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REGISTER-BASED STUDIES OF DELIVERY OUTCOME AFTER MATERNAL USE OF SOME COMMON DRUGS

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ABSTRACT

This thesis aimed to study neonatal outcome including the presence of congenital malformations and to describe maternal characteristics for women using some common drugs during pregnancy. Drugs used in one benign condition (nausea and vomiting) and one chronic disease (hypothyroidism) and the CNS-active drugs benzodiazepines and hypnotic benzodiazepine receptor agonists were selected.

The studies were based on the Swedish Medical Birth Register (MBR). The main advantages with MBR are that relatively large numbers of exposed women and their infants can be identified (coverage 98- 99% of deliveries in Sweden). Drug exposure as well as information about putative confounders are based on information retrieved early in pregnancy, before the birth of the child, and are therefore prospective. The information on the outcome is based on medical documents and is basically not affected by the exposure. Some weaknesses in MBR are that interview data will probably understate drug use, drugs may be taken but not reported/recorded, the indication for drug use is often not known and the information of exact duration and dosage is often incomplete. Further, the studies are based on born infants, aborted foetuses are not included.

Pregnant women exposed to antiemetic drugs, a surrogate marker for nausea and vomiting during pregnancy, showed an overall better neonatal outcome including prevalence at birth of malformations in the infants. For some antiemetic drugs the number of exposures was low. Young maternal age, non-smoking, low education, parity ≥2, were characteristics of women exposed to antiemetic drugs. There was an excess of girls and twins among born infants.

Women using benzodiazepines or hypnotic benzodiazepine receptor agonists during pregnancy differ in many aspects from non-users. These differences may act as confounders in the analysis of pregnancy outcome, and were adjusted for. An increased risk for preterm birth, low birth weight and when exposed late during pregnancy also an increased risk for respiratory problems was seen in neonates. The teratogenic potential does not appear to be strong, but a higher than expected number of infants with pylorostenosis or alimentary tract atresia (especially small gut) was found. No increased risk for orofacial clefts was found.

Women substituted with thyroid hormones during pregnancy had diabetes co-morbidity more often than expected as well as co-medication with, e.g., cardiovascular drugs, systemic corticosteroids and psychiatric drugs. Subfertility, previous miscarriage, pre-eclampsia, caesarean section and induction of labour were more common than in non-users. Neonates were only slightly affected, although a marginal increased risk for premature birth, increased rates of neonatal thyroid disease and a slightly increased rate of malformations was found.

In conclusion, the Swedish Medical Birth Register has advantages and disadvantages but is a powerful tool for surveillance and assessment of teratogenic risks. However, possible associations found are hypothesis generating and need to be confirmed or rejected in new studies.

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LIST OF ORIGINAL PAPERS:

The thesis is based on the following papers

I. Asker C, Norstedt Wikner B, Källén B.
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Eur J Clin Pharmacol 2005; 61: 899-906

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Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: maternal characteristics.
Pharmacoepidemiol Drug Saf 2007; 16: 988-94

III. Wikner BN, Stiller CO, Bergman U, Asker C, Källén B.
Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations.
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IV. Wikner BN, Skjöldebrand Sparre L, Stiller CO, Källén B, Asker C.
Maternal use of thyroid hormones in pregnancy and neonatal outcome.
Acta Obstet Gynecol Scand 2008; 87: 617-627

LIST OF ABBREVIATIONS

ADEC	The Australian Drug Evaluation Committee
ATC	Anatomical Therapeutic Chemical Classification System
BZD	Benzodiazepine drugs
CNS	Central nervous system
CYP P 450	Cytochrome P450
FASS	Pharmaceutical Specialties in Sweden
FDA	U.S. Food and Drug Administration
GABA	γ-amino butyric acid
HBRA	Hypnotic benzodiazepine receptor agonists
ICD	International Classification of Diseases
LMP	Last menstruation period
MBR	The Swedish Medical Birth Register
NVP	Nausea and vomiting in pregnancy
OR	Odds ratio
RR	Risk ratio
TSH	Thyroid stimulating hormone

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1 INTRODUCTION

1.1 GENERAL BACKGROUND

Early, accidental drug exposure during unplanned pregnancies or intentional drug treatment of pregnant women is a source of worry for the woman and a concern for the health care professional.

Until the middle of the 20th century, the general view in the medical community was that the placenta served as a barrier to protect the foetus from harmful exogenous agents. The observation that women afflicted by rubella during the 1st trimester gave birth to infants with anatomical defects (Gregg, 1941) brought about the insight that external factors could affect foetal outcome. Around 1960 thalidomide, a drug with anxiolytic and hypnotic/sedative properties, was prescribed to pregnant women by doctors who were unaware of its teratogenetic potential during the 1st trimester. As a result, 8-10 000 infants were born with congenital malformations, some 130 of them in Sweden. Thalidomide was shown to affect limb development in a time-restricted manner 20-36 days after conception. The thalidomide disaster intensified research on the possible effects of teratogenic drugs in man. It was also the beginning of the surveillance of drug safety during pregnancy.

Today we know that most drugs pass the placenta. However, there is still a considerable lack of data on the safety of several drugs used during pregnancy. At the time of approval of new drugs there are often no data available regarding possible teratogenic effects in humans. Furthermore, even if enough data exist to show that a drug does not carry a high risk of causing gross malformations, the long term effects in exposed children is unknown. Such long term effects may for instance be learning disabilities after in utero exposure to CNS-active drugs.

As new drugs are approved and new light is shed on old drugs by accumulating data, studies are continuously needed to improve safe drug use during pregnancy.

1.2 DRUG USE DURING PREGNANCY

Drug use during pregnancy is common, but prevalence differs between countries and also between studies. Due to differences in study design, comparisons or meta-analysis

of existing studies is difficult. Some studies include vitamins and minerals as "drugs". In addition, medications available over-the-counter (OTC drugs), in-patient medications and herbal remedies are not always captured. A drug used during the 1st, 2nd or 3rd trimester has different implications for the outcome. Use of drugs before pregnancy is also important, because approximately 50 per cent of all pregnancies are unplanned (Finer et al., 2006). Most women do not know about their pregnancy until it is confirmed by a pregnancy test at gestational week 5-7 when organogenesis has already started.

Data about drug use are obtained in different ways, e.g., by interviews with the woman either prospectively (before the infant is born) or retrospectively or with the use of prescription registers, through Medicaid or similar files, or diaries. Information about drug use from prescription registers does not necessarily reveal the timing of exposure during pregnancy. If the prescribed drug was truly ingested by the women or not can be difficult to verify.

Some 85 percent of pregnant women recall use of an average of three drugs (vitamins and minerals included) during pregnancy, when interviewed the week after delivery (Collaborative group on drug use in pregnancy, 1992). A meta-analysis including studies from the USA, the UK, and Sweden, showed an average of 4.7 drugs used (range 2.9 to 5.5). The most commonly ingested ones were vitamins, iron preparations, analgesics, antiemetics and antacids (Bonati et al., 1990).

During early pregnancy, 27 percent of women who delivered an infant at a Connecticut hospital and were interviewed before week 22, reported use of a prescription drug during the first trimester. Drugs most frequently reported were analgesics, penicillin, parasympatholytic agents, antitussives and cold and allergy preparations (Buitendijk and Bracken, 1991). The corresponding number for reported drug use during early pregnancy in Sweden during the years 1995 to 2004 is about 30 percent, but this includes OTC and herbal drugs (unpublished data).

A drug prescription register study from Norway showed that 33 and 29 per cent of pregnant women had drugs dispensed during the first and last trimester, respectively (Engeland et al., 2008). In the United States 64 per cent had a drug other than a vitamin

or mineral supplement prescribed in the 270 days before delivery (Andrade et al., 2004).

The reported use of herbal remedies during pregnancy varied between 4, 36 and 45 per cent in different studies (Refuerzo et al., 2005, Nordeng and Havnen, 2004, Glover et al., 2003).

Experience of paternal exposure related to infant malformation is limited, but paternal drug use is not believed to be any major contributor to developmental disorders. Substances like, e.g., cytostatics may cause genetic damage to the sperm or impair spermatogenesis or maturation of the sperm. Substances may also hypothetically be attached to the sperm and transported into the oocyte or act by absorption from the semen during pregnancy (Schaefer et al., 2007).

Although the use of drugs during pregnancy, both prescribed and over-the-counter, is common, the knowledge about the safety of drug use during this time is limited.

1.3 PLACENTAL DRUG TRANSFER

The placenta varies in structure among species and for each stage of gestation (Brent, 2004). Little is known about the transport of drugs during early human pregnancy, when organogenesis takes place. Most studies determine the umbilical/maternal plasma concentration ratio at birth. Also, in vitro studies have been made, but extrapolation from in vitro studies of placental transfer may be problematic (Syme et al., 2004).

Almost all drugs given to the woman during pregnancy have the potential to enter the circulation of the foetus. Transplacental exchange involves passive transfer, active transport, facilitated diffusion, phagocytosis and pinocytosis (Syme et al., 2004).

Most drugs cross the placenta by passive diffusion. The rate of transfer across the placenta via passive diffusion depends on maternal drug concentration, the properties of the placenta and the physicochemical properties of the drug, i.e., lipid solubility, polarity and molecular weight. Most drugs are small, with a molecular weight < 500 - 800 Da and are relatively lipid-soluble (Syme et al., 2004, Schaefer et al., 2007).

The human placenta has a drug metabolizing capacity with a potential to detoxify and also to bioactivate drugs. For most drugs placental metabolism is probably of relatively minor importance and does not limit the extent of the passage across the placenta (Syme et al., 2004). Drug efflux transporters such as P-glycoprotein (P-gp) may protect the foetus from drugs (Young et al., 2003).

The placenta contains multiple CYP isoenzymes and it appears that more are expressed in the first trimester than at term. It has been suggested that the expression of the CYP genes is maximum when the foetus is most susceptible for teratogens (Syme et al., 2004). The presence of CYP P-450 enzymes in foetal liver was shown in studies in the 70s (Yaffe et al., 1970).

1.4 DRUG EXPOSURE – NEONATAL OUTCOME

The foetal concentration of a drug depends mainly on the pharmacokinetic variables (absorption, distribution, metabolism, renal excretion) of the mother, which are altered due to physiological changes during pregnancy. Furthermore, the passage and metabolism through the placenta and the distribution, metabolism and excretion by the foetus influence the foetal concentration of the drug (Schaefer et al., 2007).

Adverse outcomes after exposure for a drug during embryonic or foetal life may result in different outcomes like:

- Miscarriage or foetal death.
- Malformations of different severity, isolated malformation or patterns of defects.
- Effect on foetal growth (birth weight related to gestation week) and preterm birth.
- Pharmacological adverse effects on the newborn including postnatal adaptation.
- Long term effects on the development of the central nervous system (CNS).
- Increased risk for cancer in childhood or increased risk for developing different kinds of diseases during lifetime.

Whether a drug has the potential to induce developmental disorders or not may depend on some fundamental principles like the specific substance in a particular dose, a genetically susceptible species, the developmental stage at which the exposure occurs, and the mode of action of the drug (Wilson, 1977).

Regardless of early or late exposure, there is a proposed so-called threshold dose (Brent, 2004) below which the incidence of adverse effects on the offspring is not statistically greater than that of controls. It is however difficult to prove the absence of a rare teratogenic effect at a low dose due to the huge number of exposures needed. Concerning a threshold dose for functional deficits caused by teratogen exposures there is an uncertainty due to lack of information (Finnell, 1999).

Genetic differences cause variable susceptibility of the conceptus and the manner it interacts with the environment. This explains why a drug can act as a teratogen in one species but have little or no effect in another and also why some, but not all, foetuses are malformed after exposure for a teratogen (although this phenomenon is not only an effect of genetics) (Finnell, 1999*).*

The timing of exposure to a drug during pregnancy is of crucial importance due to the developmental stage of the embryo. This implies that exposure to the same drug could constitute a risk for teratogenesis of the foetus at a specific time point but be harmless or induce functional disorders of, e.g., the central nervous system at another.

If exposure to a toxic agent occurs very early, from conception until implantation (2 weeks post conception age, 4 weeks after last menstruation period, LMP), an "all-or-none" response, either resulting in miscarriage or in intact survival, is considered. The toxic agent will either kill the conceptus or implantation will not take place. Alternatively, if only a few cells are damaged they may be replaced due to the pluripotency of the cells in this early stage (Dencker and Eriksson, 1998, Polifka and Friedman, 1999). However the "all-or none" rule does not always hold. Mice given retinoic acid in the preimplantation period were born with tail and hind leg duplication (Rutledge et al., 1994). Also, drugs given very early, before the implantation, may remain in the circulation for a long time due to a long half-life, and could theoretically have effects during early organogenesis (e.g., acitretin).

During the first trimester, or the first 12 weeks after LMP, the embryonic period (from implantation to the 10^{th} embryonic week) the crucial phases of organogenesis take place, making this the most sensitive time for teratogenic exposures (Dencker and Eriksson, 1998).

The period of sensitivity to a certain drug may be narrow or broad, depending on type of exposure and the malformation/target organ in question (Brent, 2004). Also, a malformation could arise after the organogenesis due to, e.g., a vascular incidence, e.g., small gut atresia, although a substantial group of small gut atresias probably is related to early development of the digestive tube (Harris et al., 1995).

In late pregnancy, during the foetal phase (from the end of the embryonic stage i.e. embryonic week 11 to delivery), the development of the foetus continues with rapid growth and functional maturation of organs as well as differentiation and migration, particularly in the central nervous system (Polifka and Friedman, 1999). Drug exposure during the third trimester may affect regulatory mechanisms or cause functional disorders. Also growth retardation may arise during the third trimester (growth retardation may however also arise earlier during pregnancy).

Drugs used during the third trimester and acting on the CNS could also affect the postnatal adaptation of the newborn from intra- to extra-uterine life. Neonatal abstinence syndrome (NAS) is a withdrawal syndrome in newborns most commonly associated with the withdrawal from maternal opiates or other drugs of dependency (Oei and Lui, 2007). Another example is exposure to SSRIs during the 3rd trimester which may carry a risk for a SSRI withdrawal syndrome, a toxic serotonergic effect or a combination of both in the neonate (Costei et al., 2002, Nordeng and Spigset, 2005).

Possible long term CNS effects later in life after exposure to CNS-active drugs (e.g., benzodiazepines) in utero are difficult to identify, although very important.

Different theories of mechanisms mediating a teratogenic effect exist. Some suggested are mitotic inhibition, altered nucleic acid function, formation of toxic metabolites, lack of precursors needed for biosynthesis, disruption in enzymatic functions and drug-induced foetal hypoxia. The hypoxia/reoxygenation hypothesis suggests that hypoxia may generate reactive oxygen species (ROS) which may result in tissue damage in the embryonic tissue. Mechanistic studies show that a malformation can be preceded by drug induced embryonic cardiac arrhythmias and periods of hypoxia/reoxygenation in embryonic tissue (Danielsson et al., 2007). Pathogenetic changes following teratogenesis could be apoptosis, impeded morphogenetic movements and mechanical disruption of tissues (Finnell, 1999).

1.5 MALFORMATION RATE

The malformation rate in a study depends on the definitions of malformations (inclusions and exclusions), the time of follow-up and methods for ascertainment.

The malformation rate will vary according to the factors mentioned above. It is important to use the same definitions etc. when comparing exposed and non-exposed individuals in a study. It is therefore not recommended to compare a malformation rate in a study with a general rate often given in the literature (2-4 %) (Fisher, 2008) or from a register of malformations, e.g., EUROCAT (A European network of population-based registries for the epidemiologic surveillance of congenital anomalies).

Malformations could be divided into major and minor ones. One definition of a major anomaly is a malformation resulting in death, serious handicap, or necessitating surgery (van Steirteghem et al., 2002), while a minor malformation does not produce severe consequences for the health or social function of the affected individual.

However, grey zones for some diagnoses exist, e.g., hip (sub)luxation, polydactyly and syndactyly, sometimes classified as major, sometimes as minor malformations. In this thesis, we have looked at all malformations in a first analysis, then excluded some common mild and variably registered malformations (e.g., preauricular tag, undescendent testicle, unstable hip, patent ductus arteriosus in preterm infants, tongue tie, nevus), and then finally studied specific groups of malformations.

Drugs may either cause malformations per se or be a part of factors that together increase the risk for malformations. Drugs confirmed as relatively strong teratogens other than thalidomide are, e.g., retinoids (vitamin A analogues) (Lammer et al., 1985), at least some antiepileptic drugs (valproate, phenytoin, carbamazepine) (Kyle, 2006, Robert et al., 1982) and warfarin (Shaul and Hall., 1977).

Also, maternal conditions like, e.g., diabetes type 1 carry an increased risk for malformations (9.5%) compared to the general population (5.7%) (Åberg et al., 2001). This implies that a risk increase found in women using drugs for a specific disease, e.g.,

diabetes or asthma, may be due to the maternal disease and not to the drugs used (Källén and Olausson, 2007).

1.6 RISK ASSESSMENT OF DRUGS USED DURING PREGNANCY

It is difficult to draw firm conclusions from associations found in one single study. New studies are often needed to verify or reject associations found. Two examples of later confirmed associations between a drug and malformations are thalidomide (Lenz, 1961, McBride, 1961) and warfarin (Kerber et al., 1968). An example of a non-confirmed association is Benedectin (the antihistamine doxylamine with pyridoxine and up to 1976 also dicyclomine, used as an antiemetic drug). The proposed association was neither confirmed in cohort studies nor in case-control studies (Orme, 1985). Due to media and public pressure the manufacturers of this drug withdrew it from the US market after it had been given from 1956 to 1983 to approximately 30 million pregnant women.

Different kinds of studies are used to assess the safety of drugs during pregnancy (Källén 2005, Irl et al., 2000). Different approaches to study this field are:

Animal studies used to screen for teratogenicity must be performed during the development of a new drug. A teratogenic effect of a drug in animal studies indicates that the drug may not be safe during human pregnancy but is no proof of it. The absence of a teratogenic effect in animal tests provides no guarantee that the substance is safe for humans. Extrapolation between species is not always possible.

Randomized controlled trials (RCT), the golden standard of evidence-based medical research, is for obvious reasons unethical on pregnant patients.

Case reports may generate a "signal" of a possible association but are limited as proof of causality, which is why the association later must be confirmed or refuted in new studies. The teratogenic effects of antiepileptic drugs were identified 40 years ago after a first observation of a high rate of epilepsy among mothers of infants with facial clefts (Meadow, 1968).

Case-control (case-referent) studies start with the identification of "cases" and the exposure rate among cases is compared with that among controls.

A problem in case-control studies may be to get exposure data (information about drug use) which is not influenced by the pregnancy outcome. Exposure data in case-control studies are usually collected after the birth of the child. The parent of a malformed child may be more eager to search the memory for an explanation of the malformation, a phenomenon called "recall bias". There is also a risk for "interviewer bias" if the interviewer is aware of the case or control status of the woman interviewed. However, it is also possible to retrieve prospective information about drug use, e.g., through studying written records completed before the birth of the child or by linkage to a prescription register. Information from the prescription registers is uncertain regarding the actual use of the drugs and not informative of OTC-drugs.

A cohort study aims to compare the outcome of pregnancy in two groups, one exposed to the drug of interest, the other not exposed. Exposure is defined, but many different outcomes can be studied. One method to find women uniform in exposure, is to define a cohort from maternal disease, e.g., epilepsy (Canger et al., 1999), asthma (Wen et al., 2001) or manic-depressive disease (Källén and Tandberg, 1983). Another way is to use a prescription register and identify, e.g., users of non-steroidal anti-inflammatory drugs (Nielsen et al., 2001).

Another approach to study drug use during pregnancy is used by Teratology information services (TIS). These are centres from which doctors and patients can receive information on drug use during pregnancy. There is also collaboration between regional centres, e.g., ENTIS (European Network of Teratology Information Services) and OTIS (Organization of Teratology Information Specialists) with members in the U.S and Canada (Schaefer et al., 2007). Studies from TIS (case-registry studies and prospective cohort-control studies) are based on women seeking advice at TIS and the outcome is often based on reports from the mothers (a follow-up form is sent to the women after the expected date of delivery or follow-up is conducted by a telephone interview). A letter may also be sent, after permission from the mother, to the child's physician to confirm medical details.

One important difference between case-control and cohort studies is that in a case-control study it is possible to study many exposures for one outcome, while in a cohort study it is possible to study many outcomes after one exposure. Both the case-control and the cohort technique are built on a sampling procedure.

In a national register like, e.g., the Swedish Medical Birth Register, all infants (and the mothers) in a defined population can be studied without sampling, which will increase the statistical power. Information about drug use is prospectively collected which reduces the risk for recall and interviewer bias. Outcome data are obtained by and large independently of exposure. Possible confounders can be identified and adjusted for when analyzing outcome data.

Systematically collected information is needed about the consequences of the use of drugs by pregnant women. The Swedish national Medical Birth Register offers a possibility to screen for such signals.

1.7 RISK CLASSIFICATION SYSTEM

Several countries have risk classification systems for often sparse data on drug safety during pregnancy. The aim of such systems is to guide the physicians in the risk of using drugs during pregnancy. A comparison between three existing systems reveals differences in the classification (Addis et al., 2000). Misunderstandings about teratogenic risk could have serious consequences possibly leading to unnecessary anxiety, untreated maternal disease, or to termination of a wanted pregnancy. Three widely used international risk classification systems are (Table1):

- FASS, the Swedish system for classification of drugs of foetal risk that was implemented 1978 and was the first of its kind.
- FDA, one year after the FASS classification the US Food and Drug Administration (FDA) introduced a system also using letters A to D together with an X category for drugs demonstrated to be teratogenic. Category A is used only if controlled studies have shown no risk.
- ADEC, the Australian Drug Evaluation Committee (ADEC) developed in 1989 a system which combined the two previous systems.

Table1. Risk classification systems FASS[1], FDA[2] and ADEC[3].

Category	FASS	FDA	ADEC
A	Safe – based on extensive use or studies	Safe – based on controlled studies	Safe- based on extensive use or studies
B	Limited data Subgroup B1-3 referring to animal data	Animal studies with no evidence of harm, but no controlled studies in humans OR Adverse effects in animal studies, but controlled studies in humans failed to show risk	Limited data Subgroup B1-3 referring to animal data
C	Pharmacological mechanism - risk for foetus or newborn without being directly teratogen	Animal data adverse effect or no data available	Pharmacological mechanism - risk for foetus or newborn without being directly teratogenic
D	Malformation risk	Malformation risk	Malformation risk
X	-	Confirmed human teratogen	Confirmed human teratogen

[1]www.fass.se, [2]www.perinatology.com/exposures/FDACategories.htm,
[3]www.tga.gov.au/docs/html/adec/adec.htm

Only 61 (26%) of 236 drugs common to all three systems are placed in the same risk factor category (Addis et al., 2000). This depends on differences in definition for the categories, but also on how the scientific literature is evaluated.

Some differences in classification of drugs of particular interest for this thesis is triazolam (a benzodiazepine), classified as teratogenic in the FDA system, but assigned to category C in the ADEC and FASS. Another example is metoclopramide (an antiemetic) classified in three different ways in the different countries, Table 2.

Table 2. Classification of two different drugs in US (FDA), Sweden (FASS) and Australia (ADEC)

Drug	FDA	FASS	ADEC
triazolam	X	C	C
metoclopramide	B	C	A

A Drugs considered to be safe

B Limited number of data, but no increased frequency in malformation or harmful effects of the foetus

C Drugs due to pharmacological effects suspected to cause harmful effects (not malformation) on the foetus/newborn child.

X Drugs demonstrated to be teratogenic.

Risk classification can be important to summarize general information on drugs but can also be misleading. It is difficult, or impossible, to classify a drug as teratogen or not, without pharmacological data about the dose, route, duration of treatment, and knowledge about the gestational timing of the exposure. Animal data cannot be directly translated to human data. The underlying disease may be an important confounder and should be considered. The drug company may label the drug taking legal aspects more into consideration than medical aspects.

It is important to avoid both under- and over- estimation of the risk. Preferably, when giving advice to the pregnant women and the physician, a risk classification system is used as a base, supplemented with a critical assessment of available data.

2 TREATMENT OF NAUSEA AND VOMITING DURING PREGNANCY

Nausea and vomiting during pregnancy (NVP) is a most common medical condition affecting up to 80 per cent of pregnant women. Approximately half of all pregnant women experience both nausea and vomiting, and a quarter have nausea alone. NVP occurs primarily during the first trimester, mostly in weeks 7-12. In most cases it has subsided by week 16, although up to 20 per cent continues to have symptoms throughout pregnancy (Gill and Einarson, 2007).

Mild and moderate NVP are associated with a decreased risk of miscarriage, preterm delivery, and stillbirth and shows no increased and even a slightly reduced risk of congenital malformations (Klebanoff, 1985, Nelson-Piercy, 1998, Huxley, 2000, Källén and Mottet, 2003). NVP should not be confused with the more serious condition hyperemesis gravidarum which affects about one per cent of pregnant women and may lead to hospitalization due to dehydration, electrolyte imbalance and weight loss.

The etiology of NVP is unclear and most likely multifactorial. Altered hormone levels (β-human chorionic gonadotropin, thyroxine, estradiol), gastric dysrythmia (decreased gastric peristalsis, delayed gastric emptying and decreased oesophageal pressure), genetic predisposition, and hyper olfaction have been proposed (Gill and Einarson, 2007, Nelson-Piercy, 1998, Goodwin, 2002). High maternal serum prostaglandin E2 levels in early pregnancy correlate with nausea and vomiting (Gadsby et al., 2000). Prostaglandins are key molecules in reproductive biology. Women prescribed NSAIDs (that interfere with prostaglandin production) during early pregnancy may be at a greater risk of having children with congenital anomalies, specifically cardiac septal defects (Ericson and Källén, 2001, Ofori et al., 2006). Psychological factors (depression, anxiety, and eating disorders) once thought upon as etiological factors, may actually be a result of the nausea and vomiting. A functional role for the nausea and emesis in stimulating placental growth has been proposed (Huxley, 2000).

The severity of symptoms of NVP varies and in most cases pharmacological treatment is not necessary. Dietary adjustment, herbal supplements (ginger), acupuncture,

acupressure, and change of life style is common advice given to women with mild NVP. However, many women with NVP require pharmacological treatment.

The possible risk of teratogenicity of antiemetic drugs used during early pregnancy may be a concern of pregnant women as well as care givers (Mazzotta et al., 1999). On the other hand, untreated long-standing NVP may result in dehydration and the need of intravenous fluids, as demonstrated in one study after the withdrawal of the widely used antiemetic drug Benedictin (doxylamine/pyridoxine/dicyclomine) from the US market in 1983. In the two years following the withdrawal of the drug, hospital admissions for NVP increased by 50 per cent (Neutel et al., 1995).

The vomiting centre, located in the medulla, receives input from the chemoreceptor trigger zone (CTZ), the higher brain stem, the vestibular apparatus and the gastrointestinal tract. Due to the multitude of neurotransmitters active in these pathways, multiple classes of drugs are used to treat vomiting, such as dopamine, histamine, and muscarinic and serotonin receptor antagonists. Antiemetic drugs can be classified according to the predominant receptor on which they are proposed to act. Especially the older agents may act at several relevant targets.

Antihistamines (meclozine, cyclizine, promethazine, diphenhydramine) inhibit the action of histamine at the histamine H_1-receptor and indirectly affect the vestibular system, decreasing the stimulation of the vomiting centre. Muscarinic receptor inhibition could contribute to antihistamine antiemetic activity of cyclizine, meclozine and diphenhydramine (Badell et al., 2006).

Dopamine, specifically the dopamine D_2-receptor, is also implicated in the emetic signalling through the CTZ. Dopamine receptors in the gastrointestinal tract mediate inhibition of gastric motility**.** Dopamine antagonists include metoclopramide (a benzamide) and the phenothiazines among which promethazine is also an antihistamine (Badell et al., 2006).

Metoclopramide blocks central dopamine receptors in the CTZ. Via a peripheral prokinetic effect on gastrointestinal smooth muscle metoclopramide has been shown to increase the oeosophageal sphincter tone. In high doses metoclopramide may block 5-HT_3-receptors.

Phenothiazines such as prochlorperazine, dixyrazine and thiethylperazine exert their antiemetic action by D_2 receptor antagonism at the CTC, by anticholinergic (M-receptors) mechanism and also by blocking the H_1-receptor.

5-HT_3-receptor antagonists (ondansetron), primarily used for the treatment of chemotherapy-induced nausea, exert their effects at the 5-hydroxytryptamine (5-HT_3) receptors both centrally and peripherally. The combined action on the small intestine, the vagus nerve and CTZ is considered to provide decreased stimulation of the vomiting center (Gill and Einarson, 2007).

The choice of drug to treat NVP varies between and sometimes also within countries. In Scandinavia (in Sweden and Norway for mild NVP and in Denmark and Finland for moderate NVP) the antihistamine meclozine is widely used, in Southern Europe metoclopramide is often the first choice. In several East European and Balkan countries the drug of choice is thietylperazine (a phenothiazine) (Einarson et al., 1998).

The safety classification also differs between countries, e.g., meclozine is believed to be safe in Sweden but France and the UK have a pregnancy warning for this drug (Källén and Mottet, 2003). In the US meclozine has the pregnancy classification B (more about risk classification system, under 1.7). Animal studies from the 60s showed teratogenic effects of antihistamines on rats (Giurgea and Puigdevall, 1966).

The use of antihistamines during pregnancy has been widely studied. Single case reports of malformed infants born after exposures to specific antihistamines during foetal life are published, however most studies could not detect any teratogenicity. A meta-analysis of 24 studies (Seto et al., 1997) with more than 200 000 first-trimester exposure to anti-histamines revealed no increased risk for congenital malformations (pooled OR 0.76, 95% CI 0.60-0.94). In addition, the delivery outcome after maternal use of antihistamine drugs in 17 266 women during early pregnancy, failed to demonstrate any adverse effect for the child (Källén B, 2002). The protective effect of preterm birth, low birth weight, being small-for-gestational-age and perinatal death among singleton infants after maternal use of antihistamines for the indication NVP, but not for the indication allergy, are most probably related to the underlying condition of nausea and vomiting in pregnancy (Källén B, 2002).

Phenothiazines and metoclopramide have not been as extensively studied as the antihistamines. There are isolated case reports of congenital malformations after exposure to prochlorperazine but neither the Michigan Medicaid surveillance study (704 newborns) nor the Collaborative Perinatal Project (877 pregnancies) reported any increased risk for congenital malformations after first trimester exposure (Heinonen et al., 1977, Briggs et al., 1998, Gill and Einarson, 2007). Also, other studies found no association between maternal use of prochlorperazine and birth defects (Kullander and Källén, 1976, Miklovich and van den Berg, 1976). A case-control study with another phenothiazine, tiethylperazine, found a weak association between use of tiethylperazine during early pregnancy and orofacial clefts (Czeizel and Varga, 2003).

Safety data concerning metoclopramide in the treatment of NVP is limited. Three different studies involving 309, 175 and 192 women exposed to metoclopramide during the first trimester could not find an increased risk for malformation (Sørensen et al., 2000, Berkovich et al., 2002, Gill and Einarson, 2007). However, larger cohorts are needed to confirm these observations.

Data about 5-HT_3 receptor antagonists with respect to teratogenicity are sparse with only small sample sizes studied with low power to detect any effect. One observational study of 176 women (Einarson et al., 2004) treated with ondansetron during the first trimester, reported no increased risk of major malformation.

3 BENZODIAZEPINES AND HYPNOTIC BENZODIAZEPINE RECEPTOR AGONISTS AND PREGNANCY

Benzodiazepines (BZD) are potent drugs with anxiolytic, anticonvulsant, hypnotic-sedating, and muscle-relaxing properties. The newer hypnotic benzodiazepine receptor agonists (HBRA) (in Sweden zolpidem, zopiclone and zaleplon) have been on the market the last decades and are used as hypnotics.

The reported use of BZD and HBRA during early pregnancy in Sweden differs between the counties with the highest reported use during early pregnancy in the middle and the south part of Sweden ("Västmanland" 3.1 per 1000, "Kronoberg" 3.0 per 1000), and the lowest reported use in the northern part ("Västerbotten" 0.5 per 1000, "Västernorrland" 0.6 per 1000). Corresponding numbers for HBRA show a similar pattern with the highest reported use in the south and the middle part ("Gotland" 1.3 per 1000," Kopparberg" 1.1 per 1000, "Gävleborg" 1.1 per 1000) and the lowest reported in the northern parts of Sweden ("Norrbotten" 0.2 per 1000, "Västerbotten" 0.3 per 1000) (unpublished data).

Concerns regarding maternal use of benzodiazepines during pregnancy include teratogenicity, perinatal symptoms with neonatal toxicity and postnatal behavioral sequels (short and long term). However, untreated psychiatric illness may result in poor compliance to prenatal care, and a risk of substituting the benzodiazepine with alcohol as self-medication of anxiety. Further, abrupt discontinuation of psychotropic drugs (antidepressants, BZD) may lead to unpleasant physical symptoms and re-emergence of the psychiatric condition (Einarson et al., 2001).

All benzodiazepines strengthen the effect of the major inhibitory neurotransmitter γ-amino butyric acid (GABA) on the $GABA_A$ receptor, a receptor coupled chloride channel. The $GABA_A$ receptor consists of several subunits which can combine (Rudolph et al., 2001). The chemical structures of the HBRA do not resemble those of the BZD, but HBRA also exert an agonistic effect on the $GABA_A$ receptor with amplification of the inhibitory GABA transmission.

The GABAergic system, one of the earliest neurotransmitter systems to develop, is excitatory in the developing brain in contrast to the inhibitory effect later in life. This shift from excitatory to inhibitory effect has been suggested to be due to increased intracellular chloride levels during the development. As the chloride pump gets more active, the intracellular chloride level decreases and a lower chloride level results in inhibition upon activation of the $GABA_A$ receptor. As a trophic factor GABA influences proliferation, migration, differentiation and synapse maturation during early brain development. Interference with transmission may affect the neuronal wiring (Herlenius and Lagercrantz, 2004) and dopaminergic disruption is believed to be involved in the patophysiology of ADHD (Biederman, 2005). GABA and serotonin (5-HT) also play a role in pain modulation. Pain reactivity, a possible marker of neuromotor development in infants (Grunau et al., 2006), is attenuated in infants exposed to SSRI and BZD during pregnancy (Oberlander et al., 2002). The mechanism may be a direct pharmacological effect or an altered brain development.

Based on pharmacokinetic parameters, the benzodiazepines are classified into short-acting ($t_{1/2}$ <6 hours e.g., midazolam), intermediate-acting ($t_{1/2}$ 6-24 hours e.g., lorazepam) and long-acting ($t_{1/2}$ > 24 hours e.g., diazepam). Some BZDs have active metabolites that are biotransformed more slowly than the parent compounds, extending the duration of action (e.g., one of the metabolites of diazepam, desmetyldiazepam, has a plasma half-life of 30-200 hours) (Iqbal et al., 2002). The half-lives of HBRA vary between 1-1.5 hours (zaleplon) and 3.5-6 hours (zopiclone) (Drover, 2004*)*. BZD may accumulate in the embryo/foetus already during the first trimester (Jauniaux et al., 1996).

Studies on the associations between the use of BZD during pregnancy and congenital malformations show conflicting results (Iqbal et al., 2002, McElhatton, 1994). Differences in methodological approach render comparisons difficult. First trimester exposure to BZD in utero were in some studies associated with facial clefts, cardiac malformations and other multiple malformations (Safra and Oakley, 1975, Saxén and Saxén, 1975, Aarskog, 1975) but this has not been confirmed in other studies (Rosenberg et al., 1983, Czeizel, 1988, Shiono and Mills, 1984). Retrospective case-control studies showed a positive association between maternal use of BZD during the first trimester and major malformation and in particular isolated oral cleft (OR oral cleft 1.79, 95 % CI 1.13-2.82). This finding was not confirmed in pooled data from

cohort studies (OR oral cleft 1.19, 95 % CI 0.34-4.15) (Dolovich et al., 1998). Most of the available data on BZD use during pregnancy are based on diazepam (Iqbal et al., 2002).

Facial dysmorphic features combined with neurological abnormalities have been described in neonates born to mothers with high BZD (oxazepam, diazepam) consumption during 1st, 2nd and 3d trimester (Lagreid et al., 1987, 1989) suggesting the existence of a benzodiazepine syndrome. Similar findings have not been reported by other groups. The effects of BZD abuse could be confounded by maternal alcoholism (Bergman et al., 1992).

Maternal use of BZD during the third trimester may cause an adverse neonatal effect called the "floppy infant syndrome" (muscular hypotonia, sedation, hypothermia and sucking problems) and also a withdrawal syndrome (hyperreflexia, restlessness, irritability and tremor) (Ibqal et al., 2002, McElhatton, 1994). These syndromes may persist from hours to months after birth.

BZD in combination with serotonin reuptake inhibitors has been associated with a higher incidence of congenital heart disease (Oberlander et al., 2008) than either drug separately, suggesting an increased risk with poly-drug synergism.

There are a limited number of studies with conflicting data on behavioural teratogenicity in the offspring of mothers using BZD during pregnancy. Deviations in neurodevelopment, during the first 18 month of life (Lagreid et al., 1992, Viggedal et al., 1993), and abnormal Boel test in children aged 7-10 month have been reported (Mortensen et al., 2003). However, other reports indicate no differences in the incidence of behavioural abnormalities at age 8 month or IQ scores at age 4 years (Hartz et al., 1975).

Information about the safety of HBRA during pregnancy is scarce. One prospective study (Diav-Citrin et al., 1999) followed 40 women exposed to zopiclone during the first trimester and concluded that larger studies are needed to verify their conclusion of zopiclone not being a major teratogen.

4 SUBSTITUTION OF THYROID HORMONES DURING PREGNANCY

Thyroid disease is the second most common endocrine disorder next to diabetes affecting women of childbearing age. In areas with sufficient iodine, autoimmune thyroiditis accounts for most cases of hypothyroidism. Thyroid hormones play a vital role in the development of the foetus and the placenta. Abnormalities of maternal thyroid function may affect the foetus in different ways.

In early pregnancy, the embryo depends on maternal thyroxine supply via the placenta. The placental transfer of thyroid hormones is not yet completely understood. Different transport proteins like organic anion transporting polypeptide (OAT), L amino acid transporters (LAT1) and monocarboxylate transporter 8 (MTC8), are proposed to be involved (James et al., 2007). Foetal thyroid function starts after 10–12 weeks gestation.

During early gestation there is an increase in thyroxin-binding globulin (TBG), the major transport protein for thyroid hormone, secondary to estrogen-stimulation and resulting in increased serum concentrations of total thyroid hormones. Human chorionic gonadotropin (hCG), structurally related to TSH, has a thyrotrophic activity contributing to the increase in total T4 and T3 concentrations. There is a reduction of available iodine related to increased renal clearance and loss of iodine to the foetal-placental unit. Placental type III monodeiododinase, deiodoinates T4 to inactive reverse T3 (rT3) and T3 to inactive T2 (Glinoer, 2004, Sack, 2003).

Thus, pregnant women with hypothyroidism will have an increased need of thyroid hormone substitution very early during pregnancy, and adequate replacement therapy with thyroid hormone is essential. However, pregnancy is usually confirmed with a pregnancy test in gestational week 5-7, which means that it could be difficult to increase the thyroxine dose on time. Deficit in iodine can result in hypothyroidism, the need of iodine is raised from 150 μg/day to 250 μg/day during pregnancy (Andersson et al., 2008). Furthermore, intake of vitamins supplemented with iron may reduce the gastrointestinal absorption of thyroxine.

Overt hypothyroidism is associated with infertility, miscarriage, pregnancy-induced hypertension, preeclampsia, placental abruption, preterm birth, low birth weight, foetal death and child intellectual impairment (Davis et al., 1988, Leung et al., 1993, Casey et al., 2005, Kyriazopoulou et al., 2008, Haddow et al., 1999).

Maternal subclinical hypothyroidism (defined as TSH above the upper limit of the reference range when serum free T4 concentration is within its reference range) has been associated with placental abruption, preterm delivery and low birth weight infants (Davis et al., 1988, Leung et al., 993, Casey et al., 2005, Kyriazopoulou et al., 2008). Also, impaired neuropsychological development in the infant has been linked to maternal subclinical hypothyroidism (Pop et al., 2003).

Maternal hypothyroxinemia (low free serumT4 and TSH within its reference range) in early gestation has been proposed as a risk factor for impaired neurodevelopment in the infant (Kooistra et al., 2006, Pop et al., 1999, 2003).

Data is inconclusive whether women with thyroxine substituted hypothyroidism have more obstetric complications than healthy controls and also if the neonatal outcome differ. It has been suggested that women supplemented with thyroid hormones are more likely to suffer from hypertension and pre-eclampsia (Wolfberg et al., 2005). Subfertility, miscarriage and also reproductive failure after in vitro fertilization have been associated with autoimmune thyroid disease (Poppe et al., 2003). No adverse neonatal outcome was found by some authors (Wolfberg et al., 2005, Tan et al., 2006, Matalon et al., 2006), but significantly lower birth weight and a smaller head circumference in this population compared to neonates born to euthyroid women has been reported (Blazer et al., 2003).

The importance of adequate substitution in hypothyroid women throughout gestation was shown in a retrospective study of 150 pregnancies (Abalovich et al., 2002). In the sub optimally treated group a significantly increased miscarriage rate and more preterm delivery was observed compared to the well substituted group.

5 AIMS OF THE STUDY

The overall aim of the thesis was to investigate some selected common drugs and/or conditions during pregnancy, to assess the teratogenic risk for those drugs and also to study neonatal outcome and describe maternal characteristics for pregnant women using these drugs.

Specific aims of the projects were:

To describe antiemetic drug use during pregnancy and to investigate the neonatal outcome after exposure for antiemetic drugs during embryonic and foetal life (paper I).

To identify maternal characteristics which will affect the use and/or reporting of benzodiazepines and hypnotic benzodiazepine receptor agonists during pregnancy (paper II) and which may act as confounders in the analyses of neonatal outcome (paper III).

To study the neonatal outcome including congenital malformations after maternal use of benzodiazepines and/or hypnotic benzodiazepine receptor agonists during pregnancy (paper III).

To study if thyroid hormone substituted pregnant women differ in pregnancy complications compared to the reference population and to study if the neonatal outcome, including the presence of congenital malformations, differs from the reference population (paper IV).

6 METHODS AND STUDY POPULATION

6.1 SWEDISH REGISTERS USED

6.1.1 The Medical Birth Register

The Swedish Medical Birth Register (MBR) is a large and continuously growing data-base which collects data on antenatal care, delivery, and the neonatal outcome of nearly all deliveries in Sweden. Live-born infants and stillbirths (according to the Swedish definition at that time, 28 completed gestational weeks) are included. MBR started in 1973 and is administered by the National Board of Health and Welfare, Stockholm.

Initially (1973-1982) the data-collection was based on "Medical Birth Reports", which summarized the contents of the medical records in a standardized form. In 1982, this form was replaced by copies of the following three medical records; the first record of antenatal care of the mother, the delivery record, and the record for the paediatric examination of the newborn infant.

Since July 1, 1994 drug use is also recorded in the register. Drug use during early pregnancy is reported at the first antenatal care visit by the woman to the midwife who records it in the form. The first antenatal care visit usually takes part between weeks 10 and 12 and mirrors the first trimester use of drugs. Drugs prescribed by the antenatal care after the first visit and up to delivery are recorded separately based on copies of records from the antenatal care. The register contains the information on the drug use, stored as ATC codes if such can be identified. If an ATC code is lacking, e.g., health preparations, homeopathic drugs, or names that cannot be interpreted, the drug name is stored in capital letters (National Board of Health and Welfare, 2003).

An advantage with the MBR is the large data base content, harbouring maternal and neonatal data of nearly all infants born in Sweden (coverage 98.6%) (National Board of Health and Welfare, 2003). Exposure data are obtained prospectively (before the birth of the child) which eliminates the problem with recall and interviewer bias. Further, information about possible confounders makes it possible to adjust for those. To maintain a high standard of the MBR, evaluations are made at regular intervals, thus far three times, in 1976, 1998, and 2001. Data from the register were then compared with

the original medical records. The conclusion was that MBR is a valuable source of information for reproduction epidemiology but it is important to understand its structure and its deficiencies.

Register linkage

The women are identified by their unique personal identification numbers (PIN). The identification number enables linking of data from different registers. The PIN of the newborn is linked to the Medical Birth register from The Birth Register of Statistics Sweden. In the register, maternal delivery diagnoses and infant diagnoses are recorded as ICD codes (Cnattingius et al., 1990). Data can be supplemented with information from the Hospital Discharge Register and from the Registry of Birth Defects (formerly called the Register of Congenital Malformations).

Register linkage between MBR, Register of Birth Defects and The Hospital Discharge Register will enhance the possibility to collect malformation diagnoses. Malformation diagnoses may be given at the maternity ward but are not always reported. For infants transferred to neonatal units, data loss of diagnoses may be a problem. It is possible to supplement data of infant diagnosis with discharge diagnoses recorded in the Hospital Discharge Register. For congenital malformations, supplementary data can also be obtained from Register of Birth Defects (The National Board of Health and Welfare, 2003).

6.1.2 Register of Birth Defects

The Register of Birth Defects, earlier called The Register of Congenital Malformations (Källén and Winberg, 1968), was started in 1964. It covers all birth in Sweden since 1973 and is based on compulsory reporting of infants with relatively severe malformations during the first month of life, for cardiac malformations until the age of one. The reports describe the malformations in details and are sometimes accompanied by a drawing of the malformations and also with copies of, e.g., autopsy reports. Up to and including 1998, malformations were registered with a special and detailed code together with the ICD code. Since 1999, only ICD codes have been used (National Board of Health and Welfare, 2004).

6.1.3 The Hospital Discharge Register

The Hospital Discharge Register contains information on all hospitalised patients in Sweden. Diagnostic information on discharge diagnoses including congenital malformations is given in the form of ICD codes. Malformations not observed during the neonatal period (e.g., pylorostenosis) can also be identified (National Board of Health and Welfare, 2004).

6.1.4 Statistics Sweden Birth Register

Statistics Sweden is a central government authority for official statistics and keeps a birth register. From this register we could get the maternal country of birth and maternal place of living. Statistics Sweden also has a register of the educational level of each inhabitant and we used this to link to the educational background of the mother. This, however, was only available up to and including deliveries in 2001 and referred to the educational level in 2002.

6.2 STUDY POPULATION

Paper I

29 804 women with 31130 infants reported use of antiemetic drugs during the period 1st of July 1995 to 31st December 2002.

Reference population, a total of 665 572 pregnant women with 676 198 infants registered in the Swedish Medical Birth Register during the same time.

Paper II

2 149 pregnant women using benzodiazepines or hypnotic benzodiazepine receptor agonists were identified from 1st of July 1995 to 31st December 2004.

Control group: 859 455 women identified in the MBR during the study period.

Paper III

1 979 infants exposed during early pregnancy

401 infants exposed during late pregnancy

Control group: 873 879 infants born during the study period 1st of July 1995 to 31st December 2004.

Paper IV

9 866 women with 10 055 infants identified as having used thyroid hormones during pregnancy from 1 July 1995 to 31 December 2004. Among these women 230 had a diagnosis of pre-existing diabetes, a further 132 women had gestational diabetes or an unspecified diabetes diagnosis. Since maternal diabetes may heavily affect pregnancy outcome, women with any diabetes diagnosis were removed from the analysis. A further two women were not included in the study due to missing personal identification numbers in the register.

Comparisons were made with 848 468 women and 861 989 neonates (women with diabetes excluded).

Overview – use of thyroid hormones	Women	Infants
Total number identified	9866	10055
Early exposure	8907	9102
Early exposure with diabetes or missing ID	364	393
Early exposure except diabetes cases	8543	8709
Prescriptions		
Total number	5006	5100
Number of women with diabetes	183	187
Prescriptions except diabetes cases	4823	4913
Prescription, but no reported use during 1st trimester	940	953
Number of women with diabetes	35	35
Number with only late exposure (diabetes excluded)	905	918

6.3 STATISTICAL ANALYSIS

Odds ratios were determined using the Mantel-Haenszel technique with adjustment for selected confounders (Mantel and Haenszel, 1959). To calculate the 95% confidence intervals (95% CI) of odds ratios (ORs), Miettinen´s method was used (Miettinen, 1974). When the expected number of a specific outcome was low (<10), the observed number of exposed cases was instead compared with the expected number, estimated with adjustment for selected confounding factors. The observed/expected ratio will then represent a risk ratio (RR) and its 95% CI was calculated using exact Poisson distributions (SABER software, CDC, Atlanta, GA). Comparisons of two stratified

ORs were made as two-tailed z-tests, based on the same variances as those used to determine the 95% CI.

6.4 CONFOUNDING FACTORS

Confounding factors covariate with both the exposure (drug use) and the outcome. The choice of confounders to be adjusted for in the outcome analysis may vary with the actual drug-outcome problem and also depends on availability of information.

By initial characterization of the pregnant women in the selected population (e.g., those exposed to benzodiazepines), some characteristics were identified which could act as confounders. These were adjusted for in the outcome analysis.

Only factors recorded in the register can be studied and adjusted for. Factors easily identifiable in the register and putative confounders are e.g., maternal age, year of birth, maternal smoking and parity. Other factors could be unknown or not available in the register, e.g., the use of alcohol and abuse of drugs. However, smoking habits are recorded (information is lacking for 4-9 per cent) and can be adjusted for, and smoking usually covariates with alcohol consumption (Hays et al., 1984).

The reason for drug use, i.e. the underlying morbidity, could be a risk factor for malformation in itself and act as a confounder in the outcome analysis. An example of this is maternal diabetes type1 which is associated with an increased risk for malformations (Allen et al., 2007) and is always associated with use of insulin. The use of insulin will then statistically correlate with an increased risk for malformations. In women with gestational diabetes, the existence of a subgroup with an increased risk for specific types of congenital malformations has been suggested (Åberg et al., 2001). In study IV we found an association between the use of thyroid hormones and gestational diabetes and a strong association with pre-existing diabetes and we therefore excluded women with a diagnosis of diabetes from the analysis.

7 MAIN RESULTS AND CONCLUSION

7.1 PAPER I

Asker C, Norstedt Wikner B, Källén B. Use of antiemetic drugs during pregnancy in Sweden. Eur J Clin Pharmacol 2005; 61: 899-906

7.1.1 Objective

To describe antiemetic drug use during pregnancy and to study the neonatal outcome after exposure to antiemetic drugs.

7.1.2 Results

The most frequently reported antiemetic drug was meclozine followed by promethazine. Cyclizine, dixyrazine and metoclopramide followed in decreasing frequency. Only a few women reported the use of thietylperazine, dimenhydrinate, prochlorperazine, or ondansetron.

Maternal characteristics associated with use of antiemetics were; young age, parity ≥2, non-smoking, a period of unwanted childlessness and low education. Women born outside Sweden had a higher use of antiemetics than women born in Sweden. Women reporting use of antiemetic drugs had an increased incidence of twin birth and there was an excess of girls among infants born. Co-medication with other drugs like drugs used for stomach ulcer, multivitamins and folic acid, analgesics, neuroleptics and cough medicines were more common in women using antiemetics while a decreased rate of co-medication was noted for drugs like; insulin, thyroxine, ovarian stimulations, anticonvulsants and anti-asthmatics.

A reduced risk for low birth weight, preterm birth, being-small-for-gestational-age and having a malformation was seen in neonates born to women reporting use of antiemetic drugs during pregnancy.

7.1.3 Conclusion

The data demonstrated that pregnant women who reported use of antiemetic drugs, a surrogate marker for nausea and vomiting during pregnancy (NVP), showed an overall better neonatal outcome with respect to several variables, including prevalence of malformations at birth. The probable explanation for the better-than-expected outcome may be an effect of a well-functioning placenta, which is associated with NVP. For some antiemetic drugs the number of exposures was low.

7.2 PAPER II

Wikner BN, Stiller CO, Källén B, Asker C. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: maternal characteristics. Pharmacoepidemiol Drug Saf 2007; 16: 988-94

7.2.1 Objective

To identify maternal characteristics which will affect the use and/or reporting of benzodiazepines (BZD) and benzodiazepine receptor agonists (HBRA) during pregnancy and which may act as confounders in the analysis of neonatal outcome (paper III).

7.2.2 Results

The most commonly reported BZD during early pregnancy was diazepam followed by oxazepam. During the second and third trimesters, use of oxazepam was more common than use of diazepam. The most commonly reported HBRA during early and late pregnancy was zopiclone.

The use of BZD and/or HBRA increased with maternal age and was strongly associated with smoking. A higher use was observed at parity 1 and parity 4+ than at parity 2 or 3. Women with a low formal education reported use of BZD and HBRA more frequently than women with higher education. Any earlier miscarriage was not associated with use of BZD or HBRA, but having had three or more was. Years of involuntary childlessness had little impact on the use of these drugs.

Women reporting use of BZD and/or HBRA in early pregnancy also reported the concomitant use of other drugs differently than the control population. Co-medication with antidepressants, antipsychotics, opioids and anticonvulsants were more common. Moderately increased ORs were seen for some other groups of drugs, for example drugs used for stomach ulcer, migraine or asthma. Reporting of vitamins was significantly low.

Women using BZD and/or HBRA in pregnancy had a statistically significantly higher incidence of preterm birth (singletons), more pronounced for women using the drugs in late pregnancy. Caesarean section, mainly restricted to term pregnancies, was more common in women reporting use of BZD and/or HBRA compared to the reference population.

7.2.3 Conclusion

This study showed that women using benzodiazepines or hypnotic benzodiazepine receptor agonists during pregnancy differ from the reference population in many aspects. The identification of putative confounders is important before studying the neonatal outcome (study III).

7.3 PAPER III

Wikner BN, Stiller CO, Bergman U, Asker C, Källén B. Use of benzodiazepines and benzodiazepine receptor agonists during pregnancy: neonatal outcome and congenital malformations. Pharmacoepidemiol Drug Saf 2007; 16: 1203-10

7.3.1 Objective

To study the neonatal outcome and presence of congenital malformations in neonates whose mothers reported use of benzodiazepines (BZD) and/or hypnotic benzodiazepine receptor agonists (HBRA) during pregnancy.

7.3.2 Results

In our study population 5.3 per cent (N=105 infants) were born with congenital malformations. Expected rate was 4.7 per cent. After exclusion of some common mild

and variable malformations the risk was increased (OR 1.24, 95 % CI 1.00-1.55), but statistical significance was marginal. This finding was mainly driven by two conditions: alimentary tract atresia (notably small gut atresia) and pylorostenosis, and could not be explained by known teratogenic maternal co-medication.

An increased risk for respiratory problems was seen in neonates exposed late during pregnancy (OR 2.21, 95% CI 1.62-3.02). There was an increased risk for low birth weight in singletons, most pronounced after late exposure for BZD or HBRA (OR 1.89, 95 % CI 1.29-2.76), but also found after early exposure (OR 1.30, 95 % CI 1.06-1.59).

An increased risk for preterm birth was described in paper II. Also a significantly increased risk for low Apgar at 5 minutes was seen in newborns after exposure for BZD or HBRA during late gestation (OR 2.02, 95% CI 1.13-3.65). When studying the two groups separately, i.e. infants exposed to BZD only or HBRA only, the ORs did not differ significantly for preterm birth and low Apgar score between the groups.

One third of women using BZD or HBRA also used antidepressants. The OR for preterm birth decreased from 2.06 (95% CI 1.61-2.62) to 1.20 (95% CI 0.97-1.50) after exclusion of women using drugs for depression. These two estimates differ significantly ($p = 0.001$).

7.3.3 Conclusion

Data in this study showed that neonates exposed to benzodiazepines and benzodiazepine receptor agonists in utero were at risk for being born prematurely and having low birth weight. The teratogenic potential does not appear to be strong. A higher than expected number of infants with pylorostenosis or alimentary tract atresia was found. These observations need independent confirmation. No increased risk for orofacial clefts was found.

7.4 PAPER IV

Wikner BN, Skjöldebrand Sparre L, Stiller CO, Källén B, Asker C. Maternal use of thyroid hormones in pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2008; 87: 617-627

7.4.1 Objective

To describe characteristics of women, substituted with thyroid hormones, and to study their offspring with regard to the presence of congenital malformations and neonatal diagnoses.

7.4.2 Results

Women reporting the use of thyroid hormones in early pregnancy were more likely to be older, to have a BMI ≥26 and parity ≥2 than other pregnant women. Subfertility and previous miscarriages were more common than expected.

The hormone substituted group had a concomitant drug use that differed from the reference population with a higher extent of use of cardiovascular drugs, systemic corticosteroids and antidepressants. The use of antiasthmatic drugs, neuroleptics, sedatives and hypnotics was also reported more often by women substituted with thyroid hormones.

Diagnoses of diabetes (pre-existing or gestational), pre-existing hypertension, pre-eclampsia, caesarean sections and induction of labour were more common in the thyroxin substituted group. As maternal diabetes may affect pregnancy outcome, women with any diabetes diagnosis were excluded from further analysis.

The infants had a marginally increased risk for premature birth and for being large-for-gestational-age. Neonatal thyroid disease was found in eight infants, the expected number was 0.2. A statistically significant, but marginally increased malformation risk was found in neonates born to mothers reporting thyroid hormone substitution in early pregnancy (OR 1.14, 95 %CI 1.05-1.26). The malformations occurring in excess were “any cardiovascular defects”, mainly serious ones, and “severe kidney malformations”.

7.4.3 Conclusion

Our data showed that women on thyroid hormone substitution during pregnancy differ from the reference population and have an increased risk for some pregnancy complications. Their infants were affected to a minor extent, although our data showed increased rates of neonatal thyroid disease and a slightly increased rate of malformations.

8 GENERAL DISCUSSION

Women report the use of antiemetic drugs, thyroid hormone substitution, and also benzodiazepines and hypnotic benzodiazepine receptor agonists during pregnancy. If these agents (or maternal conditions) carry a risk for the infant is a matter of debate.

We have used the Swedish Medical Birth Register to study the effect of the above mentioned drugs during pregnancy on the neonatal outcome, including the presence of congenital malformations. In addition, we used this registry to describe the maternal characteristics of women using these drugs.

Methodology

The main advantages of the Swedish Medical Birth Register are: 1. The relatively large numbers of exposed women and their offspring (coverage about 99% of deliveries in Sweden). 2. The information on the outcome is based on medical documents and is not affected by the exposure. 3. The information about drug use is obtained before the birth of the child and is therefore prospective. 4. Information on putative confounders (e.g., smoking, other drug use etc.) is available and also based on information retrieved early in pregnancy and before the birth of the child.

However, the MBR has some drawbacks of importance for the interpretation of data on drug use in reproduction epidemiology. Interview data will probably understate drug use. It is unlikely that all drug use is reported by the pregnant woman or recorded by the midwife. There is also a possibility of data loss due to record error. Currently, the information gathered by the midwife interview seems to be a better source to ascertain drug use during early pregnancy than the prescription register (Källén and Otterblad Olausson, 2008).

For drugs recorded at the first antenatal visit (usually between weeks 10 and 12), the exposure most probably occurred during the first trimester, but some drugs registered at this time may in reality have been used very early, even before implantation, or later after organogenesis. These women will wrongly be classified as exposed and this will bias risk estimates towards 1.0. If a woman visits the antenatal care earlier, e.g., week 8-9, drugs taken later during the first trimester will not be recorded.

The reporting rate for drugs used for epilepsy or hypertension is estimated to 60-70 per cent (Källén, 2005). This is probably true also for thyroid hormone substitution and antiemetic drugs. The reporting rate for "sensitive drugs" like benzodiazepines and hypnotic benzodiazepine receptor agonists may be lower due to unwillingness to report these drugs by the women or to record them by the midwife. This means that some infants exposed for BZD or HBRA during embryonic life will wrongly be regarded as controls. This will bias the risk estimates towards 1.0. The effect will be slight because the misclassified cases will make up a very small part of the reference population. Since all exposure data are obtained prospectively (before the birth of the neonate) it will have little effect on risk estimates. If the lack of information is random, missing data will have little impact on risk estimates but will affect estimates of prevalence. It is also possible that differences in, e.g., educational level may mirror a tendency to report drug instead of actual differences in drug use.

Information on the amount of drugs used is often incomplete, making it difficult to distinguish intake of one single tablet from regular use of high doses. This will bias the risk estimates towards unity and may hide high risks which may be present for high consumers. This may be possible for e.g., benzodiazepines (Lagreid et al., 1989).

The indication for drug use (maternal disease or complaint) is often not known through the register and maternal disease (e.g., diabetes) in itself may be associated with an increased risk for malformations.

The recording of congenital malformations as well as the recording of drug use may vary over the country. As a consequence either a false association may appear or a true association may be hidden. The use of multiple sources for malformation identification (MBR, Register of Birth Defect and The Hospital Discharge Register) reduces this risk but does not eliminate it completely.

The studies included in this thesis are based on infants born, aborted foetuses are not included. According to Swedish law, induced abortions cannot be registered with personal identification data, which makes it impossible to study such data for, e.g., drug use. That means that if a malformation nearly always leads to pregnancy interruption (like anencephaly or bilateral kidney agenesis), it is impossible to detect an association

of the malformation with a specific drug. If only some pregnancies are interrupted after prenatal diagnosis (like spina bifida) the power of the study will decrease but it will hardly influence the risk estimates.

If maternal use of a specific drug during pregnancy will influence the routines of prenatal diagnosis it could result in an underestimation of the risk for that specific malformation, due to a selectively increased rate of abortion. In Sweden however, practically all women undergo second trimester ultrasound. Therefore it seems unlikely that a pregnant woman's use of drugs, for drugs studied in this thesis, would influence the frequency of foetal diagnosis.

A teratogenic effect seen with a studied drug can obviously be due to concomitant use of another drug. We started all our studies with a careful description of maternal characteristics including all drugs reported to have the possibility to adjust for known teratogenic drugs, e.g., by exclusion of women exposed also for such drugs.

Only factors recorded in the register can be studied and adjusted for. Factors easily identifiable in the register and putative confounders are, e.g., maternal age, year of birth, and parity. Other factors could be unknown or not retrievable in the register like the true use of alcohol. However, smoking habits are recorded and can be adjusted for and smoking usually covariates with alcohol consumption (Hays et al., 1984).

Awareness of the multiple testing situations, which means that an association between a drug and a specific malformation although formally highly statistically significant, could be a random phenomenon, is important. Associations found must therefore be regarded as "signals" to be later confirmed or rejected by independent studies designed with a prior hypothesis ("Is there an association between drug x and malformation y?").

Antiemetic drugs

Our data demonstrate that neonates born to women who report use of antiemetics (in particular antihistamines) during early pregnancy had a better delivery outcome than the reference group. The odds ratio for preterm birth, low birth weight and small-for-dateness were significantly lower than in the reference group. This is in accordance with a similar study, restricted to the use of meclozine (Källén and Mottet, 2003). There were no signs of a teratogenic effect of these drugs, but for some, the number of

exposures was low. However, antiemetic therapy usually does not start during the most sensitive part of organ formation and we could not identify women who had used antiemetic drugs very early e.g., because of motion sickness. The better-than-expected infant outcome is hardly a direct drug effect but may be in line with the hypothesis that a well-functioning placenta is associated with NVP (Kullander and Källén, 1976). Previous studies have verified this for different pregnancy outcomes, such as miscarriages and preterm birth (Källén et al., 2003, Yerushalmy and Milkovich, 1965, Kullander and Källén, 1976). Placental hormones are thought to play a role in the etiology of NVP (Huxley, 2000) and a well functioning placenta may both increase the probability of NVP and contribute to a good pregnancy outcome. The negative association between some maternal conditions (use of insulin, anticonvulsants, thyroxin, antiasthmatics, progesterone, and ovarian stimulation) and drugs for NVP may be due to the effect of a chronic disease on early placental development. It is possible that some women after the first antenatal care visit used antiemetic OTC drugs that will not be recorded. This will only slightly influence the risk estimates due to the large control population (665 572 pregnant women) (Källén, 2005).

Benzodiazepines and hypnotic benzodiazepine receptor agonists

In paper II we identified maternal characteristics and possible confounders for the analysis of neonatal outcome which may affect the use and/or reporting of BZD and HBRA. We found that women reporting use of these drugs differ in many aspects (age, parity, smoking, education and concomitantly used drugs) from non-users. These putative confounders will have different significance in the analysis of different outcomes.

Maternal age is associated with an increased risk for congenital malformations (Hollier et al, 2000). There is a strong association between high maternal age and infants with chromosome anomalies. Also low maternal age has been associated with an increased risk for some types of malformations (Lindham, 1981). An increased risk for malformations at first parity is sometimes seen (Källén K, 2002). Maternal smoking is associated with a moderately increased risk for some malformations (Källén K, 2002). Among concomitantly used drugs, e.g., some antiepileptic drugs have a teratogenic effect (Dansky and Finnell, 1991). Previous miscarriage or years of involuntary childlessness, as a measure of subfertility, had little impact on the use of these drugs.

Women reporting use of BZD and HBRA had an increased risk for preterm birth and low birth weight. Preterm birth was not explained by an increased risk for preeclampsia or bleeding complications. The OR for preterm birth was higher for exposure during late pregnancy, an observation complicated by the possibility that BZD may then have been prescribed due to signs of premature labour. The use of antidepressants is associated with preterm birth (Ericson et al., 1999). In our study 31 per cent of all women who reported use of BZD or HBRA also used antidepressants, the exclusion of these women decreased the OR for preterm birth but a nearly significant effect remained. Also an increased rate of caesarean section, not explained by the increased risk for preterm birth was seen in our studies. The reason for the increased risk for caesarean section is unclear but it is possible that underlying pathology with stress and anxiety could play a role.

A statistically significant but not very strong risk for malformations was found after exposure to BZD and/or HBRA. This was mainly driven by two conditions, alimentary tract atresia (notably small gut atresia) and pylorostenosis. When these conditions were excluded, no residual risk increase was found.

Small gut atresia may arise early as a result of faulty recanalization of the gut or later during pregnancy as a secondary result of a vascular accident (Harris et al., 1995). Pseudoephedrine used during pregnancy has been associated with this type of malformation (Werler et al., 2002) and one earlier report found an indicated association with benzodiazepines (diazepam) and intestinal atresia/stenosis (Czeizel et al., 2003).

In paper III there were two infants with anal atresia. This may well be a random finding (the expected number was 0.7) but there is a report in the literature of a possible association between anal atresia and maternal use of lorazepam (Bonnot et al., 2001). Both our cases were exposed to diazepam.

Pylorostenosis is usually regarded as a condition which arises late in pregnancy or even after birth. We saw an increased risk for pylorostenosis after maternal use of BZD or HBRA. Postnatal use of erythromycin has been associated with an increased risk for pylorostenosis (Cooper et al., 2002) and also maternal use of erythromycin during pregnancy has been suggested as a cause (Källén et al., 2005). None of the mothers of the seven infants with pylorostenosis in our material reported the use of erythromycin.

A possible association between maternal use of BZD and infant orofacial cleft has been a matter of debate with a positive association mainly found in retrospective case-control analyses (Dolovich et al., 1998) which always carry the risk of recall bias. In our study we found only two infants with orofacial clefts when the expected number was 5.23 (RR 0.38, 95% CI 0.05-1.38).

Thyroid hormone substitution

We found an association between the use of thyroid hormones and gestational diabetes and a strong association with pre-existing diabetes. We confirmed the association between thyroid hormone substitution, subfertility, previous miscarriages, hypertension and pre-eclampsia (Wolfberg et al., 2005). The increased risk for caesarean section shown in our study is hard to explain, but may be due to care-giver bias.

The offspring of thyroxine-treated women had a marginally increased risk for preterm birth and being large-for-gestational age. The latter observation explains the absence of a risk for low birth weight. The slight excess of large-for-gestational age neonates may relate to unidentified cases of maternal diabetes in the register, notably so for gestational diabetes. In women not reporting use of thyroid hormones in early pregnancy but with a prescription of thyroid hormones during the 2^{nd} and 3^{rd} trimester no increased risk for congenital malformations was found.

Neonatal thyreotoxicosis occurred more often than expected in the neonates of thyroxine-substituted women. This may be explained by placental transfer of maternal residual disease-specific thyroid-stimulating antibodies (Peleg et al., 2002). The mothers of these neonates were, with one exception, previously treated with surgery or irradiation for hyperthyroidism.

A statistically significant but marginally increased malformation risk in neonates born to mothers with thyroxine substitution was noted in the form of “any cardiovascular defect”, mainly serious ones, and “severe kidney malformation”. The twelve neonates with severe kidney malformations had different subtypes, a finding unexpected for causal association. Since use of antihypertensive drugs during pregnancy has been associated with infant congenital cardiovascular defects (Källén and Otterblad Olausson, 2003) adjustments were made for this in the analysis of cardiovascular

malformations, but this did not significantly change the results. An association between anomalies of cardiac septal closure (atrial or ventricular) and thyroid hormone therapy has earlier been proposed, but was based on only six cases (Robert et al., 1994).

9 CONCLUSIONS

Compared to all other women, women using antiemetic drugs due to nausea and vomiting during pregnancy in general have a better delivery outcome with respect to several variables including prevalence at birth of malformation.

Women using benzodiazepines and/or hypnotic benzodiazepine receptor agonists during pregnancy are more likely to be older, smokers, have low education and be either primiparous or of a high parity (4 or more) than unexposed women. They reported more often concomitant drug use, notably psychoactive drugs. An increased risk for caesarean section was found.

Neonates born to women reporting use of benzodiazepines or hypnotic benzodiazepine receptor agonists during pregnancy are at risk for being born prematurely and have low birth weight but have no certain deviation in intrauterine growth. There is an increased risk for respiratory problems in neonates exposed to the studied drugs late during pregnancy. The teratogenic potential of BZD and HBRA is not strong and an increased risk for orofacial clefts was not confirmed. A higher than expected number of infants with pylorostenosis or alimentary tract atresia (especially small gut atresia) was observed. This observation needs independent confirmation.

Women on thyroid substitution during pregnancy often had diabetes as co-morbidity, as well as co-medication with cardiovascular drugs, systemic corticosteroids, psychiatric drugs and drugs for asthma. Subfertility, previous miscarriage, pre-eclampsia, caesarean section and induction of labour were more common than in non-users. Their infants were only little affected, although increased rates of preterm birth, neonatal thyroid disease and a small increased rate of malformations were seen.

As new drugs are approved and new light is shed on old drugs by accumulating data, studies are continuously needed to improve safe drug use during pregnancy. The population-based Swedish Medical Birth Register has advantages and disadvantages but is a powerful tool for assessing teratogenic risks. A risk-benefit analysis is needed when deciding upon pharmacological treatment of a pregnant woman. Perhaps a weak teratogenic risk is acceptable in order to find an optimal treatment of the mother's

disease. Our studies are based on a large number of pregnant women but single studies are not sufficient to draw firm conclusions on causality. Possible associations should be looked upon as signals which need to be confirmed or rejected in new studies.

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