of mothers who used antidepressant drugs during pregnancy had an increased risk for admission to a neonatal care unit. The risk was seen both when antidepressant medication was compared to no antidepressant use and when late pregnancy exposure was compared to early exposure only. The latter is shown in Table 6. There was a heterogeneity between the different antidepressant groups, p=0.002, with the highest associations with admission to NCU for SNRIs and TCAs.

For SSRIs, the adjusted NNH was 29 for any SSRI use compared to no use and 18 for late vs early use. The ORs for admission to NCU did not change substantially when adjustments were made for fetal factors in addition to maternal factors (the complete results are available in paper III).

The median duration of stay at NCU was after maternal use of SSRIs 5 days, SNRIs 7 days, TCAs 5 days, mirtazapine/mianserin 11 days, combinations or change of antidepressant therapy 7 days, any antidepressant drug 6 days, and after no use of antidepressants 7 days. The differences in length of stay were significant between any and no antidepressant use, p<0.001, and there was a statistically significant difference between the five antidepressant groups. Median stay for term infants only were for any antidepressant exposure: 4 days and no antidepressant exposure: 5 days, p<0.001. In these analyses, infants exposed to other neurotropic drugs were excluded.

Table 6. Admission to NCU among infants exposed to antidepressants during pregnancy. Late pregnancy use vs early pregnancy use only. All antidepressant drug groups.

Drug group	Late use, with or without early use		Early use only		Crude		Adjusted for maternal factors and use of other neurotropic drugs	
	NCU/total exposures n / N	%	NCU/total exposures n / N	%	OR	95% CI	OR	95% CI
Any antidepressant	1914/10 969	17.4	1257/11 538	10.9	1.7	1.6–1.9	1.7	1.6–1.9
SSRI	1501/9100	16.5	936/8636	10.8	1.6	1.5–1.8	1.6	1.5–1.8
SNRI	161/648	24.8	112/1034	10.8	2.7	2.1–3.5	2.7	2.0–3.5
TCA	58/216	26.9	80/649	12.3	2.6	1.8–3.8	2.6	1.7–3.4
Mirtazapine/ Mianserin	20/91	22.0	54/486	11.1	2.2	1.3–4.0	2.0	1.0–3.7
Combinations/ change of drug	170/888	19.1	60/547	11.0	1.9	1.4–2.6	1.9	1.4–2.6

Neonatal symptoms and interventions

The main neonatal diagnoses and interventions were analyzed for SSRIs. The results for the comparison between late and early exposure is presented in Figure 9. There was an increased risk for mainly mild respiratory symptoms, including treatment with CPAP, and additionally for CNS-related disorders, hypoglycemia and feeding difficulties. The median duration of CPAP-treatment was 2 days, the same as for infants not exposed to SSRIs treated with CPAP.

The increased ORs were overall more pronounced among term than preterm infants, for example, the OR for respiratory disorders adjusted for maternal factors was 1.9 (CI 95% 1.6–2.2) among term infants and 0.9 (CI 95% 0.7–1.2) among preterm infants.

We paid particular attention to PPHN which was more common among SSRI-exposed infants. Comparing late with early SSRI-exposure yielded an OR 2.1 (CI 95% 1.3–3.2) and an NNH 285. Restricting the analysis to term infants, the OR for PPHN, SSRI late versus early use, was 2.6 (95% CI 1.4–4.8) and the NNH was 322.

The mortality rate among infants with PPHN was 3.4% (3/89) for SSRI-exposed infants and 8.3% (171/2051) for non-exposed infants, OR 0.4 (95% CI 0.1–1.2). The need for ventilator treatment among children with PPHN was significantly less in infants exposed to SSRIs, 47% (42/89) than among non-exposed infants, 62% (1267/2051). However, when GA was adjusted for, no difference between the need for ventilator treatment was indicated, OR 0.9 (95% CI 0.5–1.4). The median length of

stay in NCU for neonates with PPHN was the same for infants exposed to and not exposed to SSRIs: 11 days for term infants and 63 days for preterm infants.

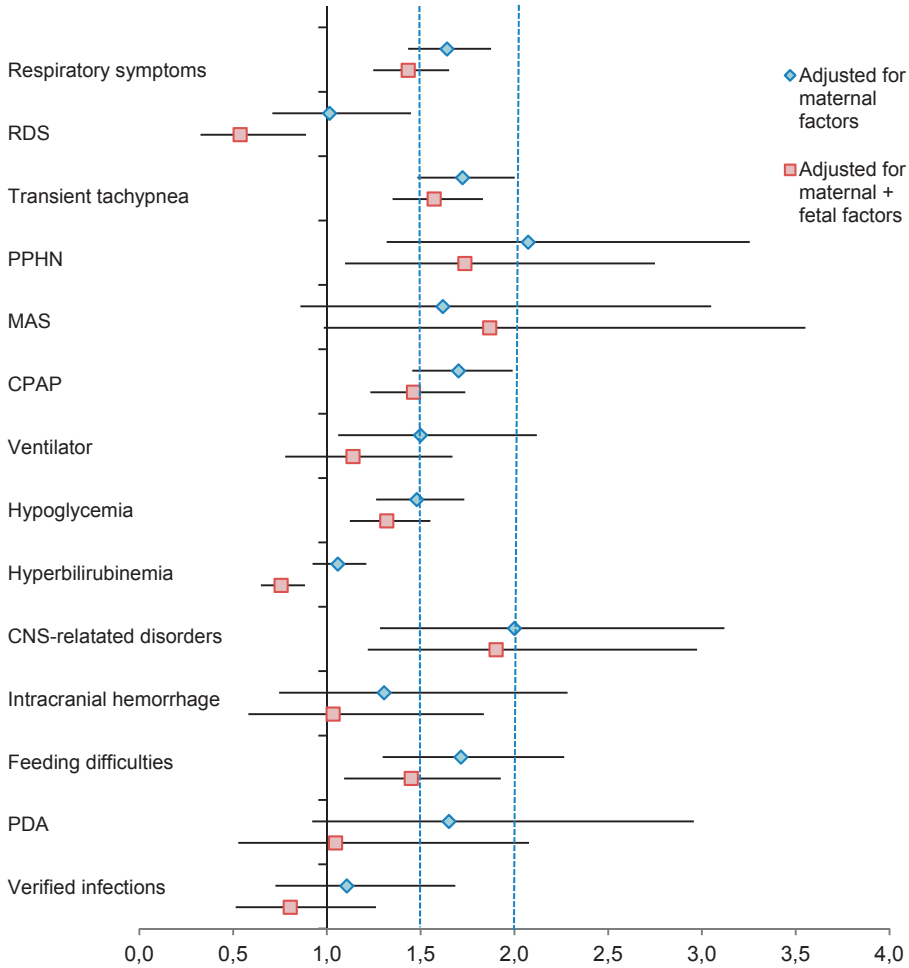


Figure 9. Neonatal diagnoses and interventions after exposure to SSRIs during late pregnancy compared to exposure during early pregancy only, ORs with 95% CI. Abbreviations: RDS, respiratory distress syndrome; PPHN, persistent pulmonary hypertension of the newborn; MAS, meconium aspiration syndrome; CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus

ADHD medication

Study population

In study number IV, we analyzed birth and perinatal outcomes for 964 734 singletons. Among them, 1591 (0.2%) were exposed to ADHD medication in utero. Stimulant drugs (approximately 90% methylphenidate) constituted 1464 of the exposures and atomoxetine 165. Most treated women discontinued the medication during the pregnancy and only 251/1591 (16%) of the infants were exposed during late pregnancy. Additionally, 9475 (1.0%) infants had mothers who were treated with ADHD medication before or after pregnancy.

There were substantial differences between women who were treated with ADHD medication and women who did not use these drugs. Treated women were younger, to larger degree smokers, they were more frequently living without the father of the child and they used other medications to a higher extent. For example, 32% used antidepressants, 35% psycholeptics, 15% opioids and 10% antiepileptic drugs. The differences in maternal characteristics were seen both when comparing women who used ADHD medications during and before/after pregnancy with non-exposed women but were more pronounced among women who were treated during pregnancy.

Birth and perinatal outcomes

Infants exposed to ADHD medication during pregnancy had an increased risk for moderate prematurity compared to non-exposed, adjusted OR 1.3 (95% CI 1.1–1.6). There was also a tendency towards a higher frequency of Apgar scores <7 at 5 minutes, but this did not reach statistical significance. We found however an association with use of ADHD medication during pregnancy and being large for gestational age (LGA), adjusted OR 1.3 (95% CI 1.0–1.7), p=0.02 compared to no use.

There was no significant increase in the rates of birth defects or perinatal death, when adjusted for maternal characteristics, OR 1.2 (95% CI 0.9-1.6) and 0.9 (95% CI 0.4-1.8) respectively vs no use.

Infants exposed to ADHD medication were more often treated at NCU, adjusted OR 1.4 (95% CI 1.2–1.6) vs no use and 1.2 (95% 1.1–1.5) vs use of ADHD medication before/after pregnancy. Concerning neonatal symptoms, the only outcome that showed an association with use of ADHD drugs during pregnancy, were CNS-related disorders, see Table 7. There were however tendencies towards an increased risk for feeding difficulties, hypoglycemia, hyperbilirubinemia and withdrawal symptoms.

Table 7. Neonatal morbidity in infants exposed to ADHD-medication during pregnancy compared to infants of mothers who used ADHD-medication before/after pregnancy and infants of mothers who did not use any ADHD drugs.

Outcome	ADHD medication during pregnancy		ADHD medication before/after pregnancy		No ADHD medication		ADHD medication during pregnancy vs ADHD medication before/after pregnancy				ADHD medication during pregnancy vs no ADHD medication			
	N=1591		N=9475		N=953 668		Crude		Adjusted		Crude		Adjusted	
	n	%	n	%	n	%	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
NCU-admission	259	16.3	1105	11.7	79 530	8.3	1.5	1.3–1.7	1.2	1.1–1.5	2.1	1.9–2.4	1.4	1.2–1.6
Any respiratory symptoms	92	5.8	511	5.4	35 479	3.7	1.1	0.9–1.4	1.0	0.8–1.2	1.6	1.3–2.0	1.0	0.8–1.2
Transient tachypnea	70	4.4	346	3.7	25 198	2.6	1.2	0.9–1.6	1.0	0.8–1.4	1.7	1.3–2.2	1.0	0.8–1.3
PPHN	7	0.4	49	0.5	3065	0.3	0.9	0.4–1.9	0.8	0.4–1.8	1.4	0.7–2.9	0.9	0.4–1.8
RDS	13	0.8	82	0.9	5101	0.5	0.9	0.5–1.7	1.0	0.5–1.8	1.5	0.9–2.6	0.9	0.5–1.6
CPAP	60	3.8	332	3.5	22 287	2.3	1.1	0.8–1.4	0.9	0.7–1.3	1.6	1.3–2.1	1.0	0.7–1.2
Ventilator treatment	15	0.9	90	0.9	5257	0.6	1.0	0.6–1.7	1.0	0.5–1.7	1.7	1.0–2.9	1.1	0.7–1.9
Hyperbilirubinemia	91	5.7	511	5.4	42 948	4.5	1.1	0.9–1.3	1.0	0.8–1.3	1.3	1.0–1.6	1.1	0.9–1.4
Hypoglycemia	66	4.1	326	3.4	23 965	2.5	1.2	0.9–1.6	1.0	0.7–1.3	1.7	1.3–2.1	1.1	0.9–1.4
Feeding difficulties	34	2.1	130	1.4	9837	1.0	1.6	1.1–2.3	1.3	0.9–2.0	2.1	1.5–2.9	1.2	0.9–1.8
CNS-related disorders	16	1.0	40	0.4	2885	0.3	2.4	1.3–4.3	1.9	1.0–3.4*	3.3	2.0–5.5	1.8	1.1–3.0
Withdrawal symptoms[A]	7	0.4	10	0.1	124	0.0	4.2	1.6–11.0	—	—	34.0	15.8–72.9	2.1	0.9–4.7

*$p<0.05$; [A] Withdrawal symptoms due to therapeutic drugs; — Not analyzed due to low number of infants

Discussion

General discussion

The impact on fetal health of maternal drug treatment during pregnancy is an issue that most pregnant women must tackle at some point. In Sweden and Norway, around 60% of pregnant women are prescribed at least one drug [1, 2]. Reports from other countries show similar results; between 50 and as many as 95% of pregnant women use prescription drugs [3-5]. In addition, many women self-medicate with OTC-drugs (over the counter) during their pregnancies [4].

The use of medications during pregnancy is also increasing [4, 95, 96, 144, 146]. This could be due to that pregnant women are older than previously and subsequently more likely to have medical conditions [4, 8]. Another reason is that current, effective treatment of chronic diseases allows more women to give birth. Probably, there has additionally been a change of attitude over the years towards an opinion that also women with quite severe chronic conditions should have the possibility to give birth. One example is the non-profit organization Pregnancy and Medicine (www.pregnancyandmedicine.org) that promotes the message *Having a disease shouldn't mean you can't have a child.*

Pregnant women are usually excluded from clinical trials and human data for new drugs are in most cases non-existing when the drug enters the market [10, 33]. It is further generally regarded that the post marketing surveillance of fetal safety is ineffective [185]. A study from the US has revealed that the mean time for a drug with undetermined pregnancy risk to get a more precise risk assessment was 27 years [186]. Apart from missing data regarding fetal safety, there is also sparse information concerning how to adjust for example dosage with respect to the changes of physiology and pharmacokinetics during pregnancy [8, 33]. Clinical trials are becoming more common in the pregnant population [187], but still prescribing drugs to pregnant women is frequently to be considered as off label.

Lately, there have been calls from specialist organizations and networks like the European Board and College of Obstetrics & Gynaecology (EBCOG) and the European Institute of Women's Health (EIWH), stating that pharmacovigilance and information concerning medications during pregnancy must be improved [185, 188].

The results from study number I in this thesis, to some degree challenge the opinion that data concerning fetal safety for most drugs are missing. For the drug substances that constitute the most common searches in the database *Drugs and Birth Defects*, we have a substantial amount of exposures in the Swedish MBR and we can detect risk ratios for weeded malformations below 1.5. Additionally, there is often information in the literature, which altogether comprise a quite good basis for assessing fetal risks.

In study number II, we confirm that medication during pregnancy is an important topic to pregnant women since almost all respondents had searched for such information. They also used several information resources, which potentially can lead to conflicting messages which in turn might impair compliance to essential drug treatment [189]. The need for access to reliable, good quality, non-biased information regarding drug treatment to pregnant women, for example via the internet, is emphasized in the call from EBCOG and EIWH [185].

E-health is overall an area which is prioritized by politicians in many countries [190]. In Sweden, the Government has endorsed a vision for E-health up to 2025 where they emphasize that increased digitization will strengthen the population's own resources for increased independence and participation [191]. To reach out to different users, it is necessary to follow the technical development and to offer different ways of accessing the information. This includes web sites, mobile apps and integrated with other personal medical data, for example in patient portals.

Providing risk assessments via a knowledge database

Production process

Unique data from MBR

The knowledge data base *Drugs and Birth Defects* was launched in 2001 to ensure that health care professionals have access to reliable and consistent information on fetal risks of drugs. The Swedish MBR was chosen as a key resource, since it is a valuable tool for studying fetal safety of medications. The register has several advantages [40, 41, 176]. Since it is population-based, the data are representative for pregnant women in Sweden. It is also usually possible to obtain higher power with this methodology than in case-control and cohort studies that are based on sampling procedures. Another advantage is that data on drug exposure are collected prospectively in relation to birth outcome. Disadvantages are that there is no information on dosage, exact timing or duration of drug treatment.

A limitation when investigating fetal risks of drugs in Sweden, is that we have no legal possibility to link drug exposure to abortions due to malformations. In fact, if a drug induces such severe malformations that most pregnant women will choose to terminate the pregnancy, we will not be able to detect the association between the malformation and the drug treatment. Hopefully, this situation will improve in the future due to a recent change of regulations concerning abortions in the National Patient Register [192].

The data from the MBR mainly concerns drug exposure during early pregnancy. Therefore, the analyses from MBR to large extent concern congenital malformations which from the beginning also were the focus of the database *Drugs and Birth Defects.* In general, the data from MBR presented in *Drugs and Birth Defects* are crude and not adjusted for differences in maternal characteristics between exposed and non-exposed women, which should be taken into consideration when interpreting the information. It is therefore important that the users read the assessments made by the authors and do not use the data out of context.

Even so, publishing analyses from the MBR for all drugs on the Swedish market provides the health care sector with unique and valuable data on teratogenic risks. It is an efficient way to bring back and make information that has initially been collected by health care professionals (mainly midwives) useful in the clinical situation.

Other resources and revisions by experts

For a comprehensive assessment of fetal safety of a substance, especially concerning exposure during later stages of the pregnancy, it is of course essential to follow the scientific literature as well as information from drug authorities and drug companies. During the last years, the database has been supplemented with more information on fetal risks of drug exposure during late pregnancy.

A crucial step in the production process of the database is review by the scientific advisory board and clinical experts. This procedure was established a few years after the database was launched and many documents have undergone substantial changes due to these revisions. The assessments have become more coherent with state-of-the-art clinical management which make them more useful in every day clinical work. The advisory board has also been helpful in discussions how to adapt the texts to different users and situations. It is delicate to present information that works well in a stressful clinical situation without compromising the quality and necessary details. Lately, we also to a larger degree take into consideration that lay people read the texts.

The classification problem

Drugs and Birth Defects is part of a concept initiated within the Stockholm County Council to provide non-commercial drug information to be used at point of care. [92] The database is thereby also available as an integrated application in electronic health

records. To generate alerts when prescribing a drug potentially harmful to the fetus, it is necessary with a pregnancy risk classification system. Even though we use a simple 3-tier system, it is often challenging to place a drug into one of these categories. The majority end up in category 2, which contains a broad spectrum of drugs from substances where we do not suspect any fetal risks but have limited data, to substances known to entail a moderate fetal risk.

Classification systems are overall problematic. They provide an oversimplification of often complicated assessments with loss of information and might be misinterpreted. For these reasons, FDA has abandoned their pregnancy categories and replaced them with a narrative, describing labeling [193]. User statistics indicate that health care professionals rely on the short initial assessment and the risk category, when *Drugs and Birth Defects* is used as an integrated part of an electronic health record. It would be preferable with a system that encourages the users to read the complete texts for all drugs where there is something to take into consideration during pregnancy. It has previously been shown that over-alerting is a problem in clinical decision support systems which might speak against that they would take the time go through the texts in detail [194]. We believe however that over-alerting is a smaller issue when it comes to information concerning fetal safety than for example drug-drug interactions.

Evaluations among users

Health care professionals

Evaluations show that the database is well-known and extensively used by the main target group, gynecologists and midwives. The health care professionals stated that that it provides answers to their questions, that the information is reliable, time saving and has an impact on clinical decisions. It is possible that the high ratings from the users, partly reflects the lack of useful information within the area, so that any easily accessible contribution of acceptable quality would be appreciated. An advantage compared to Fass and SPCs is that *Drugs and Birth Defects* is substance based. All products with the same substance and route of administration have the same assessment, thus avoiding the problem with contradictory information from different manufacturers. Compared to Fass, the assessments in *Drugs and Birth Defects* are in general less restrictive. Similar results have been shown from Norway when information from drug information centers was compared with the Norwegian Fass (Felleskatalogen) [86]. *Drugs and Birth Defects* is further in general more adapted to be used in the clinical situation than Fass. We assume that this contributes to the positive judgments from health care professionals.

A recurrent request from physicians and other personnel is treatment recommendations for diseases among pregnant women. They ask for more concrete guidance when choosing between different drugs in the prescribing situation. This wish is however

difficult to fulfill. Obviously, fetal safety of the drugs is only one aspect to consider when treating a pregnant woman. To develop treatment recommendations, more expertise within different specialist areas are needed and this is not realistic with the present staffing. Instead, we try to link to national or regional recommendations when such exist, but obviously, we cannot guarantee that they are updated. If a drug clearly has been shown to have a negative fetal safety profile compared to other similar drugs, like valproic acid among antiepileptics, we advise against use of this drug. This is under the circumstance that the pregnant woman's medical condition can be satisfactory treated with other drugs.

Pregnant women

The most important impact of the database is probably to ascertain that pregnant women continue essential treatment and to reduce anxiety due to accidental drug intake during early pregnancy. Other information services regarding fetal safety of drugs, like OTIS and ENTIS have been successful in changing women's perception of teratogenic risk and prevent abortions due to fear of fetal harm [49, 61, 72, 195]. Also counseling from physicans and clinical pharmacists has shown to decrease the women's fear of teratogenic risk and contribute to increased compliance [196, 197].

The second study in this thesis revealed that *Drugs and Birth Defects* works very well also for pregnant women, even though the contents are not adapted for this target group. It must however be noted that the respondents were not representative for the average pregnant woman in Sweden. The participants were older, they probably used continuous drug therapy to larger extent and more often had an academic degree [1, 198]. One reason for this could be that the response rate was around 50% and that the women who chose not to participate differed from the women who took part. Another reason is that many women were recruited at specialized antenatal clinics and thereby had medical conditions to larger degree. We believe that the results despite not being illustrative for all women are of importance since the respondents represent women to whom questions regarding fetal safety are of great concern. Additionally, there were no large differences in the responses between women with and without academic degree.

Another limitation with the study was that we do not know what texts the women actually read. The reason is that we wanted to simulate a real situation, where they could choose texts that they found relevant. A logical guess is that the respondents read about drugs that they had used during pregnancy. There were tendencies towards that women who used medications with the potential to cause fetal harm more often reported increased anxiety, after having read the texts, although this was not statistically significant. Most women, who reported increased anxiety due to the texts, nevertheless stated that the database was valuable. We were not able find any clear answers to what maternal characteristics that might predict how women will react towards the texts. There were though weak associations between anxiety and lower education and finding the texts difficult to understand respectively.

An important result was that most women experienced that the contents strengthened the information from their health care professionals and that it was helpful when making decisions concerning drug treatment. Women who answered that the information to a high degree strengthened information from physicians and midwives were also more positive towards the database. It has previously been demonstrated that patients searching for information on the internet, primarily use this to confirm a message from the health services but that they rely on their health care provider in the first place [199, 200]. Several pregnant women and health care professionals stated in their answers to the open questions that it is important that decisions concerning drug treatment during pregnancy are made jointly and that it is important to keep contact with antenatal care and physicians responsible for diseases not related to the pregnancy.

The health care professionals, especially physicians, were significantly more hesitant towards that pregnant women use the database, than the pregnant women themselves. The differences could be due to that health care professionals and pregnant women had different texts in mind when answering the questions. The vast majority of the health care staff was regular users of the database while the pregnant women read a few texts to be able to answer the questionnaire. However, health care professionals have had similar reservations concerning patients accessing their medical records [81, 201]. The midwives were though more positive than the doctors. This could be attributable to that some of the midwives participated in recruiting pregnant women to the study, and thereby were more positive towards the project. A second review of the material revealed that midwives in the unpublished questionnaire described above to a lesser degree found the database valuable for pregnant women, than the midwives in paper II. Another explanation could be that midwives spend more time with the pregnant women at several occasions than physicians.

The results suggest that health care professionals could recommend the database *Drugs and Birth Defects* to most women who are interested in reading about drugs during pregnancy. It is though important that they can discuss questions with a health care professional, since around 20% stated that their anxiety increased. The risks with using *Drugs and Birth Defects* seem however small compared to the non-evaluated information and media reports available on the internet. If pregnant women, health care providers and pharmacists use the same information source, this ought to facilitate communication and prevent misunderstanding. Additionally, a meta-analysis of studies regarding decision support systems has established that these are more effective if they provide information towards patients as well as practitioners [202].

To conclude, the database *Drugs and Birth Defects* seems to work well for a broad range of different users and the combination of own analyses of population based register data and assessments of published literature makes it unique.

Future perspectives and research

There are plenty of knowledge gaps to fill onwards. More studies are needed to define the optimal way of presenting information like in *Drugs and Births Defects* on web sites, in clinical decision support systems and mobile apps. This includes studying the effectiveness of classification systems versus narrative assessments as well as design and other functionality. Another track is health economic evaluations of knowledge databases and decision support systems.

Research is also needed to further evaluate how information for the medical profession works for lay people. To what extent do persons with no medical background actually understand the contents apart from rating the information as valuable? Previous research has displayed that lay people sometimes are overconfident when it comes to understanding medical terms [203]. A more structured study with selected documents and how to interpret the contents would be one way to gain more knowledge. Another question is if using information for the profession will in fact increase compliance and have an impact on the medical treatment, which our study indicates.

Mails and telephone calls from pregnant women to the editorial board of *Drugs and Birth Defects* suggest that there is a need in Sweden for information services like TIS in other countries. We believe that a special information service for individual questions regarding drug treatment during pregnancy as a complement to the antenatal clinics, would improve the situation. Additionally, more collaboration between teratology information and research centers in different countries would be beneficial, both for exchange of research data and for information to pregnant women and their relatives. Presently, there exist different initiatives around the world. It would be an advantage with a common international webpage summarizing information for both health care professionals and the public.

Antidepressant drugs and ADHD medication

Main results and novelty

Treatment at NCU

Both antidepressant drugs and ADHD medication were linked to increased neonatal morbidity primarily measured as admission to a NCU. For antidepressant drugs, similar results displaying poor neonatal adaption after exposure in utero have been presented by several other research groups [95, 105-109, 111-119, 121, 204]. Our study quantifies the neonatal morbidity on a population level by combining neonatal quality registers with the Swedish MBR. This provides more comprehensive

information as well as data on treatment and interventions, compared to earlier studies based on Swedish health registers. To our knowledge, study IV in this thesis is the largest study until today investigating perinatal outcomes of prescribed ADHD drugs. Further, it provides more detailed data on neonatal disorders than previous research.

The median treatment time at a NCU was for both antidepressant drugs and ADHD medication around 1 week (slightly shorter than 1 week for antidepressants) which is the same as for infants treated at NCU that were not exposed to these drugs. This implies that exposed infants were admitted due to considerable problems and not only as a safety measure.

Adjustment for GA and SGA did not change the odds ratios for admission to NCU considerably in the study concerning antidepressants. Also for other neonatal outcomes, the association with the antidepressant drug treatment was the same or even stronger among term than preterm infants. Thereby, other effects of antidepressant agents than increasing the risk of prematurity – which has been regularly reported [205] and also confirmed in our study – seem to be essential. Prematurity is per se associated with substantial neonatal morbidity [206]. To estimate the overall impact of antidepressant drug exposure on neonatal morbidity, both the direct effect of the drugs and the increased frequency of premature births must be considered.

Exposure to SNRIs and TCAs were linked to the highest risks for treatment at NCU among the antidepressant drug groups. Since these drugs have a broader mechanism of action, affecting more receptor sites than SSRIs, this might be reasonable [97]. On the other hand, it is likely that women treated with TCAs or SNRIs had more complicated psychiatric disorders which could have influenced the results.

Symptoms and interventions

Infants to mothers who used SSRIs had a higher frequency of respiratory disorders that were mainly mild. Even so, they had an increased risk for treatment with CPAP and ventilator (late pregnancy exposure compared to early). Coherent with previous studies, the infants also had more CNS-disorders, hypoglycemia and feeding difficulties [102, 107, 108, 113, 118, 121, 122, 207]. The neonatal problems are believed to be withdrawal symptoms or due serotonergic overstimulation [109, 122]. Apart from being a neurotransmitter, serotonin also acts as neurotrophic factor and is an important signaling molecule for embryologic development [208, 209]. Thus, changes in the serotonin levels during neurodevelopment have the potential to affect a number of processes [208].

For ADHD medication, the only neonatal conditions that were significantly increased in our study were CNS-disorders. An increased rate of CNS-related symptoms among newborns has previously been shown after intake of methamphetamine during pregnancy in a study by Lagasse et al [210]. The infants in their study showed a neurobehavioral pattern with nonoptimal reflexes, poorer quality of movement, lower

arousal and excitability and more hypotonicity [210]. Neurotoxic effects or withdrawal symptoms due to abrupt discontinuation of the drug have been suggested as causes of these problems [210]. Several infants with CNS-disorders in our material were concomitantly diagnosed with withdrawal symptoms. The association between abstinence and exposure to ADHD medication was however not significant after adjustment for i.e. use of other medications. Stimulant drugs are affecting dopamine, noradrenaline and serotonin which are key neurotransmittors in the central nervous system, but the mechanistic impact of these drugs on the developing brain is still unclear [162, 211].

Further, there were tendencies towards an increased rate of low Apgar scores, hypoglycemia and feeding difficulties among infants exposed to ADHD drugs. It might be that the increased risk for these diagnoses would have reached statistical significance in a larger material. Low Apgar scores in relation to in utero exposure to methylphenidate have previously been described in a Danish study [152]. In contrast to antidepressant drugs, we found no association between use of ADHD drugs and respiratory disorders after adjustment for maternal factors. These symptoms were the most common diagnoses among the infants in the register based studies. We would have been able to detect an increased risk for respiratory problems of 1.4 (80% power and a significance level of 0.05) for the comparison ADHD medication during pregnancy vs no ADHD medication.

An important result apart from the neonatal symptoms was that we could confirm previous results that ADHD medication does not seem to increase the overall risk for congenital malformations [151, 153, 154, 212]. It should though be noted that we almost reached statistical significance for birth defects and that our material was not large enough to study specific birth defects.

PPHN

In the analyses of SSRIs, we paid special attention to PPHN, since this side effect had been discussed frequently during the last decade. Several studies, but not all, had confirmed a risk increase for PPHN associated with in utero exposure to SSRIs during late pregnancy [130, 131, 213-215]. The mechanism is unknown but it has been hypothesized that circulating serotonin in the fetus might cause vasoconstriction and smooth muscle cell proliferation characteristic with PPHN [215].

There have been very few data concerning the symptom severity of PPHN among infants exposed to SSRIs. One theory is that these infants might be diagnosed with PPHN to a larger extent due to awareness of the association with SSRIs, so called detection bias. It has been shown for example that infants exposed to SSRIs undergo more ultrasound investigations [216]. The adjusted OR for PPHN in our study was 2.1 (95% CI 1.3–3.2) for the comparison late vs early exposure, approximately the same as in the Nordic study by Kieler et al [130]. At first sight, our results indicated

less severe symptoms among infants with PPHN who were exposed to SSRIs compared to other infants with PPHN. Exposed infants did not need ventilator treatment to the same extent and the mortality rate was 3% in the exposed sub cohort which is lower than usually reported [132]. These differences disappeared when the results were adjusted for GA. Thereby, we cannot confirm the theory that infants with PPHN linked to SSRI exposure in utero should have less severe disease. The comparison with other infants diagnosed with PPHN is though complicated since they most likely have other severe neonatal illness to larger degree than infants with PPHN related to SSRI use [132].

Overall, it should be noted that the adjusted NNH for PPHN was 285 (late vs early exposure to SSRIs), thus a very low absolute risk. It can be compared to NNH 17 for admission to NCU if the woman was treated with SSRI during late pregnancy. It might then be reasonable to focus more on the more common conditions associated with exposure to SSRI, like milder respiratory disorders, hypoglycemia and feeding difficulties.

Methodological considerations

Even though our methodology had advantages like high power, no recall bias and the possibility to adjust for many confounders, it also had its limitations. Similar to other observational studies, the most complicated issue was to differ between the effect of the drug exposure and the pregnant women's mental conditions. It is well-known that depression and anxiety are associated with similar outcomes as the drug treatment, for example preterm birth, low birth weight and neonatal adaption problems [94, 217-220]. These outcomes are thought to be connected to for example higher cortisol levels among women suffering from depression [218].

To adjust for the psychiatric conditions, we compared women who medicated with antidepressant drugs during late pregnancy with those who were treated during early pregnancy only, since neonatal symptoms mainly had been associated with late pregnancy exposure. The clearly increased risk after late compared to early use suggests a causative effect of the drug treatment. There was only a slight increased risk for treatment at a NCU after exposure to antidepressant during early pregnancy compared to no use of these drugs. However, there might still be considerable residual confounding, since it can be assumed that women who continued treatment throughout pregnancy suffered from more severe psychiatric problems. Researchers have previously displayed that the impact of the drugs disappeared when controlling for the severity of the pregnant women's depression [126, 127]. Warburton et al also showed that stopping treatment with antidepressant drugs during the last 14 days before delivery did not improve neonatal health, when the results were adjusted for the severity of maternal illness [127].

In the study regarding ADHD medication, there was an increased risk of admission to NCU among infants exposed during pregnancy also compared to infants whose mothers used these drugs before or after the pregnancy. This speaks for a real association with the drug treatment. But, in a similar way as for antidepressants, women who used ADHD medication during pregnancy may very well have more pronounced neuropsychiatric problems which could have affected the results. Overall, there were large differences in background characteristics between women who used ADHD medication and other women. Albeit we could adjust for many confounders, with such large discrepancies, the neonatal outcomes could still be influenced by other factors than the ADHD medication. Use of alcohol or illicit drugs is for example not recorded in the MBR. A Swedish report has stated that 26% of women between 26 and 34 years of age who used methylphenidate had a diagnosis of substance abuse/dependency [221]. Alcohol use is however closely related to smoking, which we have adjusted for.

Another limitation with the methodology is that compliance is not known. It is reasonable to assume that the real exposure was lower than estimated. This would however, only slightly have affected the risk estimates. The exact timing is also not known. In case, the women interrupted their treatment or lowered the dose, they would not have needed a refill from the pharmacy after 3 months. This could have resulted in that some infants who were classified as exposed to antidepressant drugs during early pregnancy, in fact were exposed during late pregnancy. The ORs for the comparison late vs early exposure would then be an underestimation of the real risk. We believe that misclassification could especially be the case for ADHD medication where some patients seem to temporarily interrupt the treatment for example during weekends to avoid adverse effects. This was together with low number of exposures during late pregnancy, reasons why we did not compare late with early pregnancy exposure in this study.

Clinical implications

The fetal safety after use of antidepressant drugs and ADHD medication is only one aspect to take into consideration when deciding whether to treat a woman with these drugs during pregnancy or not. It must be emphasized that most infants exposed to these medications (85%) in our studies did not need special care at a NCU. If the drug therapy is essential for the pregnant woman's health, our results are scarcely reasons to refrain from use of antidepressant or ADHD drugs. Stopping antidepressant treatment during pregnancy can result in a relapse in depression [222], which can have profound risks for both the mother and her child. For pregnant women with ADHD, symptoms like impulsivity and inattention could impair their daily function [223]. This might lead to an unhealthier lifestyle and increased stress that can have a negative impact on the fetus.

It is however important to consider other treatment options than pharmacotherapy. For mild to moderate depression and anxiety disorders, cognitive behavior therapy (CBT) has been demonstrated to be at least as efficient as antidepressant drugs [224, 225] and is first line treatment for these conditions [99]. Also for treatment of ADHD, CBT and psychoeducational interventions are emphasized in the current recommendations for pregnant women [99].

Apart from the fetal effects of antidepressant drugs and ADHD medication respectively, the crude results in our studies deserve mentioning. Especially concerning ADHD medications, the unadjusted ORs for several neonatal symptoms were much larger than the adjusted estimates. The reason was that these women had many characteristics that could influence the unborn child negatively. They used for example other psychoactive medications to larger degree, were more often smokers and obese and had other characteristics implying that they were a vulnerable group. This has also previously been shown by other researchers [146, 152]. Maternal smoking and obesity during pregnancy are for instance associated with substantial risks for the unborn child [226, 227]. All these risk factors must be addressed to achieve the best possible environment for both the pregnant woman and her child.

Future research

For antidepressant drugs, there is by now good knowledge regarding neonatal symptoms and congenital malformations on a group level and for the most commonly used substances. Randomized, clinical trials might otherwise be a way to finally distinguish between the pregnant woman's disease and the effects of the drugs. Researchers have brought forward that clinical trials would be ethical for antidepressant drug treatment during pregnancy [228]. Clinical trials are however not the answer to all questions. Apart from the ethical issues, it would be unmanageable to include enough patients to detect rare outcomes as specific malformations.

Concerning ADHD medication, our finding of an increased frequency of CNS-disorders must be confirmed in an independent study. Further, a larger material might provide clearer answers concerning some of the neonatal outcomes that almost reached statistical significance in our study. More research would also yield information whether there is a difference between stimulant drugs and atomoxetine. The latter has not been associated with addiction and withdrawal symptoms and might thereby theoretically be an advantageous choice of drug during pregnancy.

For both drug groups, the most essential question is likely the long-term impact on the children's development after exposure in utero. This is delicate to study, since it is even more difficult to distinguish between confounding factors and the drug treatment, years after the exposure. Randomization to drug treatment or not during pregnancy, followed by long term surveillance of the children might be feasible. It will though take a long

time before results are available. Well performed register based observational studies is another way but the results must be interpreted with caution. Information from registers could also be combined with data from electronic health records, for example from pediatric routine health care checkups of exposed and unexposed children.

Lately, there has been an increasing amount of research focusing on the impact of epigenetics to explain differences in fetal susceptibility to antidepressant drugs [229, 230]. It is believed that the vulnerability of the epigenetic programming to external exposure might differ between individuals [230]. Further knowledge in this area might increase our understanding on how antidepressant drugs and ADHD medication could impair fetal development.

Altogether, different kinds of studies with diverse methodology are needed to yield a complete comprehension of how these drugs might affect the unborn child.

Conclusions

- There is a pronounced need for information concerning fetal effects of maternal drug treatment during pregnancy, both among pregnant women and health care professionals.
- *Drugs and Birth Defects* – a non-commercial knowledge database available on the internet and as an integrated part of electronic health records – seems to be an effective tool to provide information on fetal safety of drugs. Based on analyses of the Swedish Medical Birth Register apart from the scientific literature, the database offers unique data that in most cases are not published elsewhere.
- The database is extensively used and highly valued by health care professionals. Also, pregnant women appreciate the information, even though it is not primarily intended for lay people. If pregnant women and health care professionals use the same information source, this will likely improve communication and favor compliance to necessary drug therapy.
- Treatment with antidepressant drugs and ADHD medication during pregnancy is associated with an increased risk for neonatal morbidity and admission to neonatal care units, according to our studies. The risk for severe disease is however low. The results suggest a causal relationship between exposure to the drugs and the neonatal problems. We can however not exclude that confounding factors like the women's mental and neuropsychiatric conditions per se, contributed to the findings. Especially when it comes to use of ADHD medication, there were large differences in maternal background characteristics between exposed and unexposed women.
- The increased risk of neonatal morbidity linked to antidepressant drugs and ADHD medication warrant attention. It is however, hardly a reason to abstain from these drugs during pregnancy, if treatment is essential for the pregnant woman's health.

Acknowledgements

This thesis would never have been accomplished without the support and inspiration from a large number of wonderful individuals. Owing to you, I will always remember this period as a fantastic time!

First, I am deeply grateful to my main supervisor *Karin Källén.* Thank you so much for offering me to be your PhD-student, a suggestion which came as a completely unexpected but most welcome surprise. You have a unique combination of brilliant intelligence, extraordinary pedagogic skills, great sense of humor and a big heart. In times of trouble, you always come up with creative solutions and I am immensely thankful for everything you taught me. You believed much more in my capacity than I did myself, which made me grow during this inspiring journey. It is a pleasure to spend time with you and I am looking forward to many more years of cooperation!

I also want to express my warmest appreciation towards my co-supervisor *Birger Winbladh,* whose experience, profound knowledge and down to earth way of discussing both clinical and other aspects of our studies, have been invaluable. Apart from having a great time, I learned so much from the presentations regarding drug treatment during pregnancy that we made together at different places all over the country. I can't thank you enough for always being there for me, taking the time to listen and offer your advice, especially during the periods when life has been difficult.

I am very grateful to co-supervisor *Seher Korkmaz,* for giving me this opportunity to do research partly during my ordinary office hours at the Stockholm County Council. I know that this was something extraordinary and I am glad that you trusted that I would manage my usual tasks at the same time. Thank you also for providing considerate advice and trying to keep me from working too hard.

A very special thanks to *Lars L Gustafsson,* who founded the Janus concept and initiated the work with the database *Drugs and Birth Defects.* Without your visionary ideas and endless creativity, nothing of this would have been possible. I am grateful for the guidance with the concept article, which was the start of this thesis and for everything else that I have learned from you. Hopefully, I have adopted some of your attitude that there are no limits to what one can achieve.

I could not have wished for a better coauthor than *Lisa Forsberg,* when I took my first shaky steps into epidemiological research. It is always fun and inspiring to work with

you. Even Bromma airport at 6.30 a dark winter morning was enjoyable when we chatted over a cup of coffee. I would also like to thank *Katarina Wide,* for always coming up with wise points of view, both regarding the study concerning antidepressants and in the work with *Drugs and Birth Defects.*

My warmest thank you to present and previous colleagues at the Stockholm County Council: *Emma Hultén, Margaretha Julander, Elisabeth Törnqvist, Tero Shemeikka* (coauthor of the second paper), *Britt Wessel, Anette Rickebjer* (thank you for recruiting pregnant women to the second study), *Birgit Eiermann* (coauthor of the first paper), *Siv Martini, David Finer* (english language editor for the first paper), *Linnéa Karlsson Lind, Anikó Vég* and many more. I am fortunate to be surrounded with such ambitious and competent people and friends. We will see more of each other from now on!

A very big thank you to specialist midwife *Ann-Marie K Molin*, who contributed in both planning and accomplishing the questionnaire survey. Your help was invaluable! I am also deeply grateful to all other midwives, who recruited pregnant women at the antenatal clinics and of course to the pregnant women and health care professionals who answered the questionnaires.

The discussions with the scientific advisory board for *Drugs and Birth Defects* have yielded lots of important input to the work with the database but also with this thesis. I would therefore like to thank all members for fruitful and inspiring cooperation.

I am very lucky to have fantastic support also outside the professional world. I would never have achieved this project without my amazing two and four legged friends at Mälarhöjdens ridskola and ryttarsällskap. It doesn't matter how stressed out I am, after spending time with you, I am back to normal!

To my long-term friend *Ingrid Schmidt*: thank you for sharing both good and bad times with me, for always being encouraging, full of creative ideas, and for letting me borrow your lovely dogs.

I am immensely grateful for the unconditional love and support throughout my life from my mother *Gail.*

My gratitude also to my dear friends, relatives and colleagues not acknowledged by name here – you are not forgotten!

I dedicate this thesis to *Marcus*, *Klara* and *Ella.* There are simply not enough words to express how important you are in my life. Thank you for putting up with me!

This thesis was partly financed by my employer, the Stockholm County Council, Department of E-health and Strategic IT. I am most grateful that I had this possibility to acquire new knowledge and develop professionally.

References

1. Stephansson O, Granath F, Svensson T, Haglund B, Ekbom A, Kieler H. Drug use during pregnancy in Sweden – assessed by the Prescribed Drug Register and the Medical Birth Register. Clinical Epidemiology. 2011;3:43-50.
2. Engeland A, Bramness JG, Daltveit AK, Ronning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004-2006. Br J Clin Pharmacol. 2008;65(5):653-60.
3. Bakker MK, Jentink J, Vroom F, Van Den Berg PB, De Walle HE, De Jong-Van Den Berg LT. Drug prescription patterns before, during and after pregnancy for chronic, occasional and pregnancy-related drugs in the Netherlands. BJOG. 2006;113(5):559-68.
4. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011;205(1):51 e1-8.
5. Palmsten K, Hernandez-Diaz S, Chambers CD, Mogun H, Lai S, Gilmer TP, et al. The Most Commonly Dispensed Prescription Medications Among Pregnant Women Enrolled in the U.S. Medicaid Program. Obstet Gynecol. 2015.
6. Lacroix I, Hurault C, Sarramon MF, Guitard C, Berrebi A, Grau M, et al. Prescription of drugs during pregnancy: a study using EFEMERIS, the new French database. Eur J Clin Pharmacol. 2009;65(8):839-46.
7. Crespin S, Bourrel R, Hurault-Delarue C, Lapeyre-Mestre M, Montastruc JL, Damase-Michel C. Drug prescribing before and during pregnancy in south west France: a retrolective study. Drug Saf. 2011;34(7):595-604.
8. Thomas SHL, Yates LM. Prescribing without evidence - pregnancy. British Journal of Clinical Pharmacology. 2012;74(4):691-7.
9. Thorpe PG, Gilboa SM, Hernandez-Diaz S, Lind J, Cragan JD, Briggs G, et al. Medications in the first trimester of pregnancy: most common exposures and critical gaps in understanding fetal risk. Pharmacoepidemiol Drug Saf. 2013;22(9):1013-8.
10. Food and Drug Administration (FDA). Reviewer Guidance. Evaluating the Risks of Drug Exposure in Human Pregnancies. 2005. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071645.pdf. Accessed March 28, 2017.

11. Griffiths S, Campbell, JP. Placental structure, function and drug transfer. Continuing Education in Anaesthesia, Critical Care & Pain. 2015;15(2):84-9.
12. Eshkoli T, Sheiner E, Ben-Zvi Z, Holcberg G. Drug transport across the placenta. Current pharmaceutical biotechnology. 2011;12(5):707-14.
13. Gedeon C, Koren G. Designing pregnancy centered medications: drugs which do not cross the human placenta. Placenta. 2006;27(8):861-8.
14. Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. Am J Gastroenterol. 2009;104(1):228-33.
15. Briggs GG, Freeman RK. Drugs in Pregnancy and Lactation. A reference guide to fetal and neonatal risk. 10th ed: Wolters Kluwer Health; 2015.
16. Moore KL. The developing human. Clinically oriented embryology. 10th ed: Elsevier; 2016.
17. Fisher B, Rose NC, Carey JC. Principles and practice of teratology for the obstetrician. Clin Obstet Gynecol. 2008;51(1):106-18.
18. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. Birth Defects Res A Clin Mol Teratol. 2015;103(8):652-5.
19. Holmes LB. Human teratogens: update 2010. Birth Defects Res A Clin Mol Teratol. 2011;91(1):1-7.
20. Glen CD, Dubrova YE. Exposure to anticancer drugs can result in transgenerational genomic instability in mice. Proceedings of the National Academy of Sciences of the United States of America. 2012;109(8):2984-8.
21. Brent RL. Addressing environmentally caused human birth defects. Pediatrics in review/ American Academy of Pediatrics. 2001;22(5):153-65.
22. van Gelder MM, van Rooij IA, Miller RK, Zielhuis GA, de Jong-van den Berg LT, Roeleveld N. Teratogenic mechanisms of medical drugs. Human reproduction update. 2010;16(4):378-94.
23. Caton AR, Bell EM, Druschel CM, Werler MM, Lin AE, Browne ML, et al. Antihypertensive medication use during pregnancy and the risk of cardiovascular malformations. Hypertension. 2009;54(1):63-70.
24. European Medicines Agency. Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labeling. 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003307.pdf. Accessed March 28, 2017.
25. Lagercrantz. H, Hellström-Westas L, Norman M. Neonatalogi: Studentlitteratur; 2015.
26. Weikum WM, Brain U, Chau CM, Grunau RE, Boyce WT, Diamond A, et al. Prenatal serotonin reuptake inhibitor (SRI) antidepressant exposure and serotonin transporter

promoter genotype (SLC6A4) influence executive functions at 6 years of age. Frontiers in cellular neuroscience. 2013;7:180.

27. Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. Seizure. 2015;28:46-50.
28. McBride WG. Thalidomide and congenital abnormalities. The Lancet. 1961;278(7216):1358.
29. Lenz W. Kindlische missbildungen nach medikament-einnahme während der gravidität? Dtsch Med Wochenschr. 1961;37:1863-6.
30. Sales Luiz Vianna F, Kowalski TW, Fraga LR, Sanseverino MT, Schuler-Faccini L. The impact of thalidomide use in birth defects in Brazil. European journal of medical genetics. 2017;60(1):12-5.
31. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth defects research Part C, Embryo today : reviews. 2015;105(2):140-56.
32. European Medicines Agency (EMA). Assessment report for Thalidomide Pharmion. 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000823/WC500037054.pdf. Accessed March 12, 2017.
33. Noah, Barbara A. The Inclusion of Pregnant Women in Clinical Research (2014). St. Louis University Journal of Health Law and Policy, Vol. 7, p. 353, 2014; Western New England University School of Law Legal Studies Research Paper No. 14-9. Available at: http://ssrn.com/abstract=2468310. Accessed March 28, 2017.
34. Einarson A, Egberts TC, Heerdink ER. Antidepressant use in pregnancy: knowledge transfer and translation of research findings. J Eval Clin Pract. 2015;21(4):579-83.
35. Källén B. Epidemiology of human congential malformations. Switzerland: Springer International Publishing; 2014.
36. Shepard TH. "Proof" of human teratogenicity. Teratology. 1994;50(2):97-8.
37. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. N Engl J Med. 1998;338(16):1128-37.
38. Källén B. Drugs in pregnancy – the dilemma of labeling. Drug Information Journal. 1999;33(4):1135-43.
39. Brent RL. Utilization of animal studies to determine the effects and human risks of environmental toxicants (drugs, chemicals, and physical agents). Pediatrics. 2004;113(4 Suppl):984-95.
40. Källén B. Drugs during pregnancy. New York: Nova Science Publisher; 2009.
41. Källen BA. Methodological issues in the epidemiological study of the teratogenicity of drugs. Congenit Anom (Kyoto). 2005;45(2):44-51.
42. Källén, B. Bakgrund och forskningsmetodik. [Background and research methodology]. 2002. Available at: www.janusinfo.se/Beslutsstod/Om-lakemedel-och-fosterpaverkan/Bakgrund-och-forskningsmetodik/. Accessed September 26, 2016.

43. Rothman K. Epidemiology. An introduction. New York: Oxford University Press; 2012.
44. Ehrenstein V, Sorensen HT, Bakketeig LS, Pedersen L. Medical databases in studies of drug teratogenicity: methodological issues. Clin Epidemiol. 2010;2:37-43.
45. Pregnancy Registries. In: Registries for Evaluating Patient Outcomes: A User's Guide: 3rd Edition. Ed: Richard E Gliklich; Nancy A Dreyer; Michelle B Leavy. Agency for Healthcare Research and Quality (US) 2014;13(14)-EHC1112014.
46. Coscia LA, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Maley WR, et al. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. Clin Transpl. 2010:65-85.
47. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology. 2015;85(10):866-72.
48. Food and Drug Administration. Pregnancy Exposure Registries and other Post-Approval Studies: Current Status and Observations. 2014. Available at: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM399660.pdf. Accessed December 12, 2016.
49. Hancock RL, Koren G, Einarson A, Ungar WJ. The effectiveness of Teratology Information Services (TIS). Reprod Toxicol. 2007;23(2):125-32.
50. Chambers C. The role of teratology information services in screening for teratogenic exposures: challenges and opportunities. Am J Med Genet C Semin Med Genet. 2011;157(3):195-200.
51. Castilla EE, Orioli IM. ECLAMC: the Latin-American collaborative study of congenital malformations. Community Genet. 2004;7(2-3):76-94.
52. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case-control study. Teratology. 1998;58(1):2-5.
53. Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, et al. The National Birth Defects Prevention Study: A review of the methods. Birth Defects Res A Clin Mol Teratol. 2015;103(8):656-69.
54. Luteijn JM, Morris JK, Garne E, Given J, de Jong-van den Berg L, Addor MC, et al. EUROmediCAT signal detection: a systematic method for identifying potential teratogenic medication. Br J Clin Pharmacol. 2016;82(4):1110-22.
55. Lisi A, Botto LD, Robert-Gnansia E, Castilla EE, Bakker MK, Bianca S, et al. Surveillance of adverse fetal effects of medications (SAFE-Med): findings from the international Clearinghouse of birth defects surveillance and research. Reprod Toxicol. 2010;29(4):433-42.
56. Garne E, Hansen AV, Morris J, Zaupper L, Addor MC, Barisic I, et al. Use of asthma medication during pregnancy and risk of specific congenital anomalies: A European case-malformed control study. The Journal of allergy and clinical immunology. 2015;136(6):1496-502 e1-7.

57. Poletta FA, Lopez Camelo JS, Gili JA, Leoncini E, Castilla EE, Mastroiacovo P. Methodological approaches to evaluate teratogenic risk using birth defect registries: advantages and disadvantages. PLoS One. 2012;7(10):e46626.

58. De Santis M, Cesari E, Ligato MS, Nobili E, Straface G, Cavaliere A, et al. Prenatal drug exposure and teratological risk: one-year experience of an Italian Teratology Information Service. Med Sci Monit. 2008;14(2):PH1-8.

59. Einarson A, Selby P, Koren G. Abrupt discontinuation of psychotropic drugs during pregnancy: fear of teratogenic risk and impact of counselling. J Psychiatry Neurosci. 2001;26(1):44-8.

60. Koren G, Bologa M, Pastuszak A. Women's perception of teratogenic risk. Can J Public Health. 1991;82(3):S11-4, S33-7.

61. Koren G, Pastuszak A. Prevention of unnecessary pregnancy terminations by counselling women on drug, chemical, and radiation exposure during the first trimester. Teratology. 1990;41(6):657-61.

62. Sanz E, Gomez-Lopez T, Martinez-Quintas MJ. Perception of teratogenic risk of common medicines. Eur J Obstet Gynecol Reprod Biol. 2001;95(1):127-31.

63. Nordeng H, Ystrom E, Einarson A. Perception of risk regarding the use of medications and other exposures during pregnancy. Eur J Clin Pharmacol. 2010;66(2):207-14.

64. Csajka C, Jaquet A, Winterfeld U, Meyer Y, Einarson A, Panchaud A. Risk perception by healthcare professionals related to drug use during pregnancy: a Swiss survey. Swiss medical weekly. 2014;144:w13936.

65. Petersen I, McCrea RL, Lupattelli A, Nordeng H. Women's perception of risks of adverse fetal pregnancy outcomes: a large-scale multinational survey. BMJ open. 2015;5(6):e007390.

66. Mulder E, Davis A, Gawley L, Bowen A, Einarson A. Negative impact of non-evidence-based information received by women taking antidepressants during pregnancy from health care providers and others. J Obstet Gynaecol Can. 2012;34(1):66-71.

67. Einarson A, Davis W. Barriers to the pharmacological treatment of women with psychiatric disorders during pregnancy and breastfeeding: results of a survey. J Obstet Gynaecol Can. 2013;35(6):504-5.

68. Einarson A, Schachtschneider AK, Halil R, Bollano E, Koren G. SSRI'S and other antidepressant use during pregnancy and potential neonatal adverse effects: impact of a public health advisory and subsequent reports in the news media. BMC pregnancy and childbirth. 2005;5:11.

69. Lupattelli A, Spigset O, Nordeng H. Adherence to medication for chronic disorders during pregnancy: results from a multinational study. International journal of clinical pharmacy. 2014;36(1):145-53.

70. Petersen I, Gilbert RE, Evans SJW, Man S-L, Nazareth I. Pregnancy as a Major Determinant for Discontinuation of Antidepressants. The Journal of Clinical Psychiatry. 2011;72(07):979-85.

71. Sawicki E, Stewart K, Wong S, Leung L, Paul E, George J. Medication use for chronic health conditions by pregnant women attending an Australian maternity hospital. Aust N Z J Obstet Gynaecol. 2011;51(4):333-8.
72. Bonari L, Koren G, Einarson TR, Jasper JD, Taddio A, Einarson A. Use of antidepressants by pregnant women: evaluation of perception of risk, efficacy of evidence based counseling and determinants of decision making. Archives of women's mental health. 2005;8(4):214-20.
73. Goodman JH. Women's attitudeds, preferences and perceived barriers to treatment for perinatal depression. Birth. 2009;36(1):60-9.
74. Bennett IM, Marcus SC, Palmer SC, Coyne JC. Pregnancy-related discontinuation of antidepressants and depression care visits among Medicaid recipients. Psychiatr Serv. 2010;61(4):386-91.
75. Ram D, Gowdappa B, Ashoka HG, Eiman N. Psychopharmacoteratophobia: Excessive fear of malformation associated with prescribing psychotropic drugs during pregnancy: An Indian perspective. Indian journal of pharmacology. 2015;47(5):484-90.
76. Peters SL, Lind JN, Humphrey JR, Friedman JM, Honein MA, Tassinari MS, et al. Safe lists for medications in pregnancy: inadequate evidence base and inconsistent guidance from Web-based information, 2011. Pharmacoepidemiol Drug Saf. 2013;22(3):324-8.
77. Daw JR, Hanley GE, Greyson DL, Morgan SG. Prescription drug use during pregnancy in developed countries: a systematic review. Pharmacoepidemiol Drug Saf. 2011;20(9):895-902.
78. Stevens G, Thompson R, Watson B, Miller YD. Patient decision aids in routine maternity care: Benefits, barriers, and new opportunities. Women and birth : journal of the Australian College of Midwives. 2016;29(1):30-4.
79. Lagan BM, Sinclair M, Kernohan WG. What is the impact of the Internet on decision-making in pregnancy? A global study. Birth. 2011;38(4):336-45.
80. Larsson M. A descriptive study of the use of the Internet by women seeking pregnancy-related information. Midwifery. 2009;25(1):14-20.
81. Huvila I MG, Cajander Å. Empowerment or Anxiety? Research on Deployment of Online Medical E-health Services in Sweden. Bulletin of the Association for Information Science. 2013;39(5):30-3.
82. Bartlett C, Simpson K, Turner AN. Patient access to complex chronic disease records on the Internet. BMC Med Inform Decis Mak. 2012;12:87.
83. Ammenwerth E, Schnell-Inderst P, Hoerbst A. The impact of electronic patient portals on patient care: a systematic review of controlled trials. J Med Internet Res. 2012;14(6):e162.
84. Bjerrum L, Foged A. Patient information leaflets – helpful guidance or a source of confusion? Pharmacoepidemiol Drug Saf. 2003;12(1):55-9.

85. Fusier I, Tollier C, Husson MC. Infovigilance: reporting errors in official drug information sources. Pharm World Sci. 2005;27(3):166-9.

86. Frost Widnes SK, Schjott J. Advice on drug safety in pregnancy: are there differences between commonly used sources of information? Drug Saf. 2008;31(9):799-806.

87. Warrer P, Aagaard L, Hansen EH. Comparison of pregnancy and lactation labeling for attention-deficit hyperactivity disorder drugs marketed in Australia, the USA, Denmark, and the UK. Drug Saf. 2014;37(10):805-13.

88. Clauson KA, Marsh WA, Polen HH, Seamon MJ, Ortiz BI. Clinical decision support tools: analysis of online drug information databases: BMC Med Inform Decis Mak 7:7; 2007. Availabe at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1831469/?tool=pubmed. Accessed September 9, 2016.

89. Ohman B, Lyrvall H, Tornqvist E, Alvan G, Sjoqvist F. Clinical pharmacology and the provision of drug information. Eur J Clin Pharmacol. 1992;42(6):563-7.

90. Frost Widnes SK, Schjott J. Drug use in pregnancy-physicians' evaluation of quality and clinical impact of drug information centres. Eur J Clin Pharmacol. 2009;65(3):303-8.

91. Regionale legemiddelinformasjonssentre (RELIS). Bergen. Available at: http://www.tryggmammamedisin.no. Accessed 2016-10-23.

92. Sjoborg B, Backstrom T, Arvidsson LB, Andersen-Karlsson E, Blomberg LB, Eiermann B, et al. Design and implementation of a point-of-care computerized system for drug therapy in Stockholm metropolitan health region – Bridging the gap between knowledge and practice. Int J Med Inform. 2007;76(7):497-506.

93. Stewart DE. Clinical practice. Depression during pregnancy. N Engl J Med. 2011;365(17):1605-11.

94. Goodman JH, Chenausky KL, Freeman MP. Anxiety disorders during pregnancy: a systematic review. J Clin Psychiatry. 2014;75(10):e1153-84.

95. Ornoy A, Koren G. Selective serotonin reuptake inhibitors in human pregnancy: on the way to resolving the controversy. Seminars in fetal & neonatal medicine. 2014;19(3):188-94.

96. National Board of Health and Welfare.The Swedish Medical Birth Register. 2016. Available at: http://www.socialstyrelsen.se/register/halsodataregister/medicinskafodelseregistret. Accessed October 15, 2016.

97. Feighner JP. Mechanism of action of antidepressant medications. J Clin Psychiatry. 1999;60 Suppl 4:4-11; discussion 2-3.

98. Medical Products Agency. Depression, ångestsyndrom och tvångssyndrom hos barn och vuxna. [Depression, anxiety and obsessive compulsive disorders in children and adults]. 2016. Available at: https://lakemedelsverket.se/malgrupp/Halso---sjukvard/Behandlings--rekommendationer/Behandlingsrekommendation---listan/Depression-angestsyndrom-och-tvangssyndrom-hos-barn-och-vuxna/ Accessed March 13, 2017.

99. Stockholm County Council. Psykisk sjukdom i samband med graviditet och spädbarnsperiod. Regionalt vårdprogram. [Psychiatric disease during pregnancy and the infant period. Regional treatment recommendations]. 2014. Available at: http://www1.psykiatristod.se/Global/Psykiatristod/Bilagor/RVP_GravDepp_webb.pdf. Accessed February 16, 2017.
100. Swedish Council on Health Technology Assessment. Behandling av depressionssjukdomar. [Treatment of depression]. 2004. Available at: http://www.sbu.se/sv/publikationer/sbu-utvarderar/behandling-av-depressionssjukdomar/. Accessed March 14, 2017.
101. Myles N, Newall H, Ward H, Large M. Systematic meta-analysis of individual selective serotonin reuptake inhibitor medications and congenital malformations. Aust N Z J Psychiatry. 2013;47(11):1002-12.
102. Kallen B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. Pharmaceuticals. 2013;6(10):1221-86.
103. Gentile S. Tricyclic antidepressants in pregnancy and puerperium. Expert Opin Drug Saf. 2014;13(2):207-25.
104. Reefhuis J, Devine O, Friedman JM, Louik C, Honein MA, National Birth Defects Prevention S. Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports. BMJ. 2015;351:h3190.
105. Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med. 1996;335(14):1010-5.
106. Costei AM, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. Arch Pediatr Adolesc Med. 2002;156(11):1129-32.
107. Ferreira E, Carceller AM, Agogue C, Martin BZ, St-Andre M, Francoeur D, et al. Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. Pediatrics. 2007;119(1):52-9.
108. Forsberg L, Naver L, Gustafsson LL, Wide K. Neonatal adaptation in infants prenatally exposed to antidepressants- clinical monitoring using neonatal abstinence score. PLoS One. 2014;9(11):e111327.
109. Grigoriadis S, VonderPorten EH, Mamisashvili L, Eady A, Tomlinson G, Dennis CL, et al. The effect of prenatal antidepressant exposure on neonatal adaptation: a systematic review and meta-analysis. J Clin Psychiatry. 2013;74(4):e309-20.
110. Grzeskowiak LE, Gilbert AL, Morrison JL. Neonatal outcomes after late-gestation exposure to selective serotonin reuptake inhibitors. Journal of clinical psychopharmacology. 2012;32(5):615-21.
111. Hayes RM, Wu P, Shelton RC, Cooper WO, Dupont WD, Mitchel E, et al. Maternal antidepressant use and adverse outcomes: a cohort study of 228,876 pregnancies. Am J Obstet Gynecol. 2012;207(1):49 e1-9.
112. Kallen B. Neonate characteristics after maternal use of antidepressants in late pregnancy. Arch Pediatr Adolesc Med. 2004;158(4):312-6.

113. Leibovitch L, Rymer-Haskel N, Schushan-Eisen I, Kuint J, Strauss T, Maayan-Metzger A. Short-term neonatal outcome among term infants after in utero exposure to serotonin reuptake inhibitors. Neonatology. 2013;104(1):65-70.

114. Levinson-Castiel R, Merlob P, Linder N, Sirota L, Klinger G. Neonatal abstinence syndrome after in utero exposure to selective serotonin reuptake inhibitors in term infants. Arch Pediatr Adolesc Med. 2006;160(2):173-6.

115. Lund N, Pedersen LH, Henriksen TB. Selective serotonin reuptake inhibitor exposure in utero and pregnancy outcomes. Arch Pediatr Adolesc Med. 2009;163(10):949-54.

116. Malm H, Klaukka T, Neuvonen PJ. Risks associated with selective serotonin reuptake inhibitors in pregnancy. Obstet Gynecol. 2005;106(6):1289-96.

117. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Neonatal outcomes after prenatal exposure to selective serotonin reuptake inhibitor antidepressants and maternal depression using population-based linked health data. Arch Gen Psychiatry. 2006;63(8):898-906.

118. Oberlander TF, Warburton W, Misri S, Aghajanian J, Hertzman C. Effects of timing and duration of gestational exposure to serotonin reuptake inhibitor antidepressants: population-based study. The British journal of psychiatry : the journal of mental science. 2008;192(5):338-43.

119. Rampono J, Simmer K, Ilett KF, Hackett LP, Doherty DA, Elliot R, et al. Placental transfer of SSRI and SNRI antidepressants and effects on the neonate. Pharmacopsychiatry. 2009;42(3):95-100.

120. Suri R, Altshuler L, Hellemann G, Burt VK, Aquino A, Mintz J. Effects of antenatal depression and antidepressant treatment on gestational age at birth and risk of preterm birth. The American journal of psychiatry. 2007;164(8):1206-13.

121. Wen SW, Yang Q, Garner P, Fraser W, Olatunbosun O, Nimrod C, et al. Selective serotonin reuptake inhibitors and adverse pregnancy outcomes. Am J Obstet Gynecol. 2006;194(4):961-6.

122. Moses-Kolko EL, Bogen D, Perel J, Bregar A, Uhl K, Levin B, et al. Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. JAMA. 2005;293(19):2372-83.

123. Ter Horst PG, Jansman FG, van Lingen RA, Smit JP, de Jong-van den Berg LT, Brouwers JR. Pharmacological aspects of neonatal antidepressant withdrawal. Obstetrical & gynecological survey. 2008;63(4):267-79.

124. Stahl MM, Lindquist M, Pettersson M, Edwards IR, Sanderson JH, Taylor NF, et al. Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system. Eur J Clin Pharmacol. 1997;53(3-4):163-9.

125. Engelstad HJ, Roghair RD, Calarge CA, Colaizy TT, Stuart S, Haskell SE. Perinatal Outcomes of Pregnancies Complicated by Maternal Depression with or without Selective Serotonin Reuptake Inhibitor Therapy. Neonatology. 2014;105(2):149-54.

126. Nordeng H, van Gelder MM, Spigset O, Koren G, Einarson A, Eberhard-Gran M. Pregnancy outcome after exposure to antidepressants and the role of maternal depression: results from the Norwegian Mother and Child Cohort Study. Journal of clinical psychopharmacology. 2012;32(2):186-94.
127. Warburton W, Hertzman C, Oberlander TF. A register study of the impact of stopping third trimester selective serotonin reuptake inhibitor exposure on neonatal health. Acta psychiatrica Scandinavica. 2010;121(6):471-9.
128. Wisner KL, Sit DK, Hanusa BH, Moses-Kolko EL, Bogen DL, Hunker DF, et al. Major depression and antidepressant treatment: impact on pregnancy and neonatal outcomes. The American journal of psychiatry. 2009;166(5):557-66.
129. Ross LE, Grigoriadis S, Mamisashvili L, Vonderporten EH, Roerecke M, Rehm J, et al. Selected pregnancy and delivery outcomes after exposure to antidepressant medication: a systematic review and meta-analysis. JAMA psychiatry. 2013;70(4):436-43.
130. Kieler H, Artama M, Engeland A, Ericsson O, Furu K, Gissler M, et al. Selective serotonin reuptake inhibitors during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries. BMJ. 2011;344:d8012.
131. t Jong GW, Einarson T, Koren G, Einarson A. Antidepressant use in pregnancy and persistent pulmonary hypertension of the newborn (PPHN): a systematic review. Reprod Toxicol. 2012;34(3):293-7.
132. Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatric clinics of North America. 2009;56(3):579-600, Table of Contents.
133. Pedersen LH, Henriksen TB, Bech BH, Licht RW, Kjaer D, Olsen J. Prenatal antidepressant exposure and behavioral problems in early childhood--a cohort study. Acta psychiatrica Scandinavica. 2013;127(2):126-35.
134. Gentile S, Galbally M. Prenatal exposure to antidepressant medications and neurodevelopmental outcomes: a systematic review. J Affect Disord. 2011;128(1-2):1-9.
135. Sorensen MJ, Gronborg TK, Christensen J, Parner ET, Vestergaard M, Schendel D, et al. Antidepressant exposure in pregnancy and risk of autism spectrum disorders. Clin Epidemiol. 2013;5:449-59.
136. Hviid A, Melbye M, Pasternak B. Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism. N Engl J Med. 2013;369(25):2406-15.
137. Boukhris T, Sheehy O, Mottron L, Berard A. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. JAMA pediatrics. 2016;170(2):117-24.
138. Castro VM, Kong SW, Clements CC, Brady R, Kaimal AJ, Doyle AE, et al. Absence of evidence for increase in risk for autism or attention-deficit hyperactivity disorder following antidepressant exposure during pregnancy: a replication study. Translational psychiatry. 2016;6:e708.

139. Rai D, Lee BK, Dalman C, Golding J, Lewis G, Magnusson C. Parental depression, maternal antidepressant use during pregnancy, and risk of autism spectrum disorders: population based case-control study. BMJ. 2013;346:f2059.
140. Brown HK, Ray JG, Wilton AS, Lunsky Y, Gomes T, Vigod SN. Association Between Serotonergic Antidepressant Use During Pregnancy and Autism Spectrum Disorder in Children. JAMA. 2017;317(15):1544-52.
141. Sujan AC, Rickert ME, Oberg AS, Quinn PD, Hernandez-Diaz S, Almqvist C, et al. Associations of Maternal Antidepressant Use During the First Trimester of Pregnancy With Preterm Birth, Small for Gestational Age, Autism Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA. 2017;317(15):1553-62.
142. Kooij SJ, Bejerot S, Blackwell A, Caci H, Casas-Brugue M, Carpentier PJ, et al. European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD. BMC psychiatry. 2010;10:67.
143. Medical Products Agency. Läkemedel vid ADHD - behandlingsrekommendation. [Recommendations for treatment of ADHD]. 2016. Available at: https://lakemedelsverket.se/adhd. Accessed November 3, 2016.
144. Louik C, Kerr S, Kelley KE, Mitchell AA. Increasing use of ADHD medications in pregnancy. Pharmacoepidemiol Drug Saf. 2015;24(2):218-20.
145. National Board of Health and Welfare. The Prescribed Drug Register 2015. Available at: http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel. Accessed March 31, 2017.
146. Haervig KB, Mortensen LH, Hansen AV, Strandberg-Larsen K. Use of ADHD medication during pregnancy from 1999 to 2010: a Danish register-based study. Pharmacoepidemiol Drug Saf. 2014;23(5):526-33.
147. Thapar A, Cooper M. Attention deficit hyperactivity disorder. The Lancet. 2015.
148. Walker DJ, Mason O, Clemow DB, Day KA. Atomoxetine treatment in adults with attention-deficit/hyperactivity disorder. Postgraduate medicine. 2015;127(7):686-701.
149. Huss M, Chen W, Ludolph AG. Guanfacine Extended Release: A New Pharmacological Treatment Option in Europe. Clinical drug investigation. 2016;36(1):1-25.
150. Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biological psychiatry. 2004;55(10):1031-40.
151. Pottegard A, Hallas J, Andersen JT, Lokkegaard EC, Dideriksen D, Aagaard L, et al. First-trimester exposure to methylphenidate: a population-based cohort study. J Clin Psychiatry. 2014;75(1):e88-93.
152. Bro SP, Kjaersgaard MI, Parner ET, Sorensen MJ, Olsen J, Bech BH, et al. Adverse pregnancy outcomes after exposure to methylphenidate or atomoxetine during pregnancy. Clin Epidemiol. 2015;7:139-47.

153. Dideriksen D, Pottegard A, Hallas J, Aagaard L, Damkier P. First trimester in utero exposure to methylphenidate. Basic Clin Pharmacol Toxicol. 2013;112(2):73-6.

154. Diav-Citrin O, Shechtman S, Arnon J, Wajnberg R, Borisch C, Beck E, et al. Methylphenidate in Pregnancy: A Multicenter, Prospective, Comparative, Observational Study. J Clin Psychiatry. 2016;77(9):1176-81.

155. Beckman DA, Schneider M, Youreneff M, Tse FL. Developmental toxicity assessment of d,l-methylphenidate and d-methylphenidate in rats and rabbits. Birth Defects Res B Dev Reprod Toxicol. 2008;83(5):489-501.

156. Besag FM. ADHD treatment and pregnancy. Drug Saf. 2014;37(6):397-408.

157. Humphreys C, Garcia-Bournissen F, Ito S, Koren G. Exposure to attention deficit hyperactivity disorder medications during pregnancy. Canadian family physician Medecin de famille canadien. 2007;53(7):1153-5.

158. Milkovich L, van der Berg BJ. Effects of antenatal exposure to anorectic drugs. Am J Obstet Gynecol. 1977;129(6):637-42.

159. Elliott L, Loomis D, Lottritz L, Slotnick RN, Oki E, Todd R. Case-control study of a gastroschisis cluster in Nevada. Arch Pediatr Adolesc Med. 2009;163(11):1000-6.

160. Levin JN. Amphetamine ingestion with biliary atresia. The Journal of pediatrics. 1971;79(1):130-1.

161. Nora JJ, Vargo TA, Nora AH, Love KE, McNamara DG. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. Lancet. 1970;1(7659):1290-1.

162. Oei JL, Kingsbury A, Dhawan A, Burns L, Feller JM, Clews S, et al. Amphetamines, the pregnant woman and her children: a review. J Perinatol. 2012;32(10):737-47.

163. Eriksson M, Jonsson B, Zetterstrom R. Children of mothers abusing amphetamine: head circumference during infancy and psychosocial development until 14 years of age. Acta Paediatr. 2000;89(12):1474-8.

164. Chomchai C, Na Manorom N, Watanarungsan P, Yossuck P, Chomchai S. Methamphetamine abuse during pregnancy and its health impact on neonates born at Siriraj Hospital, Bangkok, Thailand. The Southeast Asian journal of tropical medicine and public health. 2004;35(1):228-31.

165. Thaithumyanon P, Limpongsanurak S, Praisuwanna P, Punnahitanon S. Perinatal effects of amphetamine and heroin use during pregnancy on the mother and infant. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2005;88(11):1506-13.

166. Ladhani NN, Shah PS, Murphy KE, Knowledge Synthesis Group on Determinants of Preterm LBWB. Prenatal amphetamine exposure and birth outcomes: a systematic review and metaanalysis. Am J Obstet Gynecol. 2011;205(3):219 e1-7.

167. Smith L, Yonekura ML, Wallace T, Berman N, Kuo J, Berkowitz C. Effects of prenatal methamphetamine exposure on fetal growth and drug withdrawal symptoms in infants

born at term. Journal of developmental and behavioral pediatrics : JDBP. 2003;24(1):17-23.

168. Plessinger MA. Prenatal exposure to amphetamines. Risks and adverse outcomes in pregnancy. Obstetrics and gynecology clinics of North America. 1998;25(1):119-38.
169. Cernerud L, Eriksson M, Jonsson B, Steneroth G, Zetterstrom R. Amphetamine addiction during pregnancy: 14-year follow-up of growth and school performance. Acta Paediatr. 1996;85(2):204-8.
170. Eiermann B, Bastholm Rahmner P, Korkmaz S, Landberg C, Lilja B, Shemeikka T, et al. Knowledge Bases for Clinical Decision Support in Drug Prescribing – Development, Quality Assurance, Management, Integration and Evaluation of Clinical Value Croatia: Decision Support Systems. InTech 2010;9:139-64. Available at: http://www.intechopen.com/source/pdfs/6866/InTech-Knowledge_bases_for_clinical_decision_support_in_drug_prescribing_development_quality_assurance_management_integration_implementation_and_evaluation_of_clinical_value.pdf. Accessed November 11, 2016.
171. Holden RJ, Karsh BT. The technology acceptance model: its past and its future in health care. J Biomed Inform. 2010;43(1):159-72.
172. Meades R, Ayers S. Anxiety measures validated in perinatal populations: a systematic review. J Affect Disord. 2011;133(1-2):1-15.
173. Socialstyrelsen. National Board of Health and Welfare. Hälsodataregister räddar liv och förbättrar livskvalitet. [Health data registers save lives and improve quality of life]. 2008. Available at: http://www.socialstyrelsen.se/publikationer2008/2008-126-27. Accessed April 23, 2017.
174. Emilsson L, Lindahl B, Koster M, Lambe M, Ludvigsson JF. Review of 103 Swedish Healthcare Quality Registries. Journal of internal medicine. 2015;277(1):94-136.
175. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. European journal of epidemiology. 2009;24(11):659-67.
176. National Board of Health and Welfare. Centre for Epidemiology. The Swedish Medical Birth Register – a summary of content and quality. 2003. Available at: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3_20031123.pdf. Accessed November 11, 2016.
177. Statistics Sweden (SCB). Available at: http://ww.scb.se. Accessed November 27, 2016.
178. Swedish Council on Health Technology Assessment. Routine ultrasound during pregnancy 1999. Available at: http://www.sbu.se/en/publications/sbu-assesses/routine-ultrasound-examination-during-pregnancy/. Accessed November 14, 2016.
179. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register-opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.

180. Kallen B, Nilsson E, Olausson PO. Antidepressant use during pregnancy: comparison of data obtained from a prescription register and from antenatal care records. Eur J Clin Pharmacol. 2011;67(8):839-45.

181. Swedish Neonatal Quality Register. Available at: http://www.medscinet.com/PNQ/. Accessed November 14, 2016.

182. Molin J. A regional perinatal database in southern Sweden-a basis for quality assurance in obstetrics and neonatology. Acta obstetricia et gynecologica Scandinavica Supplement. 1997;164:37-9.

183. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

184. Marsal K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. Acta Paediatr. 1996;85(7):843-8.

185. Position Statement from the European Board and College of Obstetrics & Gynaecology (EBCOG). The use of medicines during pregnancy - Call for Action. Available at: http://www.ebcog.org/single-post/2016/05/09/position-paper-medicines-pregnancy?Itemid=276&id=304&option=com_content&view=article. Accessed February 4, 2017.

186. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet. 2011;157C(3):175-82.

187. Endicott S, Haas DM. The current state of therapeutic drug trials in pregnancy. Clinical pharmacology and therapeutics. 2012;92(2):149-50.

188. European Initiative of Women's Health. Safe Use of Medicines During Pregnancy and Lactation. Available at: http://eurohealth.ie/2016/10/18/safe-use-of-medicines-during-pregnancy-and-lactation/. Accessed February 4, 2017.

189. Hameen-Anttila K, Nordeng H, Kokki E, Jyrkka J, Lupattelli A, Vainio K, et al. Multiple information sources and consequences of conflicting information about medicine use during pregnancy: a multinational Internet-based survey. J Med Internet Res. 2014;16(2):e60.

190. Currie WS, JM. A cross-sectional analysis of eHealth in the European Union: Some policy and research directions. 2014;51:783-97.

191. The Government of Sweden. Vision for e-health 2025. 2016. Available at: http://www.government.se/information-material/2016/08/vision-for-ehealth-2025/. Accessed March 16, 2017.

192. The Swedish Government. Förbättrade förutsättningar för kvalitetsutveckling av abortvården. [Improved conditions for improving quality of abortion care]. 2016. Available at: http://www.regeringen.se/pressmeddelanden/2016/09/forbattrade-forutsattningar-for-kvalitetsutveckling-av-abortvarden/. Accessed April 13, 2017.

193. Food and Drug Administration (FDA). Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. 2014. Available at: http://www.fda.gov/downloads/Drugs/.../Guidances/ucm071645.pdf. Accessed February 5, 2017.

194. Shah NR, Seger AC, Seger DL, Fiskio JM, Kuperman GJ, Blumenfeld B, et al. Improving acceptance of computerized prescribing alerts in ambulatory care. J Am Med Inform Assoc. 2006;13(1):5-11.

195. Clementi M, Di Gianantonio E, Ornoy A. Teratology information services in Europe and their contribution to the prevention of congenital anomalies. Community Genet. 2002;5(1):8-12.

196. Behringer T, Rollman BL, Herbeck-Belnap B, Houck PR, Mazumdar S, Schwarz EB. Impact of physician counseling and perception of teratogenic risks: a survey of 96 nonpregnant women with anxiety. The primary care companion to CNS disorders. 2011;13(2).

197. Al-Saffar A, Deshmuk AA, Carter P, Adib SM. Effect of information leaflets and counselling on antidepressant adherence: opened randomised controlled trial in a psychiatric hospital in Kuwait. International Journal of Pharmacy Practice. 2005;13(2):123-31.

198. National Board of Health and Welfare. Graviditeter, förlossningar och nyfödda barn. Medicinska födelseregistret 1973–2012. Assisterad befruktning 1991–2011. [Pregnancies, deliveries and newborn babies. The Swedish Medical Birth Register 1973-2012. Assisted conception 1991-2011]. 2013.

199. Song FWW, J.E. Lundy, L. Smith Dahmen, N. Women, Pregnancy, and Health Information Online: The Making of Informed Patients and Ideal Mothers. Gender and Society. 2012;26:773-98.

200. Cutilli CC. Seeking health information: what sources do your patients use? Orthop Nurs. 2010;29(3):214-9.

201. Lövtrup M. Åsa Cajander, forskare i människa–datorinteraktion:»Bra reform som kunde införts på ett bättre sätt«. [Åsa Cajander, researcher in human–computer interaction:»Good reform that could have been implemented in a better way«]. Lakartidningen. 2014;111:CS63.

202. Roshanov PS, Fernandes N, Wilczynski JM, Hemens BJ, You JJ, Handler SM, et al. Features of effective computerised clinical decision support systems: meta-regression of 162 randomised trials. BMJ. 2013;346:f657.

203. Anntaa K. "Mot patientvänligare epikriser. En kontrastiv undersökning". [Patients interpreting the medical language of discharge summaries]. MA thesis, Åbo University. 2012.

204. Malm H, Sourander A, Gissler M, Gyllenberg D, Hinkka-Yli-Salomaki S, McKeague IW, et al. Pregnancy Complications Following Prenatal Exposure to SSRIs or Maternal

Psychiatric Disorders: Results From Population-Based National Register Data. The American journal of psychiatry. 2015:appiajp201514121575.

205. Huybrechts KF, Sanghani RS, Avorn J, Urato AC. Preterm birth and antidepressant medication use during pregnancy: a systematic review and meta-analysis. PLoS One. 2014;9(3):e92778.
206. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. Lancet. 2008;371(9608):261-9.
207. Colvin L, Slack-Smith L, Stanley FJ, Bower C. Early morbidity and mortality following in utero exposure to selective serotonin reuptake inhibitors: a population-based study in Western Australia. CNS drugs. 2012;26(7):e1-14.
208. Olivier JD, Akerud H, Kaihola H, Pawluski JL, Skalkidou A, Hogberg U, et al. The effects of maternal depression and maternal selective serotonin reuptake inhibitor exposure on offspring. Frontiers in cellular neuroscience. 2013;7:73.
209. Sadler TW. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. Reprod Toxicol. 2011;32(4):484-9.
210. LaGasse LL, Wouldes T, Newman E, Smith LM, Shah RZ, Derauf C, et al. Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. Neurotoxicology and teratology. 2011;33(1):166-75.
211. Bolea-Alamanac BM, Green A, Verma G, Maxwell P, Davies SJ. Methylphenidate use in pregnancy and lactation: a systematic review of evidence. Br J Clin Pharmacol. 2014;77(1):96-101.
212. Wajnberg R, Diav-Citrin O, Shechtman S, Ornoy A. Pregnancy outcome after in-utero exposure to methylphenidate: A prospective comparative cohort study. Reproductive Toxicology. 2011;31(2):267.
213. Andrade SE, McPhillips H, Loren D, Raebel MA, Lane K, Livingston J, et al. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol Drug Saf. 2009;18(3):246-52.
214. Grigoriadis S, Vonderporten EH, Mamisashvili L, Tomlinson G, Dennis CL, Koren G, et al. Prenatal exposure to antidepressants and persistent pulmonary hypertension of the newborn: systematic review and meta-analysis. BMJ. 2014;348:f6932.
215. Huybrechts KF, Bateman BT, Palmsten K, Desai RJ, Patorno E, Gopalakrishnan C, et al. Antidepressant use late in pregnancy and risk of persistent pulmonary hypertension of the newborn. JAMA. 2015;313(21):2142-51.
216. Bar-Oz B, Einarson T, Einarson A, Boskovic R, O'Brien L, Malm H, et al. Paroxetine and congenital malformations: meta-Analysis and consideration of potential confounding factors. Clin Ther. 2007;29(5):918-26.
217. Davalos DB, Yadon CA, Tregellas HC. Untreated prenatal maternal depression and the potential risks to offspring: a review. Archives of women's mental health. 2012;15(1):1-14.

218. Field T, Diego M, Hernandez-Reif M. Prenatal depression effects and interventions: a review. Infant behavior & development. 2010;33(4):409-18.

219. Bonari L, Pinto N, Ahn E, Einarson A, Steiner M, Koren G. Perinatal risks of untreated depression during pregnancy. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2004;49(11):726-35.

220. Jarde A, Morais M, Kingston D, Giallo R, MacQueen GM, Giglia L, et al. Neonatal Outcomes in Women With Untreated Antenatal Depression Compared With Women Without Depression: A Systematic Review and Meta-analysis. JAMA psychiatry. 2016.

221. National Board of Health and Welfare. Förskrivning av centralstimulerande läkemedel vid ADHD [Prescribing of stimulant drugs for ADHD]. 2012. Available at: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18874/2012-10-30.pdf Accessed February 16, 2017.

222. Cohen LS, Altshuler LL, Harlow BL, Nonacs R, Newport DJ, Viguera AC, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. JAMA. 2006;295(5):499-507.

223. Eddy LD, Jones HA, Snipes D, Karjane N, Svikis D. Associations Between ADHD Symptoms and Occupational, Interpersonal, and Daily Life Impairments Among Pregnant Women. Journal of attention disorders. 2017:1087054716685839.

224. Cuijpers P, Sijbrandij M, Koole SL, Andersson G, Beekman AT, Reynolds CF, 3rd. The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: a meta-analysis of direct comparisons. World psychiatry : official journal of the World Psychiatric Association. 2013;12(2):137-48.

225. Cuijpers P, Hollon SD, van Straten A, Bockting C, Berking M, Andersson G. Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ open. 2013;3(4).

226. Hemond J, Robbins RB, Young PC. The Effects of Maternal Obesity on Neonates, Infants, Children, Adolescents, and Adults. Clin Obstet Gynecol. 2016;59(1):216-27.

227. Banderali G, Martelli A, Landi M, Moretti F, Betti F, Radaelli G, et al. Short and long term health effects of parental tobacco smoking during pregnancy and lactation: a descriptive review. Journal of translational medicine. 2015;13:327.

228. Coverdale JH, McCullough LB, Chervenak FA. The ethics of randomized placebo-controlled trials of antidepressants with pregnant women: a systematic review. Obstet Gynecol. 2008;112(6):1361-8.

229. Gurnot C, Martin-Subero I, Mah SM, Weikum W, Goodman SJ, Brain U, et al. Prenatal antidepressant exposure associated with CYP2E1 DNA methylation change in neonates. Epigenetics : official journal of the DNA Methylation Society. 2015;10(5):361-72.

230. Olivier JD, Akerud H, Sundstrom Poromaa I. Antenatal depression and antidepressants during pregnancy: unraveling the complex interactions for the offspring. European journal of pharmacology. 2015;753:257-62.