PRESCRIPTION DRUG UTILIZATION IN PREGNANCY: A SYSTEMATIC REVIEW AND POPULATION-BASED STUDY IN BRITISH COLUMBIA, CANADA

by

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Abstract

Background – There is little evidence on the patterns of prescription drug use during pregnancy in Canada. To address this knowledge gap, the primary objectives of this thesis were to: 1) systematically review published antenatal drug utilization studies, and 2) provide the first Canadian evidence on prescription drug utilization across the pregnancy period, overall, by therapeutic category and fetal risk classification, in the province of British Columbia (BC).

Methods - This thesis is comprised of two original studies. The first, a systematic review of antenatal drug utilization studies, was conducted according to an *a priori* protocol and included a double independent review process for the selection of articles and data abstraction. The second, a population-based empirical study in BC, was based on pharmacy claims records linked to maternal hospital records. The period of pregnancy was constructed from the recorded gestational age and prescriptions filled before, during, and after this period were analyzed. Drugs were classified according to the World Health Organization Anatomical Therapeutic Classification System and US Food and Drug Administration risk categories indicating potential for fetal harm (categories D and X).

Results – Published drug utilization studies reveal wide variation in estimates of overall prescription drug use in pregnancy (27% to 93% excluding vitamins and minerals). However, estimates are difficult to compare due to differences in methodology, data sources, classification of prescription medicines, and inadequate reporting. In BC, the majority of pregnant women (63%) filled at least one prescription in pregnancy and approximately 1 in 12 filled a prescription for a drug with potential risks (category D or X). The most commonly used medicines were anti-infectives, doxylamine, dermatologicals, and drugs acting on the nervous system.

Conclusion - A methodological framework and template for reporting exposures in pregnancy should be developed to improve the quality and comparability of antenatal drug utilization studies. Evaluation of medicines with unknown risks that are commonly used in pregnancy should be a priority for pharmacoepidemiological research. The use of drugs with potential risks should be targeted by programs to improve appropriate prescribing in pregnancy.

Preface

The work presented in this thesis was conducted and written by Jamie Daw (JD). JD developed the research objectives, study design and analytical approach with the assistance of the thesis committee (Drs. Steve Morgan, Barbara Mintzes and Michael Law).

JD managed the systematic review process from protocol design to writing of the final research chapter. JD developed search strategies for the systematic review with Devon Greyson, the information specialist at the Centre for Health Services and Policy Research (CHSPR). Devon Greyson conducted the database searches based on this strategy. Gillian Hanley and Steve Morgan acted as second reviewers and/or third adjudicators in the study selection and data abstraction processes of the systematic review. JD compiled all abstracted data, analyzed results and wrote all material related to the review.

The empirical study contained in this thesis is a contribution to a broader research project managed by Steve Morgan entitled "Return on investment from pharmaceutical care: measuring population-based causes and consequences of prescription drug utilization and expenditure". The empirical study was approved by the Behavioural Research Ethics Board at the University of British Columbia (certificate number: H09-00625). With the assistance of Steve Morgan, Gillian Hanley and Colleen Cunningham, JD completed the documentation for data access requests and data extractions from Population Data BC related to this project. Lixiang Yan, a programmer at CHSPR, extracted the data according to JD's requests and removed all personal identifiers prior to providing the dataset for analysis, as per confidentiality data agreements. JD designed the empirical approach, conducted all data analyses, compiled results and drafted all material related to the empirical study.

The thesis committee provided guidance at various steps in the research process and offered critical feedback on earlier drafts prior to submission of this thesis to the UBC Faculty of Graduate Studies.

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List of Abbreviations

ADEC	Australian Drug Evaluation Committee
ATC	Anatomical Therapeutic Chemical
BC	British Columbia
CHSPR	UBC Centre for Health Services and Policy Research
FASS	Farmaceutiska Specialiteter i Sverige (Swedish compendium of pharmaceuticals)
FDA	US Food and Drug Administration
ICD	International Classification of Diseases
LHA	Local health area
OECD	Organisation for Economic Co-Operation and Development
UBC	University of British Columbia
WHO	World Health Organization

Glossary

Antenatal	Occurring or existing between conception and birth.
Gestational age	The interval, in completed weeks, between the first day of the mother's last menstrual period and the day of delivery (that is, the duration of pregnancy).
Live birth	The complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, whether or not the umbilical cord has been cut or the placenta is attached.
Parity	The number of live births a woman has had to date (excludes fetal deaths or stillbirths).
Pharmacovigilence	The science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.
Plurality	Refers to whether the delivery results in the birth of one or more live born or stillborn infants.
Pre-term	A period of gestation less than 37 completed weeks
Spontaneous abortion	A miscarriage, that is, any pregnancy that is not viable or in which the fetus is born before the 20^{th} week of pregnancy.
Stillbirth	Death prior to the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life. Only fetal deaths where the product of conception has a birth weight of 500 grams or more or the duration of pregnancy is 20 weeks or longer are registered in Canada.
Teratogen	Any chemical or biological exposure that can have an adverse effect on a developing fetus.
Therapeutic abortion	The termination of pregnancy by medical or surgical means.

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1 Introduction

1.1 Background

Fifty years after the thalidomide tragedy and despite calls for public health action and research, evidence on the safety of most marketed prescription medicines in pregnancy remains limited [1]. Pregnant women continue to be routinely excluded from clinical trials during drug development, and application of post-market pharmacovigilence to pregnancy has not been widespread [2, 3]. Animal toxicology studies and clinical experience remain the primary sources of teratogenic risk information [3, 4]. However, animal studies do not always generalize to human cases, and it often takes years of human use before a medicine can be established as safe in pregnancy, or alternatively, for teratogenic effects to be identified [4]. As of 2002, an estimated 91.2% of the 486 drugs approved by the FDA from 1980 to 2000 had unknown risks if used in pregnancy [5].

Insufficient evidence regarding efficacy and safety makes appropriate prescribing in pregnancy a considerable challenge for women and their providers. While refraining from drug use in pregnancy is generally encouraged, avoiding therapy is not always possible. Pregnant women may require pharmacological treatment for a variety of chronic, acute and pregnancy-related conditions. In some cases, therapy is essential for a healthy pregnancy, for example, in the treatment of chronic conditions such as diabetes, hypertension, and epilepsy [2].

The appropriate use of medicines in pregnancy requires careful consideration of risks in light of potential benefits for the mother and developing fetus. The evaluation of the risks of a given medication in pregnancy is complicated by limited information and the fact that teratogenic effects depend on several factors including dose, route, duration and timing of exposure, the use of concurrent medications, and the presence of other predisposing risk factors [12]. Uncertain risks may result in pregnant women forgoing necessary treatment when in fact it is safe. In some cases, anxiety over potential risks may result in the unnecessary termination of otherwise wanted pregnancies [13, 14]. On the other hand, women may take medicines with potential risks when it is not necessary or while safer options are available. Studies in several countries have shown that the use of prescription drugs with known potential for fetal harm during pregnancy is not

uncommon [15-19]. While in some cases, these drugs may be prescribed after consideration of maternal benefits, in others, drug consumption may be inadvertent prior to pregnancy recognition or a result of insufficient communication of risk information to health care providers. Despite the clear implications of the lack of knowledge surrounding appropriate drug use in pregnancy, maternal-fetal pharmacoepidemiology remains an orphan field [2, 20].

Supporting the rational use of medicines in pregnancy is important for ensuring the delivery of high quality maternal-fetal health care in Canada. The first step in this process is to develop an understanding of the current environment: how are prescription drugs being utilized in pregnant populations? There is little Canadian evidence on the extent of prescription drug use in pregnancy, nor the patterns of use or profiles of drugs being used. Without this information it is difficult to establish priorities for pharmacoepidemiological research or to determine the need for strategies to improve the appropriateness of prescribing.

The Role of Descriptive Drug Utilization Research

Descriptive drug utilization research is intended to profile the population's use of medicines in order to identify areas deserving of further study or where interventions to address the irrational use of medicines may be appropriate. The importance of conducting descriptive drug utilization studies in high-risk populations such as pregnant women, children, and the elderly is widely recognized [3, 21, 22]. Specifically, antenatal drug utilization research can provide insights into the following aspects of drug use and prescribing in pregnancy [21]:

1) Patterns of use: measurement of the extent of drug use in pregnancy and profiles of the types of drugs used.

2) Quality of use: audit of the appropriateness of prescribing practices through the application of established fetal risk classification systems to drug utilization patterns.

3) Trends in use: monitoring of changes in the patterns and quality of use over time.

4) Determinants of use: measurement of variations in the patterns and quality of use according to maternal, provider, and/or health system characteristics.

Given the scarcity of evidence, understanding how prescription drugs are being used in pregnancy is a necessary step towards an ideal where antenatal prescribing is based on high quality evidence and achieves the objective of optimizing maternal-fetal health outcomes while minimizing the potential for harm. Based on this rationale, the overarching purpose of this thesis is to advance knowledge surrounding the nature of drug utilization during pregnancy: first, by reviewing previously published drug utilization studies, and second, by conducting the first known population-based drug utilization study of overall prescription drug exposures during pregnancy in Canada.

1.2 Research Objectives

Several antenatal drug utilization studies have been conducted in developed countries. Studies draw on a variety of strategies for identifying pregnancies, defining the pregnancy period, and categorizing prescription drugs. Drug exposure information may be obtained through maternal interview, survey, medical chart review, or administrative claims databases. As a result of these varying approaches, the literature in this area is often characterized as being difficult to compare [9, 23, 24].

There is a need for a meaningful synthesis of published drug utilization studies in pregnancy. Taking into account methodological differences between studies, such a synthesis may reveal patterns in drug utilization, allow for comparisons across jurisdictions, and inform recommendations for future research and methods development. The last review of this kind was published in 1990 and evaluated antenatal drug utilization studies published from 1960 to 1988 [23]. In order to update and expand upon this review, the first component of this thesis comprises a systematic review of antenatal prescription drug utilization studies conducted in OECD countries and published from 1989 to 2010. Specifically, the objective of the systematic review, and the first objective of this thesis is:

1) To quantify the prevalence of prescription drug utilization in the community setting by pregnant women, overall, by therapeutic categories, and by potential for fetal risk.

The findings of the review are then used to inform the second component of this thesis: an original antenatal drug utilization study in British Columbia, Canada's third most populous province. Currently, Canadian evidence on the use of prescription medicines in pregnancy is limited to three studies: one drawing on national survey data and two studies of the use of prescription drugs with established potential for fetal harm [15, 25, 26]. No previous Canadian study has examined the utilization of all drugs by trimester or by therapeutic category. Thus, in order to address the need for comprehensive information on prescription drug use in pregnancy, the second objective of this thesis is:

2) To measure the frequency, variety, and duration of prescription drug utilization before, during, and after pregnancy, by therapeutic category and fetal risk classification in British Columbia, Canada.

Previous research, primarily from specific insurance populations in the United States, suggests that maternal characteristics such as age, education, and socio-economic status are associated with the use of prescription drugs in pregnancy [27-29]. To our knowledge, no previous study has explored small area variations in the use of medicines in pregnancy. Thus, in order to explore the potential determinants of both overall drug use and drug use with potential for fetal harm in British Columbia, the third and final objective of this thesis is:

3) To measure the rates of overall and potentially harmful drug utilization according to maternal characteristics, namely, maternal age, social assistance status, plurality of pregnancy, and local health area of maternal residence.

It is hoped that the information produced by the empirical component of this thesis will add substantial new understanding to the issue of prescription drug use during pregnancy in the Canadian population. This study will provide recent and detailed information on this important component of prenatal health care. The exploratory nature of the study presents the descriptive evidence required to identify priority areas for further research and policy attention. The demonstrated methods for ascertaining drug exposures in pregnancy using administrative datasets and the findings related to the frequency of specific drug exposures can serve as a

reference for future risk-assessment studies linking maternal and infant health outcomes to drug exposures.

1.3 Thesis Outline

This thesis is presented in four chapters. Research chapters two and three contain a complete description of the rationale, methods, results, interpretation, and conclusions of the two original studies conducted: 1) a systematic review of antenatal drug utilization studies in OECD countries, and 2) a population-based study of drug utilization in pregnancy in British Columbia, Canada. Drawing on the findings of both research chapters, chapter four provides a summary of overall findings, strengths and limitations of the thesis research, and recommendations for future research.

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2 Prescribing in pregnancy: a systematic review of drug utilization studies in OECD countries

2.1 Introduction

Due to the potential effects on the fetus during critical periods of development, prescription drug use is a significant concern for pregnant women and their providers. Studies of prescription drug utilization in pregnancy can provide important information on the frequency and patterns of drug use during this important period. This evidence can be used to establish priorities for pharmacoepidemiological research, for example, by identifying medications with unknown risks that are frequently used by pregnant women. In addition, drug utilization data are useful for monitoring the use of prescription drugs with known or potential teratogenic risks. These findings can help decision makers assess the need to develop programs or policies aimed to improve the quality of prenatal prescribing practices.

Beyond providing original data on drug use, utilization studies provide key methodological groundwork for observational research on drug exposures in pregnant women by demonstrating and piloting sampling strategies to identify pregnancies, algorithms to construct periods of exposures and methods to accurately ascertain and quantify drug exposures. Drug utilization studies also reveal the capacity of data sources that may be used by epidemiologists aiming to answer research questions about drug safety and effectiveness.

A number of published studies have reported estimates of the prevalence and patterns of drug use during pregnancy. To our knowledge, the only review of this literature was conducted by Bonati and colleagues in 1990. This review examined thirteen studies published from 1960-1988 [1]. At that time, the majority of studies (69%) originated from the United States or Western Europe (31%) and used maternal interviews to ascertain exposures (69%). Bonati and colleagues' review found estimates of the percentage of women using pharmaceuticals ranged from 82 to 100% including vitamins and minerals. Among three comparable studies, a median of 4.7 drugs were used by each woman. The most commonly used medicines were vitamins and iron preparations, analgesics, anti-emetics and antacids.

Because of the increasing use of prescription medicines over the last twenty years and the changing profile of therapeutic classes available on the market, estimates of drug utilization prior to 1989 may no longer provide an accurate picture of current prescribing practices. Several more recent antenatal drug utilization studies have been published. Many of these draw on large administrative databases, which were not previously available in many jurisdictions, to ascertain exposures. Synthesis of recent prescription drug utilization studies in pregnancy would provide important information on the extent of drug utilization in different populations and potentially allow for comparisons across jurisdictions.

Therefore, the objective of this systematic review is to quantify the prevalence of prescription drug utilization in the community setting by pregnant women, overall, by therapeutic categories and by potential fetal risks. To investigate potential sources of heterogeneity among study estimates, we compare findings by country and research method.

2.2 Methods

2.2.1 Search Strategy

Studies were identified by searching the following electronic databases: CINAHL (Ebsco), EMBASE (Ovid), International Pharmaceutical Abstracts (Ovid), MEDLINE (Ovid), Web of Knowledge databases (ISI/Thompson) and POPLINE. This review was limited to peer-reviewed literature. We excluded books, theses and conference proceedings from the search. We developed search strategies with a Master's trained information specialist (DG) combining the concepts of pharmaceuticals and pregnancy. We limited searches to studies of human subjects, published in English from January 1989 to April 2010. We chose the year 1989 as the starting date because this was the last year of publication for studies included in the previous review by Bonati and colleagues. As an example, the search strategy used for one database is provided in Table 2.1. The full search strategy and number of articles yielded for all databases can be found in Appendix A.

Table 2.1 Example search strategy: MEDLINE (Ovid)

1. Pregnancy/
2. Drug Prescriptions/ or Prescription Drugs/ or Pharmaceutical Preparations/ or Drug Utilization/
3. 1 and 2
4. limit 3 to (english language and humans and yr="1989 -Current")
5. limit 4 to (comparative study or "corrected and republished article" or evaluation studies or journal article or letter or meta analysis or multicenter study or "review" or technical report or validation studies)

2.2.2 Inclusion Criteria

The inclusion criteria, system for study selection and methods of analysis were specified in advance and documented in a review protocol. We included original studies that evaluated individual-level exposures to prescription drugs in the community setting for the entire pregnancy period. There was no limitation on the method of exposure ascertainment. Studies could have drawn on various data sources, such as administrative databases, surveys, interviews or maternal chart review. We limited studies to those examining populations residing in OECD countries. We did not restrict studies by sampling frame, which could have included members of the general public or specific subpopulations defined by demographics, socio-economic status, ethnicity or enrolment in a particular insurance plan.

We excluded studies that only analyzed pharmaceuticals available over-the-counter, illicit drugs or drugs used in hospital (or if it was not possible to distinguish between utilization rates reported for these types of drugs from prescription drugs), analyzed only a single period of gestation (e.g. only first trimester use) or a specific therapeutic category (e.g. only antidepressants or only teratogenic drugs) without providing an estimate of drug utilization for all prescription drugs. Studies were also excluded if the unit of analysis was not a pregnancy or pregnant women (e.g. analysis of the number of prenatal care visits ending in a prescription).

2.2.3 Study Selection

Citations identified in our search strategy were subject to a three-stage process for study selection: title review, abstract review and full text review. At each stage, two independent reviewers (JD, GH) assessed citations against inclusion criteria. Differences in inclusion assessment at the abstract and full text review stages were resolved by consensus, failing which a third independent adjudicator (SM) assessed the data and method sections of the relevant study for potential inclusion.

2.2.4 Data Collection

Data to be extracted from studies were specified in advance and documented in a data extraction form containing thirty six questions (available in appendix B). The form was pilot-tested on three randomly-selected articles by three independent reviewers (JD, GH, SM) and refined accordingly. The revised data abstraction form was then applied to all included studies. Data from each study were abstracted by at least two independent reviewers: JD abstracted all citations and SM and GH each repeated abstraction for one half of the citations. Disagreements in data extraction were then resolved by consensus. If consensus could not be reached, a third reviewer (DG) would decide. We contacted twelve authors via email for further clarification or additional data and seven replied.

We assessed the following characteristics of all studies that met the eligibility criteria for data extraction: study sample, types of pregnancies included (in terms of birth outcome, location of birth, parity or plurality), identification of pregnancies and the construction of the pregnancy period (including delivery date and gestational age assumptions), data sources used for exposure information, and exposure measurement (including the inclusion and classification of prescription drugs).

We extracted four outcome measures from each study: 1) the proportion of women who filled one or more prescriptions during pregnancy and by trimester, 2) the mean or median number of different drugs used among pregnant women, 3) the most frequently used therapeutic categories and the proportion of women using drugs within each category, and 4) the most frequently used drugs with potential risks and the proportion of women using each drug. If an author provided estimates of exposures according to a risk classification system, this was also recorded.

2.2.5 Risk of Bias Assessment

Given the inclusion of a range of study designs of variable methodological rigour and the potential for the introduction of biases that may affect estimates of drug exposures, we appraised included studies according to set of criteria designed to reflect the primary sources of bias in antenatal drug utilization studies (Table 2.2). The development of this table was informed by items contained in the Newcastle-Ottawa risk of bias tool for nonrandomised observational studies (e.g. representativeness of the cases, selection, ascertainment of exposure) and modified

for our use in antenatal drug utilization studies [2]. This tool was used to ensure included studies were of sufficient quality so prevent a misinterpretation of the results of this review.

Table 2.2 Tool for assessing the primary risks of bias in antenatal drug utilization studies

Domain	Description
Sample selection (pregnancies)	Was the sample of pregnancies representative of all pregnancies in the population of interest? For example, did the sample contain all eligible individuals over a defined period of time, in a defined catchment area, health maintenance organisation, or an appropriate sample (e.g. random) within these bounds? Was the sample defined by some criteria (e.g. socio-demographics, ethnicity or other) that may affect the generalizability of the results? Was the sampling method population-based, random, convenience or other?
Construction of pregnancy period	Did the authors make assumptions about the length of pregnancy or delivery date that may have affected the results or introduced misclassification?
Sample selection (prescription drugs)	Were included prescriptions limited by some criteria (e.g. reimbursed drugs only) that would affect the results? If vitamins and minerals were included, were separate estimates of drug exposure both including and excluding them reported?
Exposure ascertainment	Was prescription drug exposure information gathered in a way that reduced maternal recall and social desirability biases? If a survey was used, how long after delivery were women asked to recall drug exposures? Was there any attempt to verify drug exposures, for example, with a medical chart review or prescription database?

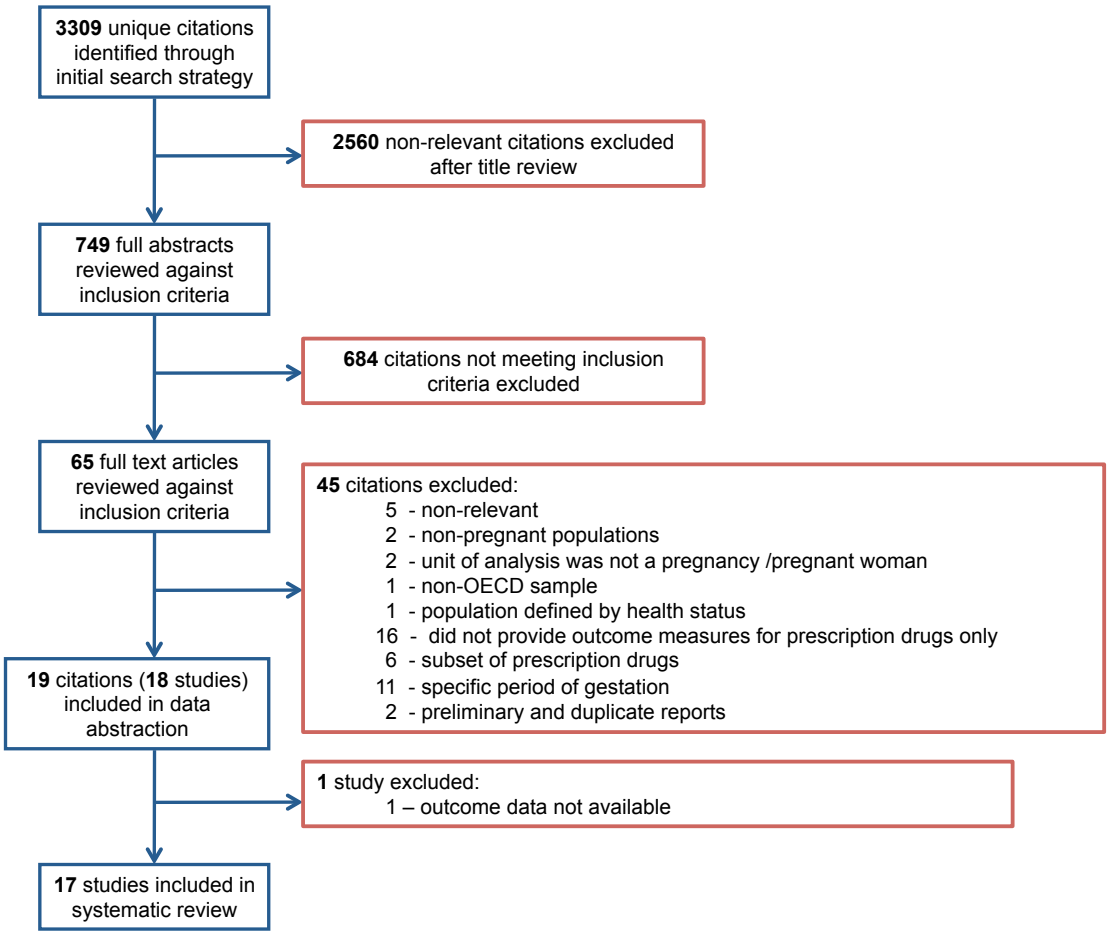
2.3 Results

2.3.1 Study Selection

Our search strategy identified 3,309 unique citations (Figure 2.1). These citations were subject to title, abstract, and full-text review by two independent reviewers (JD, GH). First, the reviewers independently screened the titles of each citation for potential relevance. This process yielded 749 citations identified by one or both of the reviewers as potentially relevant. These citations were then subject to full abstract review. This process yielded 65 citations for full-text review (Agreement: 97.1%, Kappa: 0.82, 95% CI: 0.75, 0.89). Full-text review resulted in the selection of 19 citations that met our inclusion criteria (Agreement: 92.3%, Kappa: 0.84, 95% CI: 0.70, 0.97). While a third adjudicator (SM) was available if needed, consensus was reached in all cases following discussion of initial discrepancies.

Two citations, using the same study cohort and covering the same years of data were abstracted as one study [3, 4]. One study was excluded during data abstraction because the report did not provide exposure rates overall or by therapeutic categories for the entire pregnancy period, outcome measures which must be presented for inclusion in this review [5]. The author was contacted in case these estimates could be made available, but did not reply with the additional data required. Without this information, the study could not be included in this review. This study was based on a small, convenience sample of women delivering at a single centre in the US and relied on maternal self-report to ascertain exposures.

Figure 2.1 Study Selection Process



2.3.2 Study Characteristics

Table 2.3 presents the study characteristics for the resulting seventeen studies included in the systematic review. The studies were based primarily in Europe (12 studies; 70.6%) with three studies from the US (17.7%) and two from Canada (11.7%). All but three were published in the last decade (2000-2010). The sampled years of delivery ranged from 1981 to 2006 with most studies reporting results from pregnancies ending in the late 1990s and early 2000s.

Sampling method and identification of pregnancies

In many studies, the sampling frame consisted of beneficiaries of a particular health insurance scheme, for example, a statutory sickness fund or a health maintenance organization (6 studies; 35%). A national population was the sampling frame in four studies: a national survey from Canada and studies based on prescription databases in Finland, Norway and the Netherlands. Five studies drew samples from the general population residing in a particular region of a country. Only two studies sampled from multiple health centres (e.g. multiple hospitals or clinics). Within insurance or geographically-based sampling frames, sampling was most often population-based (i.e. included all pregnant individuals within the frame). The studies of multiple health centres employed random [6] or convenience sampling [7].

The included studies most often identified pregnancies using pregnancy registries (29%) – databases which generally require women to register their pregnancy after a specified gestational age (e.g. 12 weeks in Norway) [8-11]. Hospital records (17%) [6, 12, 13] and birth registrations (12%) were also commonly used [3, 14]. When using hospital records, researchers generally identified pregnancies using diagnostic codes indicating delivery on the maternal record (ICD-9 and 10 codes O00-O99). In the two studies from the Netherlands, the sole women aged 15-50 years residing in the same residence as a child born within the study period was identified as pregnant [15, 16]. Using this method, authors estimate that 65% of mothers could be identified. For the remaining studies, pregnancies were identified by a national survey of mothers with children under age five [17], from a previous cohort study [7], or it was unclear [18-20].

Few authors explicitly reported the birth outcomes that were included in the study. Based on the limited information reported, it appears that most studies ascertained exposures only for pregnancies ending in live births [4, 14, 15, 17]. Some studies using hospital records or

Table 2.3 Characteristics of studies included in the systematic review

Study			Sample				Prescription Drug Use in Pregnancy		
Authors	Year Published	Country	Sampling Frame	Sampling Method	Year(s) of Delivery	N (pregnancies)	Exposure Data Source[a]	% Users (% excl. vitamins/minerals)	Mean Different Drugs
Garriguet [17]	2006	Canada	National	Random	2002-2003	20 738	Survey	(27)	.
Kulaga et al. [21]	2009	Canada	Insurance	Population	1998-2002	109 344 women	PDB	56	.
Olesen et al. [3, 4]	1999	Denmark	Region	Population	1991-1996	16 001	PDB	(44.2)	2.6[f]
Olesen et al. [14]	2006	Denmark	Region	Population	1991-1998	19 874	PDB	(46.8)	2.6[f]
Malm et al. [11]	2005	Finland	National	Population	1999	43 470	PDB	(46.2)	2.1
Lacroix et al. [20]	2000	France	Insurance	Random	1996	1 000	Chart[c]	99	13.6[g]
Beyens et al. [8]	2003	France	Insurance	Random	1996-1997	911	PDB	91.5	10.9
Lacroix et al. [10]	2009	France	Insurance	Population	2004-2005	10 008	PDB	95 (93)	11.0
Reimann et al. [6]	1996	Germany	Multi-centre	Random	1987	300	Survey + Chart[d]	61	2.5
Egen-Lappe et al. [19]	2004	Germany	Insurance	Population	2000-2001	41 293	PDB	96.4 (85.2)	4.0
Gagne et al. [13]	2008	Italy	Region	Population	2004	33 343	PDB	70.3 (48.0)	1.8[f]
Schirm et al. [16]	2004	Netherlands	Region	Other[b]	1995-2001	7 500 women	PDB	85.6 (69.2)	.
Bakker et al. [15]	2006	Netherlands	National	Other[b]	1994-2004	5 412	PDB	79.1[e]	.
Engeland et al. [9]	2008	Norway	National	Population	2004-2006	106 329	PDB	57	3.3[f]
Rubin et al. [18]	1993	USA	Multi-region	Random	1981-1987	2 752	Survey	(35)	1.8[f]
Andrade et al. [12]	2004	USA	Insurance	Population	1996-2000	152 531	PDB	82 (64)	1.7[h]
Riley et al. [7]	2005	USA	Multi-centre	Convenience	2001-2002	1 626	Chart	(56)	2.2, 1.9[f]

a. PDB: prescription database.
b. The study cohort comprised women believed (on the basis of address of primary residence) to be mothers of all children born during the period.
c. Review of original prescription records
d. Chart refers to the "Mutter-pass", a document given to expectant mothers in Germany, where prescription medications used may be recorded by the attending gynecologist, midwife, or the pregnant woman herself.
e. Excluding oral contraceptives.
f. Among women using one or more prescription medicines.
g. Proprietary medicines only.
h. Excluding vitamins and minerals

pregnancy registries reported the inclusion of both live and stillbirths [11-13]. Complete capture of all pregnancies was not achieved in any study, a consequence of the limited availability of data on spontaneous and therapeutic abortions. Spontaneous and therapeutic abortions were only reported to be identified in three studies that identified pregnancies using a pregnancy registry [8, 9, 21]. However, miscarriages occurring prior to a diagnosis of pregnancy and early therapeutic abortions of unregistered pregnancies could not be identified.

Exclusions based on plurality or parity were rarely made, although six studies only included the first pregnancy within the study period for each woman [3, 9, 11, 13-15]. Some made the argument that this would "reduce the influence of previous pregnancies" [11, 15], while in other studies, this was done to limit the influence of older children's prescriptions, which are recorded on maternal records [3, 14].

Seven studies (41%) had access to data on the gestational age of the infant from hospital birth records or pregnancy registries [3, 6, 7, 9, 10, 14, 21]. The remaining studies assumed all pregnancies were full-term (length of assumption varied from 270 days to 280 days) [11-13, 15, 16, 19], were based on maternal survey (and thus relied on the mother's own perception of the length of her pregnancy) [17, 18], or did not indicate how the pregnancy period was constructed [8, 20].

Data sources for prescription drug exposures

Pharmacy claims databases were the most common data source for prescription drug exposure information (12 studies; 71%). In six of these studies, the databases only recorded prescriptions reimbursed by a specific insurance plan [3, 11, 13, 14, 19, 21]. In most cases, reimbursed prescriptions comprised the vast majority of all prescriptions dispensed, although this was not always clear based on the information provided by the authors. Other studies gathered exposure information using questionnaires of mothers during pregnancy or after delivery (2 studies; 12%) and/or medical chart reviews of drugs prescribed by their primary health care provider (3 studies; 18%).

Drug classification

While most studies indicated that drugs were classified according to the WHO Anatomical Therapeutic Classification (ATC) system, few reported exposures according to ATC codes. Authors commonly constructed therapeutic categories with limited information on what ATC codes or chemical substance(s) comprised these categories. Two studies analyzed drugs in categories originally proposed by Bakker and colleagues: drugs for chronic conditions, occasional use, or pregnancy-related conditions [9, 15]. To provide a measure of the appropriateness of drug use, nearly half of the studies applied a risk classification system for drugs in pregnancy. The majority of studies with risk classification information used the FDA system [7, 12, 13, 20], Australian system [15, 16] or a combination of both [13]. One study used the Swedish system [4] and another used a unique list of potentially teratogenic medications, developed in consultation with experts [21].

The majority of studies included prescribed vitamins and minerals in counts of overall prescription drug exposures (11 studies; 65%). Only six studies provided separate estimates including and excluding vitamins and minerals (35%). Because of the different status of some vitamins and minerals in different jurisdictions, determining the extent to which their inclusion influenced exposure estimates is difficult. In most countries, vitamins and minerals are available over-the-counter. However, in others they may be more commonly prescribed by a physician. Few authors commented on the status of vitamins and minerals in their country of study when reporting results.

Measures of exposure

All studies based on pharmacy claims databases classified an exposed pregnancy as one in which the dispensed date of at least one prescription drug fell within the constructed pregnancy period. Some studies also reported the mean or median number of different drugs prescribed during each pregnancy and/or provided a measure of polypharmacy (e.g. the percentage of women on three or more different drugs). However, how ‘different’ drugs were defined was not specified in any study, making these measures difficult to compare. None of the studies provided more complex measures of drug use, such as the duration of exposure or days dispensed, adherence, persistence, switching or stopping of prescription medicines in pregnancy.

2.3.3 Outcome Measures

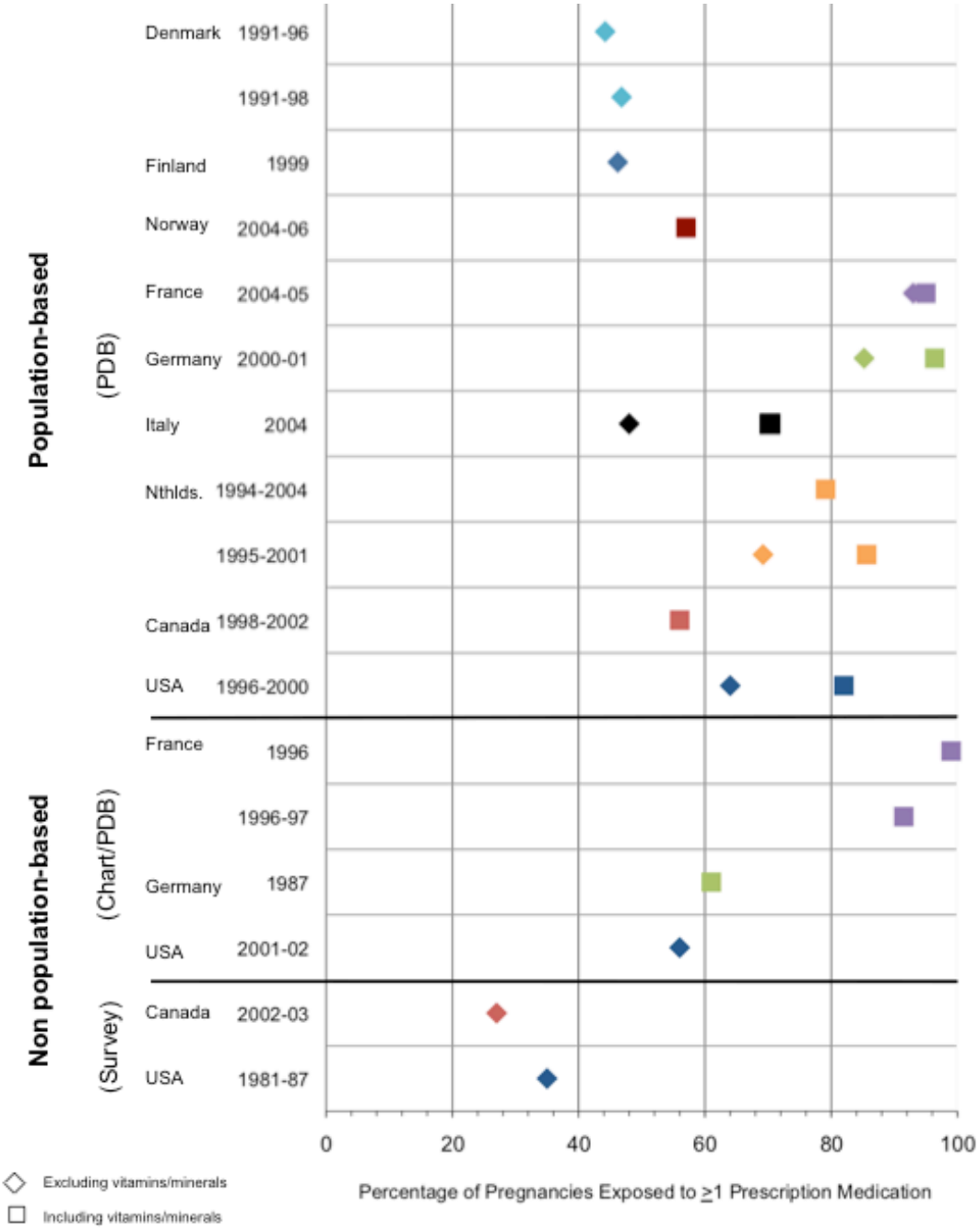
Overall Drug Use

Overall estimates of prescription drug use during pregnancy ranged from 27% to 99% (Figure 2.2). Estimates including vitamins and minerals ranged from 57% to 99%, while those excluding vitamins and minerals ranged from 27% to 93%. On average, among studies that provided separate estimates including and excluding vitamins and minerals, the inclusion of vitamins and minerals increased estimated exposure rates by 21% (range: 12-31%). The two studies relying solely on maternal self-report found the lowest estimates of drug use, with 35% reported in a questionnaire administered in the USA and 27% reported in a national survey in Canada. The mean number of different drugs used by pregnant women ranged from 2.1 to 13.6 among all women, and 1.8 to 3.3 among women using at least one prescription drug.

Studies from Nordic countries (including Denmark, Finland, and Norway) tended to have the lowest estimates of drug use in pregnancy. Higher rates were found in Western European countries. Studies of pregnant women in France found the highest rates, all reporting more than 90% of pregnant women using at least one medication in pregnancy. Even excluding vitamins and minerals, the most recent French study found 93.5% of women filled a prescription. The mean number of different drugs used found in French studies ranged from 10.9 to 13.6, far above the estimates in all other countries (all below 4.0). Germany also had higher rates of drug utilization with 96.4% of women using one or more prescription medicines, 85.2% excluding vitamins and minerals.

The higher overall exposure rates found in France and Germany may be partly explained by the fact that some medicines may be prescribed in these countries, but only available over-the-counter in others. In addition, since insurance providers may only reimburse medicines that have been prescribed by a physician, there may be incentives to obtain medicines by prescription rather than over-the-counter purchase. Examples of medicines which may be driving higher rates in France and Germany due to their prescription status include paracetamol/acetaminophen, acetylsalicyclic acid, ibuprofen, and cough and cold preparations.

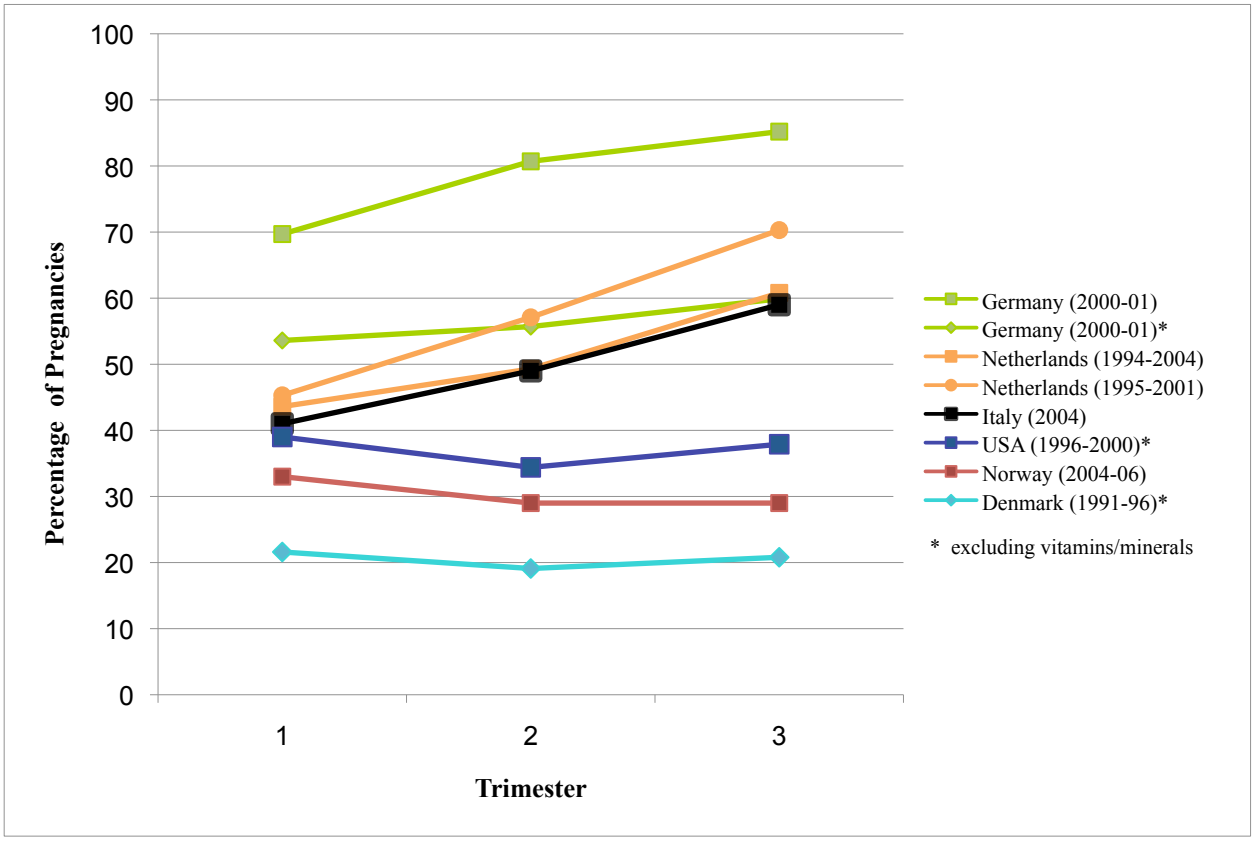
Figure 2.2 Estimates of the percentage of pregnancies exposed to one or more prescription medicines by country, year(s) of study, exposure data source, and sampling method



Prescription drug use by trimester

Seven studies reported overall drug exposures by trimester of pregnancy (Figure 2.3). These studies had a similar design: all used population-based sampling of the general population or an insurance population and ascertained exposures using pharmacy claims databases. The four studies in Germany, the Netherlands, and Italy found that the proportion of women receiving at least one prescription medicine increased from the first to third trimester of pregnancy. These studies all included vitamins and minerals; however, the German study provided separate estimates of drug exposure excluding vitamins and minerals and found that use still increased across trimester, albeit by a much smaller degree. Contrastingly, three studies found that rates of prescription drug use were highest in the first trimester of pregnancy. These three studies were conducted in the US and Denmark, excluding vitamins and minerals, and Norway, where vitamins and minerals are generally available over-the-counter (although the authors did not specify their direct exclusion).

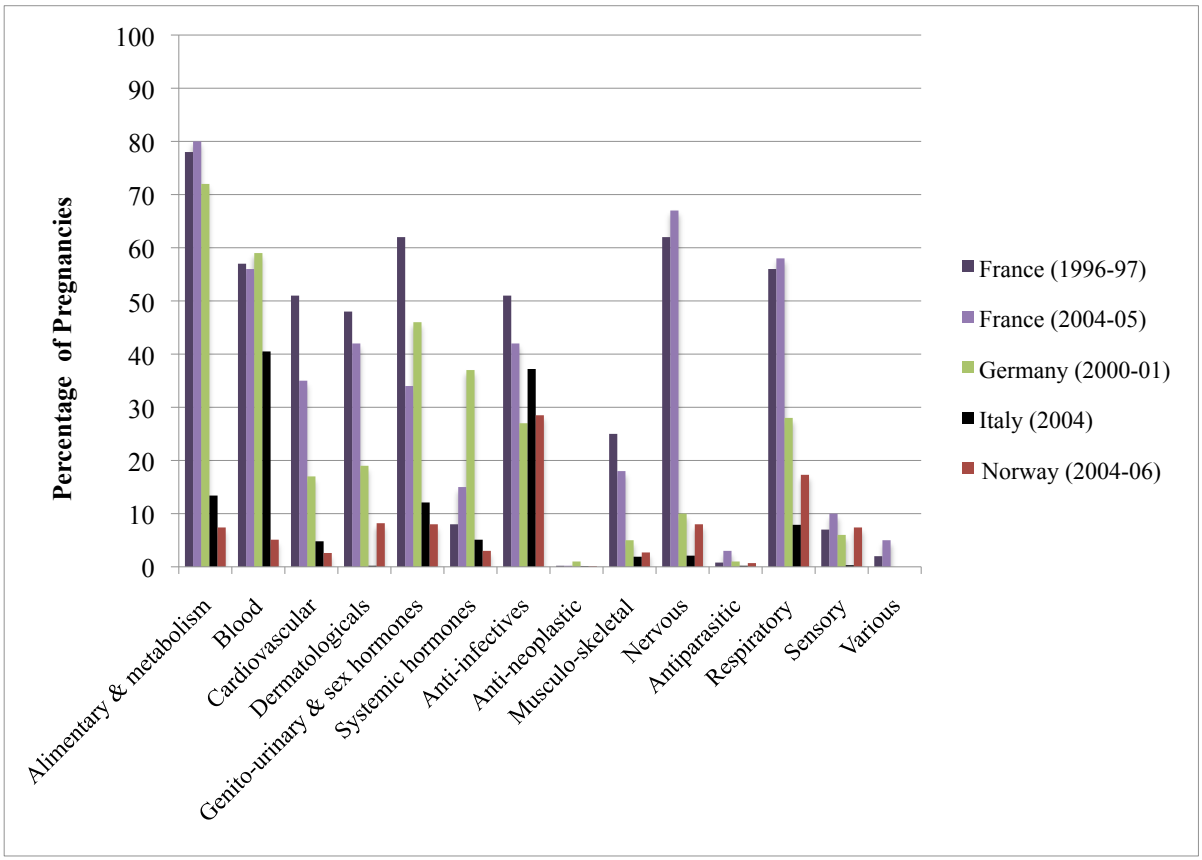
Figure 2.3 Percentage of pregnancies exposed to one or more prescription medicines, by trimester, country, and year(s) of study



Most frequently used prescription drugs in pregnancy

There was no consistent method used for reporting drug exposures by therapeutic categories. Most studies provided a list of the most used drugs, but the level at which this was classified varied. Five studies reported the percentage of pregnancies exposed to broad therapeutic categories defined at level one of the WHO ATC system (Figure 2.4). The inclusion of vitamins and minerals influenced the absolute and relative exposure measures by therapeutic category. For example, in studies in France and Germany, drugs for the alimentary tract and metabolism and drugs for blood and blood forming organs were among the most commonly prescribed. These results were driven by the use of mineral supplements: magnesium and calcium (category A), and folic acid and iron (category B). High utilization rates for drugs acting on the nervous system were found in France (67% of pregnancies). However, these high rates were comprised largely of prescriptions for paracetamol (aceteminophen), an analgesic prescribed to 63% of pregnant women in France, that would generally be available over-the-counter in other jurisdictions. Examining the use of other nervous system drugs, excluding paracetemol, the rates of utilization of nervous system drugs found in France is comparable to other countries. For example, neuroleptics (1%), antidepressants (2%), benzodiazpeines (3%), and other anxiolytics (1%) [10]. Germany's high rate of systemic hormone use is driven by the use of iodide, of which the German population has a low dietary intake [19].

Figure 2.4 Percentage of pregnancies exposed to prescription medicines, by therapeutic category (ATC L1), country, and year(s) of study



Few studies reported overall utilization rates in pregnancy at the chemical substance or active ingredient level. However, for those studies that did report the most frequently used chemical substances in pregnancy, there were some consistencies. Iron and magnesium were the most frequently used drugs in pregnancy in France and Germany. Folic acid was also among the most commonly used in France. Excluding vitamins and minerals, the most commonly used drugs in pregnancy tended to be antibiotics (e.g. amoxicillin), antifungals (e.g. terconazole), analgesics (e.g. acetaminophen/paracetamol) and anti-asthmatics (e.g. salbutamol).

Drugs used with the potential for fetal harm

Seven studies reported overall utilization rates for prescription medicines considered to have potential for harm in pregnancy based on a risk classification system (Table 2.4). Studies from France found the highest rate of potentially harmful drug use in pregnancy: 59% of pregnant women filled a prescription for a category D drug.

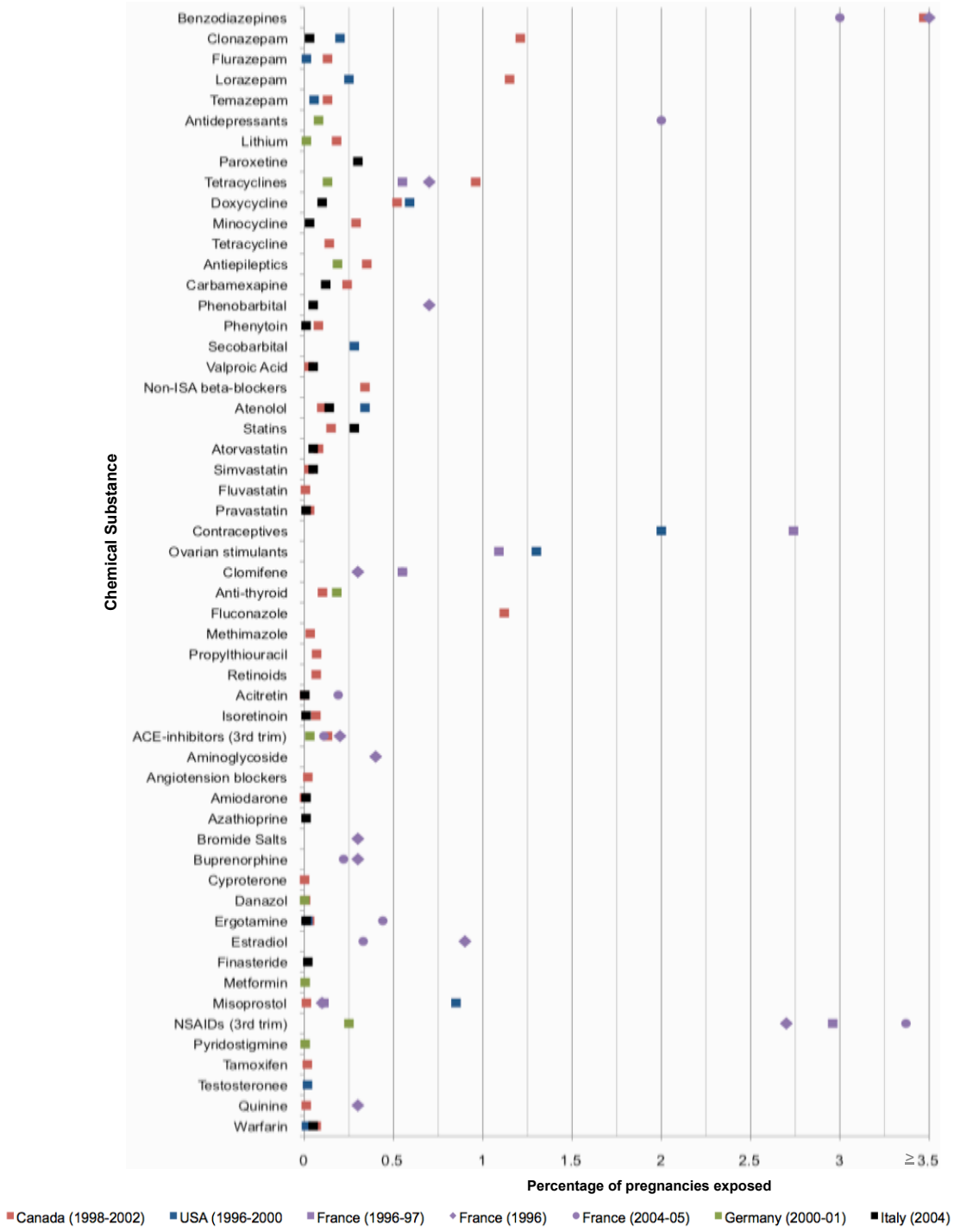
Table 2.4 Percentage of pregnancies exposed to prescription medicines with potential for harm, by risk classification system

USA (FDA)	**D**	**X**
USA (1996-00)	4.8	4.6
USA (2001-02)	3.0	1.0
Italy (2004)[1]	2.0	1.0
France (1996)	59.3	1.6
Swedish (FASS)	**C**	**D**
Denmark (1991-96)	18.7	0.9
Australian (ADEC)	**D/X**	
Netherlands (1995-01)	21	
Author Defined	**Potential Teratogen**	
Canada (1998-02)	6.3	

1. The ADEC system was used if a product label with a corresponding FDA risk classification could not be identified.

Seven studies (not necessarily the ones reporting by risk classification system) reported pregnancy exposure frequencies for drugs deemed by the authors to carry potential risks. All of the potentially harmful drugs mentioned with an estimate of the percentage of pregnant women using at least one medication in pregnancy are presented in Figure 2.5.

Figure 2.5 Estimates of the percentage of pregnancies exposed to potentially harmful prescription medications, by country, and year(s) of study



Benzodiazepines appear to be among the most commonly used drugs with potential harm in pregnancy. The use of at least one type of benzodiazepine was reported in six of the seven studies. Estimates of overall benzodiazepine use were reported in only two studies with 3.8% and 5.1% of pregnant women filling a prescription for at least one benzodiazepine in pregnancy in Canada and France, respectively. Among benzodiazepines, lorazepam (2 studies; 0.25 to 1.15%) and clonazepam (3 studies; 0.03 to 1.21%) tended to be the most frequently prescribed, although use of flurazepam and temazepam was also reported. Antiepileptic use was reported in 4 studies with estimates of use ranging from 0.19% in Germany to 0.35% in Canada. Among anti-epileptics, carbamezapine, phenytoin, and phenobarbital were the most often used. Valproic acid was also reported to be used, albeit less frequently (0.027 to 0.05%). Antidepressant use was reported in three studies (0.08 to 3.0%).

Studies from France and Germany reported the use of non-steroidal anti-inflammatory drugs (NSAIDs) in the third trimester. In three studies from France, these drugs were used by 2.7% to 3.4% of pregnant women. In Germany, the proportion was only 0.25% of pregnant women. Tetracycline antibiotics were reported to be used in six studies. Exposure rates ranged from 0.2% in Germany to 0.96% in Canada. Among tetracyclines, doxycycline was the most frequently used. Statin use was reported in two studies, but the proportion of pregnancies exposed was minimal (under 0.5%). The most commonly used statins were atorvastatin and simvastatin.

Other medicines reported to be used by pregnant women in two or more studies included oral contraceptives, anti-thyroid treatments (e.g. propylthiouracil and methimazole) ovarian stimulants (e.g. clomifene), retinoids (e.g. isoretinoin and acitrein), non-ISA beta-blockers (e.g. atenolol), ACE-inhibitors in the third trimester, buprenorphine, estradiol, ergotamine, misoprostol, quinine, and warfarin (see Figure 2.5 for complete list).

2.4 Discussion

The objective of this study was to review antenatal prescription drug utilization studies in OECD countries. We aimed to quantify the extent of prescription drug use in pregnancy overall, by therapeutic category, and by potential for fetal harm.

We found that estimates of prescription drug use in pregnancy vary widely. Comparing estimates should be done with caution and only among studies using similar measurement techniques. Particular consideration should be given to the sampling method employed, data source for exposure ascertainment, and the inclusion of vitamins and minerals. For example, we found that studies relying on self-reported drug use from a random sample of women tended to produce very low estimates of prescription drug use and should not be compared to studies using pharmacy claims databases to ascertain exposure information. Given social desirability and recall biases, particularly when the time of survey is long past the delivery date, women asked to recall and report past drug use are likely to under-report drug use in pregnancy. On the other hand, administrative data analyses may include dispensed prescriptions for medicines that, in fact, a woman did not consume.

The inclusion of vitamins and minerals in the set of prescription drugs analyzed is another important consideration when interpreting results. We found that their inclusion was associated with an often substantial increase in the estimate of exposure. This is an even greater concern when vitamins and minerals that may be available over-the-counter in some countries are only available by prescription in others. Researchers should not attempt to compare overall estimates of prescription drug use between studies including and excluding vitamins and minerals.

Another important consideration when interpreting and comparing results is the differential status of medicines as prescription or over-the-counter in different countries. The prescription of a select number of medicines in one jurisdiction that are available over-the-counter in others may result in significant differences in overall estimates of exposure, trends in utilization across the pregnancy period, and/or estimates by therapeutic category. For example, it is likely that the high rates of prescription medicine use in France is at least partly driven by the prescription status of paracetamol/acetaminophen (63% of pregnancies).

Comparing similar studies revealed variation in prescription drug utilization across countries. Considering only those studies that employed population-based sampling of the general population (defined by geography or insurance status), assessed drug utilization using pharmacy claims databases, and excluded vitamins and minerals, estimates of exposure ranged from 44.2% to 93%. Nordic countries (including Denmark, Finland and Norway) had the lowest range of estimated use, from 44.2% to 57%. Similar studies in the US and Canada found 64% and 56% of

pregnant women used one or more prescription drugs, respectively. In Western European countries, a study in Italy found 48% of pregnant women used prescription drugs, compared to 69.2% in the Netherlands. France and Germany had by far the highest rates, with 85.2% in Germany and 93% in France. These results suggest that the majority of pregnant women residing in OECD countries are prescribed medication during pregnancy, however, there are distinct differences in the extent of prescribing across regions and countries. Research is needed from additional countries at a more detailed level that would allow for comparisons across therapeutic categories. This would clarify whether the disparities in use are due to overall differences in prescribing practices for all drug classes, or whether there are specific drugs that are driving higher rates in some jurisdictions.

Although only a few studies reported results that allowed for meaningful comparisons, we found that the most commonly used drug classes in pregnancy tended to be systemic antibiotics, analgesics, anti-emetics and anti-asthmatics. The most frequently used drugs within each of these classes often varied across jurisdictions, but some consistencies were found. For example, amoxicillin was by far the most commonly used systemic antibiotic in all studies reporting at the active ingredient level. The variations found among the most commonly used drugs in different countries stress the fact that drug utilization data collected in a given jurisdiction may not be generalizable to other contexts, particularly across national boundaries.

Many studies applied an established risk classification system in order to provide an indication of the appropriateness of prescribing in pregnancy. One would expect these systems to be applied in the relevant regional context, for example, using the Australian system in studies conducted on Australian populations. This was not always the case. While American studies always applied the FDA system, European studies applied the FDA, Swedish and Australian systems. Two studies relied on a list of teratogenic medications compiled through communication with experts. This method, while justifiable based on established criticisms of risk classification systems, makes the results of these studies difficult to compare.

Many studies noted exposure rates for specific chemical substances which may be a concern if used in pregnancy. For those studies that did not use a risk classification system, it was unclear how specific substances were selected for reporting amongst all drugs with possible risks. The most commonly reported drugs with potential for harm used by pregnant women included

benzodiazepines, tetracyclines, NSAIDs in the third trimester, older anti-epileptics, statins, contraceptives, ovulation stimulants, estradiol and retinoids. The proportion of pregnancies in which a specific drug was taken was generally low (under 1.0% for most active ingredients). In some cases, the use of drugs with potential risks could have been avoided. Tetracyclines were reported to be used in six studies despite the availability of a safer therapeutic equivalent (e.g. penicillins) [22].

Based on the number of studies reporting exposures to drugs with known potential for ham, there is a clear need for continued communication of risk information to health care providers and women of childbearing age. Drugs with potential risks that are frequently used in pregnancy should form the priorities for programs to change prenatal prescribing practices. Follow-up and evaluation of such programs should be conducted with drug utilization studies similar to those included in this review. In the cases where there may be uncertainty or controversy over potential risks, pharmacoepidemiological research to clarify risks and benefits in pregnancy should be pursued.

Recommendations to Increase Study Validity and Improve Reporting

One clear conclusion to be drawn from this review is that improvements in research methodology and reporting of study methods and results are needed. The intention of drug utilization studies is to facilitate the rational use of drugs in populations by providing evidence on what drugs are being prescribed, and identifying potentially inappropriate use. This evidence can be used to inform strategies to improve prescribing practices. If studies are subject to significant threats to internal validity, are not generalizable to the populations of interest, or have insufficient reporting so as not to allow meaningful interpretation or comparison of results, the capacity to achieve this intention is greatly diminished. Given the current state of the evidence, we propose that future research should consider the following recommendations:

<u>Converging towards a gold standard: methods development</u>

Despite the fact that pharmacy claims databases are now by far the most commonly used method of ascertaining drug exposure information and that there are significant commonalities amongst these databases, there continues to be considerable variation among published studies of drug use in pregnancy. This variation makes studies difficult to compare and limits their usefulness in

informing policies and programs. As it appears claims data will continue to be the most widely used source for exposure information, researchers should make attempts to conceptualize a gold standard design to measure drug use in pregnancy using these databases. Such a framework would delineate methods for sampling, inclusion and exclusion criteria for identifying pregnancies, exposure measurements, and classifications of prescription drugs. While converging on such a design will require consultation among researchers, some of the key components of a quality study in this area may include:

- *Population-based sampling.* When administrative data is available for all individuals within a given sampling frame (e.g. a nation, a region, or insurance beneficiaries), population-based sampling (the inclusion of all individuals within a given sampling frame) is preferable to random sampling of these data. Exposure to specific chemical substances during pregnancy, particularly those with potential for harm, is often rare. Maximization of sample size is important to improve the capture of these rare exposures.

- *Comprehensive pregnancy inclusion.* If possible, all pregnancies for which data are available should be included in antenatal drug utilization studies. Exclusions based on parity, plurality, pregnancy outcome, and/or location of birth should be avoided unless data are unavailable or there is an important reason for doing so.

  Pregnancies ending in spontaneous and therapeutic abortion have a gestational period considerably shorter than those ending in live birth (nearly all occur prior to 20 weeks). Consideration of methods to adjust for gestational age or construct equivalent periods of exposure (e.g. medication use from conception to 20 weeks) in order to allow for comparisons of exposure estimates amongst these different types of pregnancies is needed.

- *Appropriate unit of analysis.* The unit of analysis should be pregnant women or pregnancies and not prescriptions (e.g. 2% of pregnant women took amoxicillin, not 2% of prescriptions were for amoxicillin). Reporting at the prescription level does not provide meaningful evidence for public health applications of drug exposure information.

- *Construction of multiple measures of drug use:* Researchers should attempt to provide more complex information on drug exposures, beyond frequency counts within a specified period.

For example, measures of the days dispensed, switching or stopping, or adherence would provide meaningful contributions to current understanding of the patterns of use.

- *Pregnancy periods for drug exposures.* Drug utilization should be measured, at a minimum, during each trimester of pregnancy *and* for the entire period of pregnancy. Providing exposure estimates for the entire study period when this may include pre and post pregnancy periods is not acceptable.

- *Pre and post pregnancy periods for drug exposures.* Measuring drug use before and after pregnancy should be considered by researchers. This information provides details on how prescribing patterns change during pregnancy and may reveal information on potential exposures in lactation. Measuring drug use before and after the first antenatal care visit may help delineate inadvertent from intentional prescriptions.

- *Meaningful construction of therapeutic categories:* The ATC classification system constructs broad therapeutic categories that limit its usefulness in this research context, particularly at ATC level one. These categories may have little clinical relevance or fail to accurately reflect the primary indications of drugs used in pregnancy (when many medications may be used for alternative purposes). The application of an existing classification system or the construction of new meaningful therapeutic categories for research in pregnancy should be a priority. To promote uptake and consistency across studies, the coding for such categories should be publicly accessible.

- *Separate reporting of vitamins and minerals:* Because the over-the-counter status of vitamins and minerals varies across jurisdictions, the inclusion of these medications may distort estimates and limit comparability across studies. Researchers should clearly outline the set of vitamins and minerals that may be relevant to exclude, and separate estimates should be provided both including and excluding these substances.

- *Stratification of prescription and over-the-counter medications.* Many studies were excluded from this review on the basis that they did not provide separate estimates for over-the-counter and prescription medications. Self-medication and medication prescribed by a provider has different implications for policy and likely would best be measured by distinct methodologies

(e.g. survey vs. claims databases). Researchers should pursue the study of OTC and prescription medications through separate methodologies or, at the least, stratify exposure estimates accordingly.

Because medicines may be classified as prescription or over-the-counter in different jurisdictions, authors should identify any medicines for which prescription status may warrant consideration in terms of the interpretation of results or comparisons with other jurisdictions. If possible, estimates excluding medicines known to be commonly available over-the-counter in the majority of jurisdictions for which comparisons are relevant should be provided.

The above list of suggestions is not meant to be exhaustive, but represents the types of issues that should be considered in developing an analytic framework for measuring drug exposures in pregnancy.

Reporting what matters: a proposed framework for reporting in antenatal drug utilization studies

Ensuring that antenatal drug utilization studies communicate meaningful information to relevant knowledge users (physicians, policymakers, and other researchers) requires that the reporting of both methods and exposures is transparent and consistent across studies. A common framework for reporting would allow for monitoring of exposures over time within a given jurisdiction and comparisons of prescribing patterns across jurisdictions. In Table 2.5, we suggest a selection of components that should be considered when reporting methods in antenatal drug utilization studies. This checklist includes elements unique to studies measuring health services use in the pregnancy period, including items such as the construction of the gestational period and the outcomes of included pregnancies.

A similar framework for the reporting of results overall, by trimesters of pregnancy and by therapeutic categories is also necessary. For example, a results reporting framework could outline how exposure information by therapeutic categories should be reported, at what level of detail and for which relevant periods (e.g. pregnancy period, first or third trimester). To ensure this information is provided in a way that is useful for policy and program development, the process of developing consistent reporting methods will require input from both researchers and relevant decision-makers.

Table 2.5: Methods Reporting Checklist For Studies of Drug Utilization in Pregnancy

Section/topic	#	Checklist item
Sample		
Location and dates of data collection	1	State start and end dates of data collection (for drug exposures) and the delivery dates for the pregnancies in the sample. Provide detail of the location (hospital, region, city) and country from which pregnancies were sampled.
Sample size	2	Indicate the number of pregnant women *and* the number of pregnancies included in the sample
Identification of pregnancies/pregnant women	3	State how pregnancies or pregnant women were identified (e.g. from birth registrations or hospital records)
Pregnancy outcomes included	4	State the pregnancy outcomes (live births, stillbirths, therapeutic or spontaneous abortions) included in the study.
Location of birth	5	State whether the sample was limited to pregnancies ending in-hospital or also included out-of-hospital births
Exclusions based on parity, plurality or number of pregnancies within study period	6	State whether any exclusions were made based on maternal parity, plurality (singleton or multiple births) or whether only the first pregnancy in the study period for each pregnant woman was included.
Representativeness of the sample	7	Comment on the representativeness of pregnancies included in the sample relative to all pregnancies in the jurisdiction of study, including any socio-demographic or other relevant differences.
Construction of the Pregnancy Period		
Gestational age assumptions	8	State whether an assumption was made about the length of pregnancy (e.g. all pregnancies were assumed to be full-term or 270 days)
Delivery date assumptions	9	State whether an assumption was made about the delivery date (e.g. maternal hospital admission date was used as a proxy for delivery date)
Trimesters	10	Indicate whether the period of pregnancy was divided into trimesters and how these trimesters were defined (e.g. three trimesters of 13 weeks each). State how pregnancies were handled that ended earlier than the second trimester.
Exposure Ascertainment		
Type of data source	11	Provide an explanation for the type of data source used to ascertain drug exposures (e.g. administrative claims data, survey or self-report, medical chart review).
Insurance (formulary) restrictions	12	State whether drug exposure data was limited to drugs reimbursed by a specific insurance plan. If so, comment on the comprehensiveness of the formulary in the context of all drugs used in the jurisdiction of study.
Exposure measurement	13	Provide an explanation for how drug use was measured for the entire pregnancy period, and if applicable, for each trimester of use (e.g. "users" were defined as women who filled at least one prescription within the constructed pregnancy period).

Section/topic	#	Checklist item
Drug Classification		
Types of pharmaceuticals included	14	State whether the study included drugs only available by prescription, over-the-counter/self-administered medications, drugs received in-hospital or illicit drugs.
Inclusion of vitamins and minerals	15	State whether or not the study included vitamins and minerals. Comment on the proportion of vitamins and minerals that are prescribed as compared to available over-the-counter in the jurisdiction of study (particularly those relevant to pregnancy, such as folic acid and other prenatal vitamins). Consider providing estimates both including and excluding vitamins and minerals.
Classification of medicines and therapeutic categories	16	State how drugs were classified and how broader therapeutic categories were constructed (e.g. according to the WHO ATC system). If referring to 'different drugs' used, indicate how 'different' was defined.
Risk classification	17	State whether a risk classification system was used to classify drugs and provide a citation or explanation for where information on these risk classifications was obtained. If an original list of medicines was developed, state how these medicines were selected and provide the final list as an appendix or provide further contact information.

2.5 Conclusion

Variations in the methods used and reporting of results make studies of drug utilization in pregnancy difficult to compare. Among studies with similar designs, we found that the majority of women in OECD countries use at least one prescription medication in pregnancy. The use of medications with known risks is not uncommon and highlights the need for continual communication of risk information to both health care providers and women. Establishing consistency in the methods used to ascertain drug use and discipline in reporting exposure estimates is essential to ensuring drug utilization studies provide information that is relevant to policymakers, health care providers and other researchers.

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3 Prescription drug use during pregnancy in British Columbia, Canada: a population-based study

3.1 Introduction

Despite recommendations for women to avoid pharmaceuticals during pregnancy, drug utilization studies consistently reveal that the majority of pregnant women in developed countries are prescribed medication [1-7]. When used appropriately, medicines help to ensure the progression of a healthy pregnancy; but when used inappropriately, medicines may carry adverse risks for both mother and child.

Monitoring drug utilization in pregnancy is important for gathering information on the extent of prescription drug utilization in pregnancy and to identify the medicines that are most frequently used. Drug utilization information can help us understand the patterns of prescribing, including the timing of exposure and potential determinants of drug use. Additionally, the use of drugs with known harms can be identified. This evidence can be used to inform priorities for observational research and to assess the need for, and inform the development of, strategies to improve the appropriateness of prescribing in pregnancy.

Few studies have examined the use of prescription drugs in pregnancy in Canada [6, 8, 9]. Research has been restricted to self-reported data from national health surveys or has focused exclusively on the use of drugs with known potential for fetal harm. No previous published study has analyzed overall prescription drug use by pregnant women in a Canadian population, by trimester and therapeutic category. To address this knowledge gap, we studied the frequency, variety and duration of medication utilization before, during, and after pregnancy, by therapeutic category and fetal risk classification in British Columbia, Canada's third most populous province.

3.2 Methods

3.2.1 Data Sources

This population-based cohort study draws data from two linked administrative health care databases in the province of British Columbia: 1) the BC PharmaNet prescription drug claims database, in which every outpatient prescription dispensed in BC must be entered by law, and 2) Population Data BC, which contains medical billings, hospital separation records, and demographic information for all individuals registered in BC's universal public health insurance program. These databases cover the entire BC population, with the exception of the approximately 4% of BC residents whom are covered under federal health insurance programs (namely status Indians, veterans, federal inmates and members of the Royal Canadian Mounted Police).

3.2.2 Study Population

The study cohort includes all pregnancies ending in a live birth in a BC hospital from April 1, 2001 to June 30, 2006. Deliveries were identified using diagnostic codes indicating delivery on the maternal hospital separation record (ICD-10 codes: O00-O99; Z37.0-Z37.9). To ensure comprehensive capture of prescription drug records, only births to women registered in the BC public health insurance plan for more than 275 days in the each of the following three years were included: the year of delivery, the calendar year preceding delivery, and the calendar year following delivery.

The unit of analysis in this study is an individual pregnancy event. Pregnant women may have delivered more than once within the study period and no exclusions were made based on parity or plurality. Due to limitations in data availability, we did not capture pregnancies ending in an out-of-hospital live birth, stillbirth, spontaneous or therapeutic abortion. Out-of-hospital births and therapeutic abortions are not included in the Population BC databases. Spontaneous abortions, defined as stillbirths that occur at less than 20 weeks, are not formally registered in British Columbia and are often not associated with a medical or hospital record [10]. Due to inconsistent use of ICD-10 codes to identify stillbirths, it was not possible to fully capture stillbirths accurately from the maternal hospital record, and so these births were also excluded from the sample. There were approximately 300 stillbirths in British Columbia annually during

the study period (Table 3.1).

Table 3.1 Birth statistics, British Columbia, Canada, 2001-2006

	2001	2002	2003	2004	2005	2006
Live births [11]	40,385	39,900	40,306	40,334	40,658	41,673
Stillbirths [11]	301	309	311	282	314	335
Therapeutic abortions [12]	na.	16,076	15,669	14,738	14,927	na.
na - not available.						

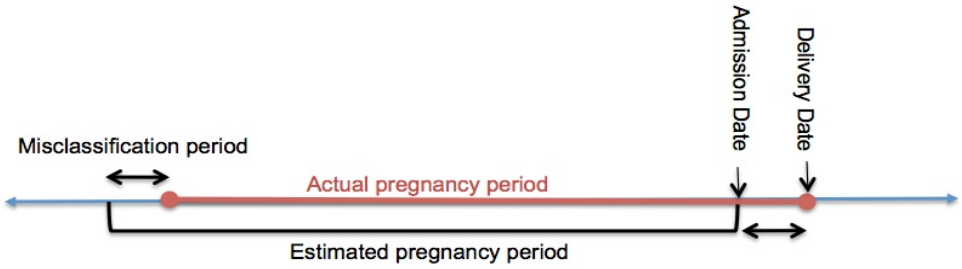
3.2.3 Construction of the Pregnancy Period

The period of pregnancy for which drug exposure was calculated, was constructed from two fields contained in the hospital record for the episode of delivery: the maternal admission date and the gestational age at delivery (the estimated age of the infant at birth in weeks). We estimated the date of conception by subtracting the reported gestational age from the date of hospital admission on the mother's hospital record. The pregnancy period was then defined as the period from the estimated date of conception to the date of maternal hospital admission.

It is mandatory for gestational age at delivery to be recorded on all newborn and obstetrics delivered cases in British Columbia hospitals. Gestational age on the hospital record may be ascertained by a physician using one of three methods: dating based on last menstrual period, ultrasound-based dating, and neonatal assessments [13]. The use of gestational age information from the hospital record in this study improves on methods which rely on maternal self-report or more commonly, assume a full-term gestational period of 270 days for all pregnancies. This assumption may lead to misclassification of drug exposures, particularly for high-risk drugs during the first trimester [14, 15].

Since the actual delivery date is not available on the maternal hospital record, the maternal admission date for the delivery episode was used as a proxy for the delivery date. This assumption may lead to misclassification of exposure at the beginning of pregnancy as each day between the admission date and delivery date would represent an additional day at the beginning of the constructed pregnancy period where in fact, the woman was not pregnant (Figure 3.1).

Figure 3.1 Potential period for misclassification based on assumption of maternal hospital admission date as delivery date.



Using administrative datasets in the United States to validate algorithms used to construct the pregnancy period, Raebel et al found that while the 270 days gestational age assumption is not optimal, the assumption that the admission date equals the delivery date is valid for the vast majority of women (within two days for 98.0% of women)[14]. We would also expect potential misclassification to be minimal for the majority of pregnancies in BC, given the average maternal length of stay for childbirth in British Columbia was 2.2 and 3.9 days for vaginal and caesarean delivery, respectively, from 2004 to 2005 [16]. Since the length of stay represents the time between antepartum admission and delivery, in addition to the time between delivery and postpartum discharge, the days between admission and delivery would in fact be shorter than the total length of stay. However, to ensure that the period of possible misclassification at the beginning of pregnancy was restricted to one week or less, we excluded pregnancies with a maternal length of stay greater than seven days, irrespective of infant length of stay (1.8% of pregnancies).

3.2.4 Classification of Prescription Drugs

This study examines prescription drug use in the community setting only. We did not investigate the use of over-the-counter products or drugs prescribed during hospitalizations (including hospitalizations during pregnancy or for the episode of delivery). Maternal hospital records were linked to prescription drug claims using a unique, non-identifying study number provided by programmers at the Centre for Health Services and Policy Research. These records contain detailed data on the date of dispensing, type of drug dispensed, days supplied, and the amounts paid by the individual and/or their insurance plan.

Drugs were coded according to the WHO Anatomical Therapeutic Chemical classification, a system that assigns drugs into hierarchical, mutually exclusive groupings at five levels of specificity [17]. Groupings are based on the organ or system on which a drug acts and/or its therapeutic and pharmacological characteristics. We used the first and third levels of the ATC system to report drug exposures by broad therapeutic categories, and the fifth level of the ATC system to report drug exposures at the level of the active ingredient. The first level indicates the main anatomical system on which a drug acts; for example, category N refers to "drugs acting on the nervous system". The third level indicates the main therapeutic group; for example, category N06A refers to "anti-depressants". The fifth level indicates the active chemical substance of the drug; for example, N06AA01 refers to "desipramine".

Previous antenatal prescription drug utilization studies have varied in the inclusion or exclusion of vitamins and minerals from the set of prescription drugs analyzed. Often it is unclear whether they have been excluded and if they were, what specific chemical entities they were considered to comprise. To improve the comparability of our results with other studies, we calculated separate estimates including and excluding vitamins and minerals. These included all drugs falling under the following ATC categories: vitamins (A11), mineral supplements (A12), iron preparations (B03A), and vitamin B12 and folic acid (B03B).

In our study, vitamins and minerals will represent only a small proportion of prescribed drugs in pregnancy. Vitamins and minerals are generally available as over-the-counter products in British Columbia and are only prescribed in the context of an indicated maternal condition, such as iron indicated for maternal anaemia. Similarly, folic acid is generally obtained via over-the-counter prenatal multivitamins, and only prescribed for women who require a higher dose of folic acid supplmentation, including women with a personal or family history of neural tube defects, diabetes or those taking anticonvulsant drugs [18].

3.2.5 Classification of Prescription Drugs by Potential Risks in Pregnancy

As there is no explicit Canadian risk classification system for drugs in pregnancy, we identified drugs used with known potential for fetal harm according to the US Food and Drug Administration (FDA) risk classification system for drugs in pregnancy and lactation (Table 3.2). The five categories of the FDA system are defined by three criteria: the presence or absence of

safety data, the source of the data (animal and/or human studies) and the results of the studies (positive or negative findings) [19].

In this study, we were primarily interested in identifying the use of drugs with known potential for fetal harm. Using the FDA system, we identified drugs classified as category D or X. Category D drugs are those for which adequate well-controlled or observational studies in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh potential risks in some circumstances. Drugs classified as category X are considered contraindicated in women who are or may become pregnant. Categories were identified using the Briggs textbook, 5th edition [20], and linked to drug identification numbers contained in the pharmacy claims records.

Table 3.2 The FDA risk classification system: categories and definitions [19].

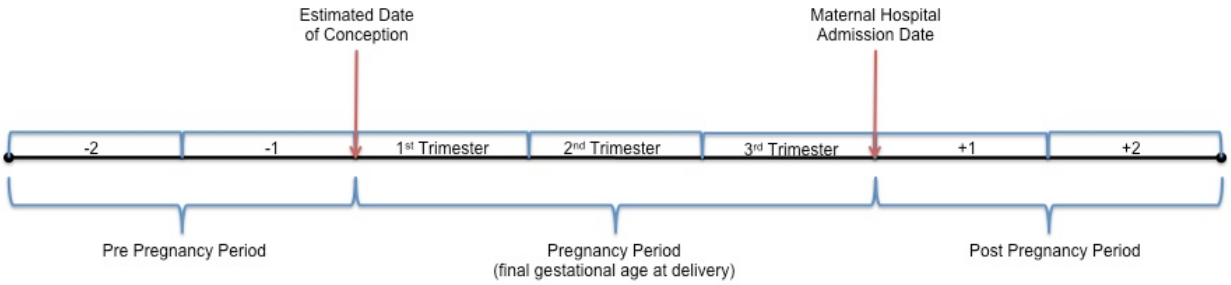
Category	Definition
A	Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, *or* animal studies demonstrate a risk and AWC studies in pregnant women have not been done during the first trimester (and there is no evidence of risk in later trimesters).
C	Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, *and* the benefits from the use of the drug in pregnant women may be acceptable despite it potential risks; *or* animal studies have not been conducted and there are no AWC studies in humans.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational *or* marketing experience *or* studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (e.g. if the drug is needed in a life threatening situation or serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or humans have demonstrated fetal abnormalities *or* there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, *or* both, *and* the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (e.g. safer drugs or other forms of therapy are available).

3.2.6 Exposure Measurement

This study uses data on prescriptions filled by women in the community setting as a proxy for prescription drug utilization. Because not all women fill the prescriptions for drugs they are prescribed, and not all women actually consume the prescriptions they fill, using pharmacy claims as a measure of exposure will result in underestimation of prescribing and overestimation of utilization. These claims do represent, however, the prescriptions a woman has purchased with the intention of use, and those that a health care provider has made the decision to prescribe (with or without knowledge of the pregnancy).

To provide a complete picture of prescription drug utilization, we measured the frequency, variety and duration of all prescriptions filled before, during, and after pregnancy. Specifically, we analyzed prescriptions filled from 6 months prior to conception to 6 months postpartum, divided into seven periods: three trimesters of pregnancy and two periods of 13 weeks each prior to conception and following delivery (Figure 3.2). While the first trimester and the periods prior to and after pregnancy were always 13 weeks in length, the third trimester, and in some cases, the second trimester, were of variable length depending on the gestational age of the infant at birth.

Figure 3.2 Construction of the pregnancy period for drug exposure



We analyzed drug use separately for the entire pregnancy and for each of the seven study periods. Within each of these periods, we constructed three measures of prescription drug utilization from the pharmacy claims data:

1) Frequency: To measure frequency of prescription drug use, we considered women to be 'users' if they filled one or more prescriptions within the period of interest. Proportions of

drug users were calculated as the number of women purchasing at least one prescription divided by the number of pregnancies within each period of interest. Pregnancies that did not continue through to the third trimester (births prior to 26 weeks gestation) were removed from the denominator in calculations for the third trimester.

2) Variety: To measure variety of use and polypharmacy, we used the third level of the ATC system to distinguish between "different drugs" and calculate the mean number of discrete therapeutic categories purchased among all pregnant women and among women who purchased one or more prescription drugs.

3) Duration of Potential Exposure: To measure duration of use, we calculated the mean days of exposure as the number of days for which drugs purchased during the study period overlapped with the trimester or pre and post pregnancy period of interest, among women who purchased one or more prescription drugs.

3.2.7 Maternal Characteristics: Age, Social Assistance and Plurality of Pregnancy

In addition to providing overall rates of prescription drug use for the province, we calculated rates of any drug use and drug use with potential for harm in pregnancy according to maternal characteristics, namely age and social assistance status. We also calculated different rates for multiple versus singleton pregnancies. The intention of this analysis was to provide some indication of the determinants of drug use in pregnancy and to identify relationships that may deserve exploration in future research.

Maternal age at delivery was calculated from data contained in the hospital record for delivery and insurance registry files. Six age categories were constructed: less than 20 years, 20-24, 25-29, 30-34, 35-39, and equal to or greater than 40 years. In order to identify low-income women on social assistance, we flagged individuals who made a prescription claim under BC's social assistance drug insurance program (Plan C) at least once during the study period. For 8.96% of pregnancies, a social assistance code could not be ascertained. Where there was a diagnostic code on the hospital record indicating plurality, we identified whether a pregnancy was multiple or singleton (ICD 10 codes for singletons: Z37.0; multiples: Z37.2, Z37.3, Z37.5, Z37.6; and

unspecified: Z37.9). For 23.0% of pregnancies, a diagnostic code indicating plurality was not available.

Age is an important predictor of prescription drug use and may cause legitimate differences between rates of drug use according to social assistance and plurality. In order to take the effects of age into account, we adjusted rates for social assistance status and plurality by maternal age at delivery. Age standardizations were completed using the direct method with six age bands (the construction of which are described above).

3.2.8 Maternal Characteristics: Local Health Area of Maternal Residence

Providing provincial rates of overall and potentially harmful drug use in pregnancy may mask important differences in utilization rates across smaller regions in the province (at the level that health services and programs are often planned and implemented). Previous research in British Columbia has found regional variation in spending per capita on prescription medicines, after accounting for differences in population age, sex and health status [21].

We hypothesize that prescription drug use in pregnancy is subject to less variation than prescription drug use in the general population. Pregnant women are a younger population within a limited age range and with most often good or excellent health status. In addition, providers may be expected to prescribe more cautiously to pregnant women and be more likely to consistently follow prescribing protocols and guidelines. Calculating regional rates allows us to explore this hypothesis and identify regions of lower or higher propensity to prescribe in pregnancy, compared to the provincial average.

We calculated rates according to the local health area (LHA) of maternal residence recorded in the mother's insurance registry file. The 89 LHAs in BC represent geographically contiguous regions with populations ranging widely from 500 to 350,000 and the number of deliveries per annum ranging from 5 to 4,595 (based on the 2006/07 fiscal year) [22]. We calculated the following five proportions for all 89 LHAs: the proportion of pregnancies in which a prescription was filled for any drug, a category D or X drug, category D drug, category X drug, and category X drug excluding contraceptives. To provide fair comparisons across regions, we adjusted all rates for maternal age at delivery.

Prior to comparing rates between regions, we calculated the sample size required within LHAs to detect meaningful differences between the overall provincial proportion and individual LHAs. Based on these calculations, to compare proportions of overall drug use, category D or X use and category D use, we excluded nine LHAs with fewer than 125 pregnancies during the study period. This allows the detection of a minimum 20% difference in overall use, and a two-fold difference in category D/X and category D use, from the provincial mean with a minimum of 80% power. For category X use and category X use excluding contraceptives, we excluded thirty-five LHAs with fewer than 400 pregnancies during the study period. This allows the detection of a minimum two-fold difference in category X use and 150% increase in category X use excluding oral contraceptives, from the provincial average with a minimum of 80% power.

Among LHAs with sufficient sample size, we summarized the extent of variation among LHAs with several statistical summary measures. Specifically, we calculated the mean, standard deviation, minmum, maximum, interquartile ratio (ratio of the third to first quartile), extremal ratio (ratio of the maximum to minimum value) and coefficient of variation (ratio of the standard deviation to the mean) for each overall measure of drug use.

3.2.9 Ethics

Ethics approval for this study was obtained from the Behavioural Research Ethics Board at the University of British Columbia (Appendix D). Data access approvals were obtained from the B.C. Ministry of Health Services and the B.C. College of Pharmacists.

3.3 Results

3.3.1 Study Sample

Between April 1, 2001 and June 30, 2006, 166 211 pregnancies ending in an in-hospital live birth were identified, born to 135 755 residents of BC. Of these, 3129 (1.8%) pregnancies were excluded with a maternal length of stay greater than seven days for the delivery episode. The final sample included 163 082 pregnancies, born to 133 416 BC residents Table 3.3 presents the characteristics of the study cohort. The mean maternal age at delivery was 30.2 years (range: 12 to 55). The mean gestational age at delivery was 39.06 weeks (95% CI: 39.05, 39.07; range: 18

to 44) and the mean length of stay in hospital for the delivery episode was 2.51 days (95% CI: 2.51, 2.52; range: 0 to 7). A total of 330 (0.20%) pregnancies ended prior to the third trimester and thus for these pregnancies, prescription drug records were not analyzed within the third trimester.

Table 3.3 Cohort characteristics (n= 163,082)

Characteristic	n (%)
Maternal age at delivery	
<20	4530 (2.78)
20-24.9	20869 (12.80)
25-29.9	44983 (27.58)
30-34.9	56196 (34.46)
35-39.9	30102 (18.46)
>=40	6402 (3.93)
Mean	**30.2**
Social assistance[1]	
No	143562 (88.03)
Yes	4893 (3.00)
Plurality[2]	
Singleton	123907 (75.98)
Multiple	1557 (0.95)
Gestational age (weeks)	
≤30	794 (4.85)
31-35	3975 (2.43)
36-40	131741 (80.8)
≥41	26571 (16.3)
Mean	**39.06**
Delivery episode length of stay (days)	
≤3	131244 (80.5)
4-5	27658 (16.9)
5-7	4180 (2.56)
Mean	**2.51**

1.14627(8.96%) pregnancies did not have a record to ascertain social assistance status
2. 37618 (23.07%) pregnancies missing an ICD-10 code indicating plurality

The results of this study are presented in three broad sections: 1) overall prescription drug use, 2) prescription drug use with potential for harm, and 3) prescription drug use by region of maternal residence. The first two sections have four main subsections: i) drug use by period of study and trimester of pregnancy, ii) drug use over the study period from 2001 to 2006, iii) drug use by therapeutic categories and/or the most frequently used medicines in pregnancy, and iv) drug use by maternal characteristics. The final section provides summary measures for both overall and potentially harmful drug use by local health area of maternal residence.

3.3.2 Overall Prescription Drug Use

Overall prescription drug use before, during and after pregnancy

Table 3.4 presents summary measures of prescription drug use for each of the seven study periods and the entire pregnancy period. Overall, at least one prescription drug was filled in 103 567 (63.5%) pregnancies with 68 888 (42.2%), 54 853 (33.6%), and 55 844 (34.3%) filling at least one prescription in the first, second, and third trimester, respectively. Among all pregnancies, the mean number of different drugs received was 1.69 (95% CI: 1.68, 1.70; range: 0 to 45). Among those who filled at least one prescription, the mean number of different drugs received was 2.66 (95% CI: 2.65, 2.68) with 39.6% filling prescriptions for three or more different drugs and 14.7% filling five or more. Excluding vitamins, minerals, iron, and folic acid supplements, at least one prescription was filled in 62.9% of pregnancies with 41.5%, 33.0% and 33.7% filled in the first, second and third trimester.

Table 3.4 Summary measures of prescription drug use before, during, and after pregnancy

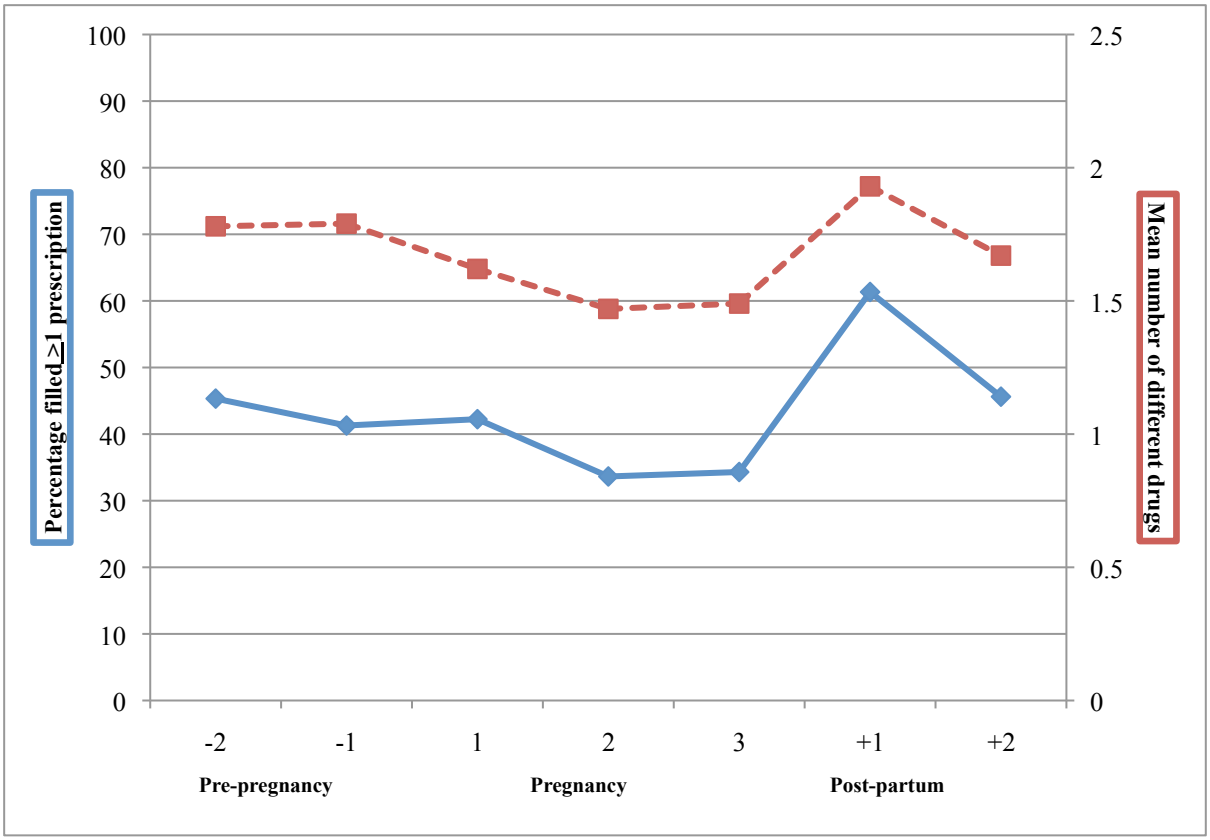
Period	% Filled ≥1 Prescription including vitamin/minerals	% Filled ≥ 1 Prescription excluding vitamin/minerals	Among Users	
			Mean days exposed	Mean number of different drugs
Pre-pregnancy				
Six to four months pre-conception (-2)	45.33	45.21	48.29	1.78
Three months to conception (-1)	41.29	41.13	58.16	1.79
Pregnancy				
1st Trimester	42.24	41.46	50.90	1.62
2nd Trimester	33.64	32.99	50.86	1.47
3rd Trimester	34.31	33.73	49.71	1.49
Total Pregnancy	**63.51**	**62.87**	**93.05**	**2.66**
Post-partum				
Delivery to three months postpartum (+1)	61.34	61.26	46.76	1.93
Four to six months postpartum (+2)	45.62	45.53	69.11	1.67

Figure 3.3 illustrates the percentage of pregnancies in which at least one prescription was filled and the mean number of different drugs used among those who filled at least one prescription for each of the seven study periods. After conception, the proportion of women who filled a prescription declined from the first to second trimester, but stayed relatively stable for the second and third trimester. The mean number of different drugs received per trimester among women who were prescribed drugs also declined from 1.62 in the first trimester to 1.47 in the second trimester, and remained stable until the third trimester at 1.49. In contrast, the duration of potential exposure in each trimester was relatively stable across the gestational period, decreasing by only approximately one day from the first to third trimester (50.9 days to 49.7 days).

Among all seven periods analyzed from prior to post-pregnancy, the period in which the largest proportion of women filled at least one prescription medicine was the first three months

immediately following delivery (61.34% of pregnancies). In contrast, the second trimester of pregnancy had the lowest prevalence of prescription fills, with 33.64% of pregnancies filling a prescription within this period.

Figure 3.3 Percentage of pregnancies in which one or more prescriptions were filled and the mean number of drugs filled among those that filled at least one prescription, by study period



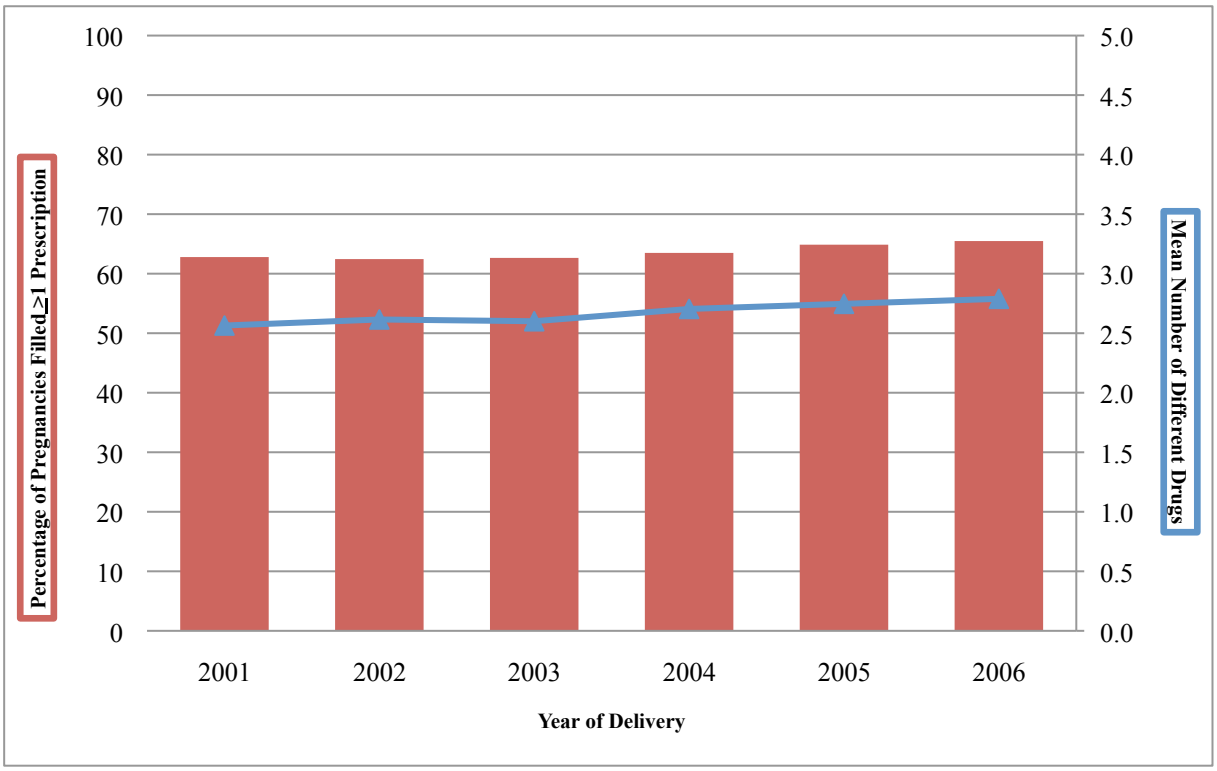
Changes in overall prescription drug use over time (2001-2006)

Figure 3.4 presents the percentage of pregnancies in which at least one prescription was filled and the mean number of different drugs used among those that filled at least one prescription, by year of delivery. Note that 2001 and 2006 were not complete years in the study period and thus estimates for these years may be influenced by seasonal variations in the use of prescription medicines.

Comparing 2002 to 2005 (complete years), we identified only a small trend towards increased prescription fills among pregnant women in recent years: the proportion of pregnancies with at least one prescription fill rose from 62.5% for pregnancies ending in 2002 to 65.5% for pregnancies ending in 2005. The mean number of different drugs filled among those with at least

one prescription fill increased from 2.6 in 2002 to 2.8 in 2005. The therapeutic categories exhibiting the greatest increase in women filling at least one prescription in pregnancy from 2002 to 2005 (in terms of absolute percentage increase) were iron preparations (B03A: 0.26 to 3.36%), antihistamines for systemic use (R06A: 17.5 to 20.4%), and drugs for peptic ulcers and acid-reflux (A02B: 2.46 to 3.88%).

Figure 3.4 Percentage of pregnancies in which one or more prescriptions were filled and the mean number of drugs dispensed among those that filled at least one prescription, by year of delivery



Overall drug use by therapeutic categories

Prescriptions for 163 different drugs (defined at ATC level three) were filled by pregnant women in British Columbia from 2001-2006. The drugs received categorized into major groupings by the first level of the ATC system, and the five most frequently used drug classes within each of these major groups, defined by the third level of the ATC system, are presented in Table 3.5. The broadly defined ATC drug groupings for which prescriptions were most frequently filled during pregnancy were anti-infectives for systemic use (30.5% of pregnancies), respiratory drugs (25.7%), dermatologicals (13.4%) and drugs acting on the nervous system (12.8%).

Prescriptions filled for anti-infectives in pregnancy were most often penicillins (18.9% of pregnancies). Among respiratory drugs, prescriptions for anti-histamines (18.9%) and anti-asthmatics including inhalants were the most common. Corticosteroids (6.8%) and miscellaneous compounded ointments, creams and lotions (3.0%) were the most frequently filled dermatological drugs. Among prescriptions for drugs acting on the nervous system, fills in pregnancy were most often for opioids (5.6%), antidepressants (4.5%) and anxiolytics (3.3%).

Table 3.5 Frequency and percentage of pregnancies in which one or more prescriptions were filled during the pregnancy period, by ATC level one categories; and top five drug classes (ATC level three) within ATC level one categories, by frequency of use.

Therapeutic Category	Pregnancies Filled ≥1 Prescription	% Pregnancies
ALIMENTARY TRACT AND METABOLISM	11,474	7.04
Insulins and analogues	2,968	1.82
Propulsives	1,052	0.65
Intestinal anti-inflammatory agents	408	0.25
Blood glucose lowering drugs, excl. insulins	357	0.22
Antiemetics and antinauseants	311	0.19
BLOOD AND BLOOD FORMING ORGANS	5, 791	3.55
Vitamin B12 and folic acid	2,657	1.63
Iron preparations	2,332	1.43
Antithrombotic agents	851	0.52
Vitamin K and other hemostatics	90	0.06
Blood and related products	39	0.02
CARDIOVASCULAR	7, 984	4.90
Agents for treatment of hemorrhoids	5,137	3.15
Beta-blocking agents	1,410	0.86
Anti-adrenergic agents, centrally acting	798	0.49
Cardiac stimulants excl. cardiac glycosides	296	0.18
Selective calcium channel blockers with mainly vascular effects	170	0.10
DERMATOLOGICALS	21, 782	13.36
Corticosteroids, plain	11,136	6.83
Compounded ointment/cream/lotion	4,937	3.03
Chemotherapeutics for topical use	2,284	1.40
Anti-acne preparations for topical use	1,970	1.21
Anti-fungals for topical use	1,674	1.03
GENITO-URINARY AND SEX HORMONES	9, 985	6.12
Anti-infectives and antiseptics, excl. combinations	3,170	1.94
Hormonal contraceptives for systemic use	2,666	1.63
Progestogens	2,244	1.38
Gonadotropins and other ovulation stimulants	2,155	1.32
Other urologicals, incl. anti-spasmodics	486	0.30
SYSTEMIC HORMONAL PREPARATIONS (excl. sex hormones)	6,593	4.04
Thyroid preparations	4,983	3.06
Corticosteroids for systemic use	1,410	0.86
Anti-thyroid preparations	186	0.11
Hypothalamic hormones	65	0.04
Glycogenolytic hormones	23	0.01

Therapeutic Category	Pregnancies Filled ≥1 Prescription	% Pregnancies
ANTI-INFECTIVES FOR SYSTEMIC USE	49,812	30.54
Penicillins	30,970	18.99
Other beta-lactam anti-bacterials	8,398	5.15
Macrolides,lincosamides and streptogramins	7,873	4.83
Other anti-bacterials	6,960	4.27
Direct acting anti-virals	2,922	1.79
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	278	0.17
Hormones and related agents	125	0.08
Immunosuppressants	65	0.04
Hormone antagonists and related agents	46	0.03
Antimetabolites	13	0.01
Immunostimulants	13	0.01
MUSCULO-SKELETAL	2,806	1.72
Anti-inflammatory and antirheumatic products, non-steroids	2,449	1.50
Muscle relaxants	483	0.30
Anti-gout preparations	21	0.01
Anti-rheumatic agents	13	0.01
Drugs affecting bone structure and mineralization	8	0.00
NERVOUS SYSTEM	20,924	12.83
Opioids	9,123	5.59
Antidepressants	7,268	4.46
Anxiolytics	5,266	3.23
Anti-epileptics	1,164	0.71
Other analgesics and antipyretics	890	0.55
ANTI-PARASITICS	232	0.14
Antimalarials	201	0.12
Antinematodal agents	29	0.02
Antitrematodals	3	0.00
RESPIRATORY	41,919	25.70
Antihistamines for systemic use	30,802	18.89
Adrenergics, inhalants	6,820	4.18
Decongestants and other nasal preparations (topical)	6,091	3.73
Other drugs for obstructive airway diseases, inhalants	3,740	2.29
Cough suppressants, excl. expectorants	1,523	0.93
SENSORY ORGANS	4,951	3.04
Anti-infectives	2,088	1.28
Corticosteroids and anti-infective combinations	1,813	0.77
Decongestants and anti-allergics	682	0.42
Anti-inflammatory agents	353	0.22
Anti-inflammatory agents and anti-infective combinations	244	0.15
VARIOUS	65	0.04
Allergens	59	0.04
Other Nutrients	5	0.00
All Other Therapeutic Products	1	0.00

Most frequently used prescription medicines in pregnancy

The twenty-five most frequently filled drugs in pregnancy, at level five of the ATC system, are presented in Table 3.6. The most commonly purchased drugs (and primary indication) were doxylamine (nausea), amoxicillin (infection), hydrocortisone (skin inflammation), codeine

(pain), cefalexin (infection) and salbutamol (asthma). Among the twenty-five most frequently used drugs, fourteen (56%) were classified as safe for use in pregnancy (FDA categories A and B), seven were classified as category C (28%) and two were classified as category D (8%). Category C indicates that studies in animals have revealed adverse effects on the fetus or that no studies in women or animals are available (Table 3.2). A sizeable proportion of pregnant women filled many of these category C drugs: hydrocortisone was used in 6.4% of pregnancies, codeine in 5.3% and salbutamol in 4.1%.

Table 3.6 Prescriptions filled in pregnancy, by generic name, top 25 by frequency of exposed pregnancies.

Generic Name	Primary Indication	FDA Category	Pregnancies Filled ≥1 Prescription	% Pregnancies
Doxylamine	Nausea	A	30,764	18.86
Amoxicillin	Infection	B	27,039	16.58
Hydrocortisone (and combinations)	Skin inflammation	C	10,487	6.43
Codeine combinations (excl. psycholeptics)	Pain	C	8,591	5.27
Cefalexin	Infection	B	6,787	4.16
Salbutamol	Asthma	C	6,754	4.14
Betamethasone	Skin inflammation	C	5,830	3.57
Erythromycin (and combinations)	Infection/Acne	B	5,458	3.35
Fluticasone	Asthma	C	5,371	3.29
Nitrofurantoin	Urinary tract infection	B	5,036	3.09
Levothyroxine sodium	Hypothyroidism	A	4,943	3.03
Misc. ointment/cream	--	Not Rated	4,937	3.03
Ranitidine	Ulcer	B	3,979	2.44
Acyclovir	Viral Infection	B	3,738	2.29
Lorazepam	Anxiety	D	3,232	1.98
Mometasone	Skin Inflammation	C	3,216	1.97
Insulin (human)	Diabetes	A	2,811	1.72
Metronidazole	Infection	B	2,757	1.69
Phenoxymethylpenicillin	Infection	B	2,625	1.61
Clindamycin (and combinations)	Infection	B	2,602	1.60
Folic acid	Prevention of neural tube defects	A	2,389	1.46
Paroxetine	Depression	D	2,361	1.45
Sulfamethoxazole and trimethoprim	Infection	C	2,122	1.30
Iron, multivitamins and minerals	--	A	2,046	1.25
Progesterone	Progesterone supplementation (IVF)	Not Rated	1,973	1.21

v) Overall drug use by maternal characteristics

Table 3.7 presents summary measures for overall prescription drug use in pregnancy by maternal age, social assistance status and plurality of pregnancy (singleton or multiple).

Table 3.7 Overall prescription drug utilization during the pregnancy period (trimesters 1 to 3), by maternal characteristics

		Among Users in Pregnancy	
Maternal characteristic	**% Pregnancies Fill ≥1 Prescription**	**Mean Days Dispensed**	**Mean Number of Different Drugs**
Maternal Age at Delivery			
<20	68.5	66.3	2.63
20-24.9	66.7	75.4	2.67
25-29.9	63.7	86.5	2.65
30-34.9	61.9	96.4	2.62
35-39.9	62.8	106.8	2.70
>=40	65.1	126.6	2.94
Social Assistance Status			
No	69.7[1]	92.0	2.64
Yes	74.6[1]	121.5	3.49
Plurality of Pregnancy			
Singleton	63.6[1]	93.2	2.68
Multiple	72.9[1]	117.8	3.23
1. Age-standardized.			

The proportion of women filling at least one prescription drug in pregnancy varied across maternal age categories with the highest proportion among teenage women under twenty years of age (68.5%), twenty to twenty-five year-olds (66.7%) and women forty years and older (65.1%). The lowest rates of prescription drug purchases were among thirty to thirty-five year olds (61.9%). Duration of exposure increased linearly with age, ranging from an average of 66 days in teenage women to 126 days in women forty and over.

Women on social assistance had higher age-standardized rates of overall drug purchases (74.7% of those social-assistance compared to 69.7% non-social assistance). After standardizing for maternal age, multiple pregnancies also had a higher rate of overall drug purchases, compared with singleton pregnancies.

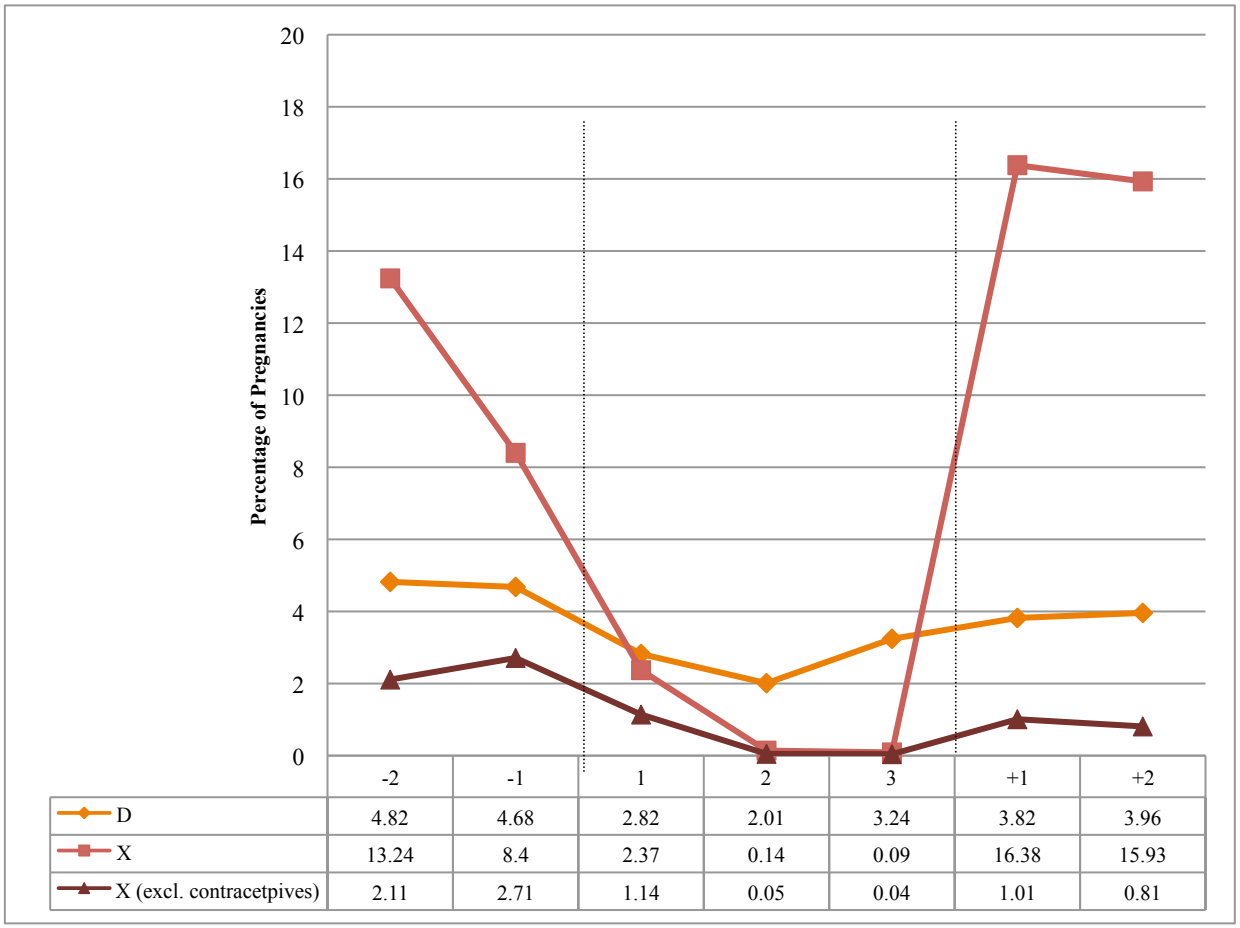
3.3.3 Prescription Drug Use with Potential for Fetal Harm

Prescription drug use with potential for fetal harm before, during and after pregnancy

Among all pregnancies in the study cohort, a prescription with potential for fetal harm (FDA category D or X) was filled in 12 676 (7.8%) pregnancies. Overall, 9 000 (5.5%) received a category D drug and 4 072 (2.5%) received a category X drug. Among those that received at least one prescription for any drug, a D or X drug was purchased in 12.2% of pregnancies, a D drug in 8.7%, and an X drug in 3.9%.

Figure 3.5 presents the percentage of pregnancies in which a prescription for a drug classified as category D, category X and category X excluding contraceptives, before, during and after pregnancy. The proportions of pregnancies in which both D and X drugs were received declined from the period six months prior to conception to the first trimester of pregnancy. Category X drug use declined the most dramatically after conception, driven largely by the discontinuation of oral and injectable contraceptives (ATC codes: G03AA, G03AB, G03AC). After exclusion of contraceptives, category X drugs were filled in only 1.2% of pregnancies. These fills were largely in the first trimester of pregnancy (1.1%). In the second and third trimesters, category X drugs excluding contraceptives were filled in only 0.05% and 0.04% of pregnancies. In contrast, the proportion of pregnancies in which a prescription was filled for a category D drug was relatively stable across the three trimesters of pregnancy and in fact, increased in the third trimester (2.8% of pregnancies).

Figure 3.5 Percentage of pregnancies in which one or more prescriptions were filled with potential for fetal harm (Category D, X, and X excluding contraceptives), by period



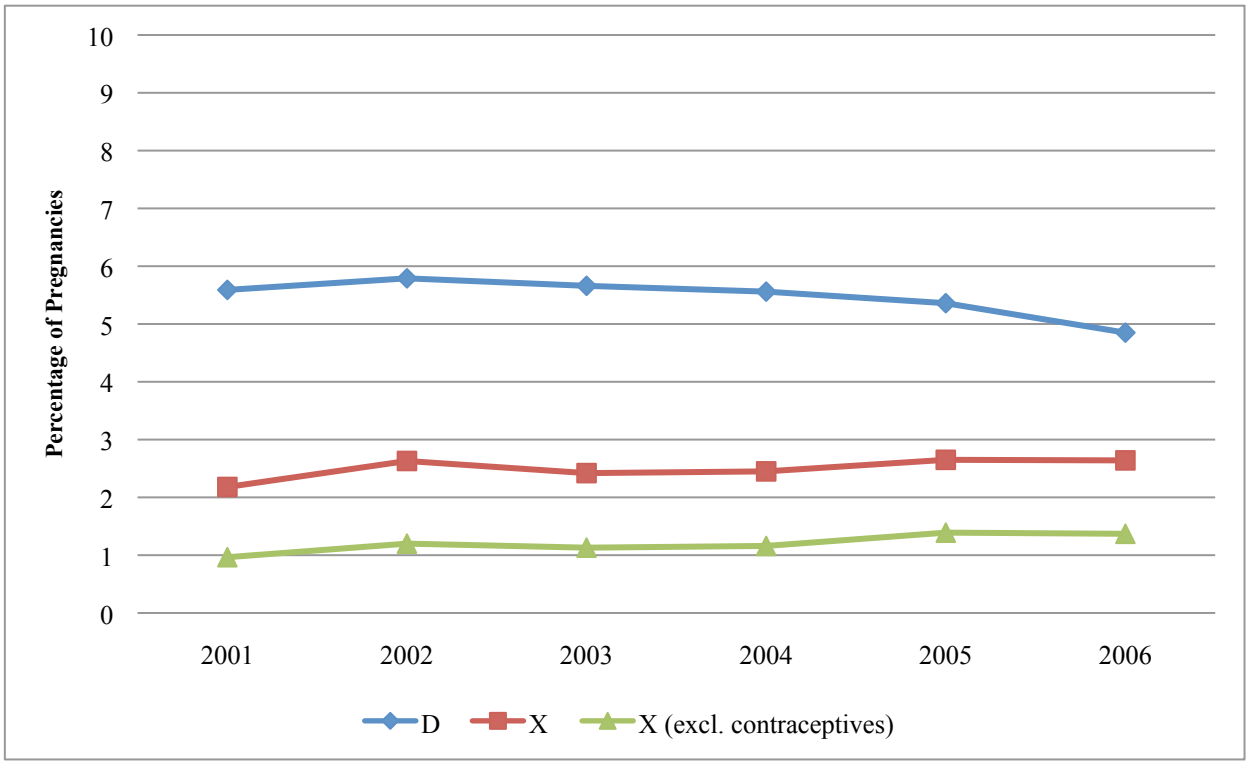
	-2	-1	1	2	3	+1	+2
D	4.82	4.68	2.82	2.01	3.24	3.82	3.96
X	13.24	8.4	2.37	0.14	0.09	16.38	15.93
X (excl. contracetpives)	2.11	2.71	1.14	0.05	0.04	1.01	0.81

Changes in prescription drug use with potential for harm over time (2001-2006)

Figure 3.6 presents the proportion of pregnancies in which a prescription was filled in pregnancy for a category D, category X, and category X excluding contraceptives, by year of delivery. We did not find a significant increase in category D or X prescriptions filled in pregnancy over the study period. In fact, there was a small decrease in the number of pregnancies that filled one or more D drugs from 5.8% of pregnancies in 2002 to 5.4% in 2005. The majority of this decline was a result of decreased used of paroxetine (likely due to advisories issued by Health Canada and the FDA during the study period). In 2006, only 4.9% of pregnancies filled a D prescription, but it is not possible to determine whether this was a real change over time or due to seasonal variations due to the incomplete data for 2006. The purchase of category X drugs during pregnancy was relatively stable over the study period. Looking only at category X drugs

excluding oral contraceptives revealed a small increase in X drug purchases from 1.2% of pregnancies in 2002 to 1.4% in 2005.

Figure 3.6 Percentage of pregnancies in which one or more prescriptions were filled with potential for fetal harm, by year of delivery



Most frequently used prescription medicines with potential for harm in pregnancy

The twenty most frequently filled category D and X prescriptions in pregnancy are presented in Table 3.8. Nearly half of all category D purchases were for benzodiazepines, among which lorazepam, oxazepam, and clonazepam were the most frequently purchased. The number of pregnancies in which a prescription for lorazepam or clonazepam was filled increased markedly in the third trimester compared to the first and second trimester, and the pre-pregnancy period. Other category D drugs filled in pregnancy included anti-depressants (paroxetine and amitriptyline), anti-epileptics (carbamezapine, valproic acid, phenobarbital and phenytoin), and tetracycline antibiotics (doxycycline, tetracycline and minocycline).

The majority of prescriptions for category X drugs in pregnancy were for contraceptives, including depo-provera/medroxyprogesterone (accounting for 48% of X drug purchases). Excluding contraceptives, the most commonly purchased X drugs were related to fertility

treatment, including clomiphene, an ovarian stimulant, and non-contraceptive forms of medroxyprogesterone, a progestin that may be used to stimulate menstruation prior to starting clomiphene or other ovulation stimulants. Medroxyprogesterone, along with conjugated estrogens and estradiol, may be be prescribed prior to in-vitro fertilization if cryopreserved embryos are used. Prescriptions for all other category X drugs, excluding oral contraceptives and drugs related to fertility treatment, were filled in only a small number of pregnancies (less than 0.5%). These drugs included benzodiazepines (temazepam and triazolam), statins, misoprostol, tazarotene and ergotamine. Over the six-year period, there were nine prescriptions for isotretinoin (accutane), a potent teratogen that is known to cause birth defects in more than 35% of infants whose mothers use the drug during pregnancy and has been subject to various programs to reduce its use among pregnant women [23, 24].

Table 3.8 Prescription medicines filled in pregnancy with potential for fetal harm, top 20 by frequency of pregnancy events in which at least one prescription was filled, by generic name and trimester

Generic Name	Primary Indication	Pregnancy (%)	1st Trimester (%)	2nd Trimester (%)	3rd Trimester (%)
Category D					
Lorazepam	Anxiety	3,232 (1.98)	858 (0.53)	755 (0.46)	1,975 (1.21)
Paroxetine	Depression	2,361 (1.45)	1,606 (0.98)	1,417 (0.87)	1,533 (0.94)
Oxazepam	Anxiety	1,222 (0.75)	166 (0.10)	167 (0.10)	962 (0.59)
Clonazepam	Seizures	516 (0.32)	345 (0.21)	218 (0.13)	230 (0.14)
Amitriptyline	Depression	427 (0.26)	299 (0.18)	136 (0.08)	141 (0.09
Doxycyline	Infection	356 (0.22)	328 (0.20)	17 (0.01)	11 (0.01)
Carbamezapine	Epilepsy/seizures	286 (0.18)	225 (0.14)	214 (0.13)	214 (0.13)
Tretinoin	Acne	232 (0.14)	161 (0.10)	65 (0.04)	35 (0.02)
Diazepam	Anxiety	164 (0.10)	114 (0.07)	45 (0.03)	38 (0.02)
Valproic Acid	Epilepsy/seizures	159 (0.10)	130 (0.08)	73 (0.04)	79 (0.05)
Tobramycin	Infection	144 (0.09)	52 (0.03)	50 (0.03)	44 (0.03)
Alprazolam	Anxiety	135 (0.08)	93 (0.06)	40 (0.02)	44 (0.03)
Propylthiouracil	Graves' disease	135 (0.08)	96 (0.06)	82 (0.05)	48 (0.03)
Tetracycline	Infection	133 (0.08)	119 (0.07)	11 (0.01)	7 (<0.01)
Atenolol	Hypertension	112 (0.07)	68 (0.04)	51 (0.03)	56 (0.03)
Minocycline	Infection	101 (0.06)	95 (0.06)	6 (<0.01)	1 (<0.01)
Phenytoin	Epilepsy/seizures	70 (0.04)	51 (0.03)	50 (0.03)	56 (0.03)
Phenobarbital	Epilepsy/seizures	68 (0.04)	38 (0.02)	36 (0.02)	44 (0.03)
Methimazole	Graves' disease	57 (0.03)	40 (0.02)	29 (0.02)	24 (0.01)
Lithium	Bipolar depression	56 (0.03)	46 (0.03)	26 (0.02)	30 (0.02)
TOTAL D		**9000 (5.51%)**	**4606 (2.82%)**	**3279 (2.01%)**	**5281 (3.24%)**
Category X					
Oral Contraceptives	Contraception	1,939 (1.19)	1,839 (1.13)	101 (0.06)	66 (0.04)
Clomiphene	Infertility	1,071 (0.66)	1,064 (0.65)	6 (<0.01)	2 (<0.01)
Estradiol	Infertility	408 (0.25)	407 (0.25)	0	1 (<0.01)
Medroxyprogesterone	Menopause	276 (0.17)	266 (0.16)	11 (0.01)	1 (<0.01)
Medroxyprogesterone	Contraception	201 (0.12)	185 (0.11)	46 (0.03)	11 (0.01)
Temazepam	Insomnia	98 (0.06)	65 (0.04)	28 (0.02)	28 (0.02)
Estrogens, conjugated	Menopause	35 (0.02)	17 (0.01	15 (0.01)	10 (0.01
Misoprostol	Ulcers	29 (0.02)	23 (0.01)	4 (<0.01)	2 (<0.01)
Atorvastatin	Hypercholesterol-emia	20 (0.01)	19 (0.01)	1 (<0.01)	2 (<0.01)
Tazarotene	Acne	19 (0.01)	14 (0.01)	3 (<0.01)	2 (<0.01)
Triazolam	Insomnia	18 (0.01)	9 (0.01)	3 (<0.01)	7 (<0.01)
Leuprolide	Endometriosis	16 (0.01)	16 (0.01)	0	0
Warfarin	Thromboembolic disease	13 (0.01)	9 (0.01)	1 (<0.01)	3 (<0.01)
Dihydroergotamine	Migraines	12 (0.01)	11 (0.01)	1 (<0.01)	2 (<0.01)
Ergotamine	Migraines/labour induction	11 (0.01)	11 (0.01)	1 (<0.01)	0
Methotrexate	Ectopic pregnancy	10 (0.01)	9 (0.01)	1 (<0.01)	1 (<0.01)
Isotretinoin	Acne	9 (0.01)	9 (0.01)	0	0
Simvastatin	Hypercholesterol-emia	6 (<0.01)	1 (<0.01)	3 (<0.01)	2 (<0.01)
Quinine	Malaria	5 (<0.01)	4 (<0.01)	0	1 (<0.01)
Flourouracil	Cancer	2 (<0.01)	1 (<0.01)	0	1 (<0.01)
TOTAL X		**4072 (2.50)**	**3858 (2.37)**	**223 (0.14)**	**142 (0.09)**
TOTAL X (excluding contraceptives)		**1959 (1.20)**	**1858 (1.14)**	**76 (0.05)**	**66 0.04)**

Prescription drug use with potential for fetal harm by maternal characteristics

Summary measures for category D and X prescription drug use in pregnancy by age, social-assistance status, and plurality are presented in Table 3.9. Older women (over 40) and younger women (under 20) had higher rates of D and X drug purchases as compared to women aged 20 to 39. The specific D and X drugs filled during pregnancy were similar among these two age groups with lorazepam, paroxetine, oxazepam, and oral contraceptives all among the top five D and X drugs in both age groups in terms of the percentage of pregnancies that filled one or more prescription. Older women, however, did have exposures to fertility treatments not found in the younger age group, namely clomiphene (the second most commonly used D or X drug in women over 40) and estradiol.

Table 3.9 Drug utilization with potential for harm (category D and X) during the pregnancy period (trimesters 1 to 3), by maternal characteristics

Maternal characteristic	% Pregnancies Filled ≥1 D or X Prescription	% Pregnancies Filled ≥1 D Prescription	% Pregnancies Filled ≥1 X Prescription	% Pregnancies Filled ≥1 X Prescription excluding contraceptives
Maternal Age at Delivery				
<20	9.8	5.81	4.42	0.38
20-24.9	8.8	6.12	3.22	0.54
25-29.9	7.72	5.43	2.51	1.05
30-34.9	6.99	5.12	2.04	1.21
35-39.9	7.69	5.67	2.25	1.54
>=40	10.3	7.06	3.83	3.36
Social Assistance[1]				
No	8.29	5.85	2.68	1.33
Yes	18.1	14.6	4.89	1.34
Plurality[1]				
Singleton	7.81	5.58	2.47	1.13
Multiple	13.4	6.93	7.01	6.41

1. Age-standardized.

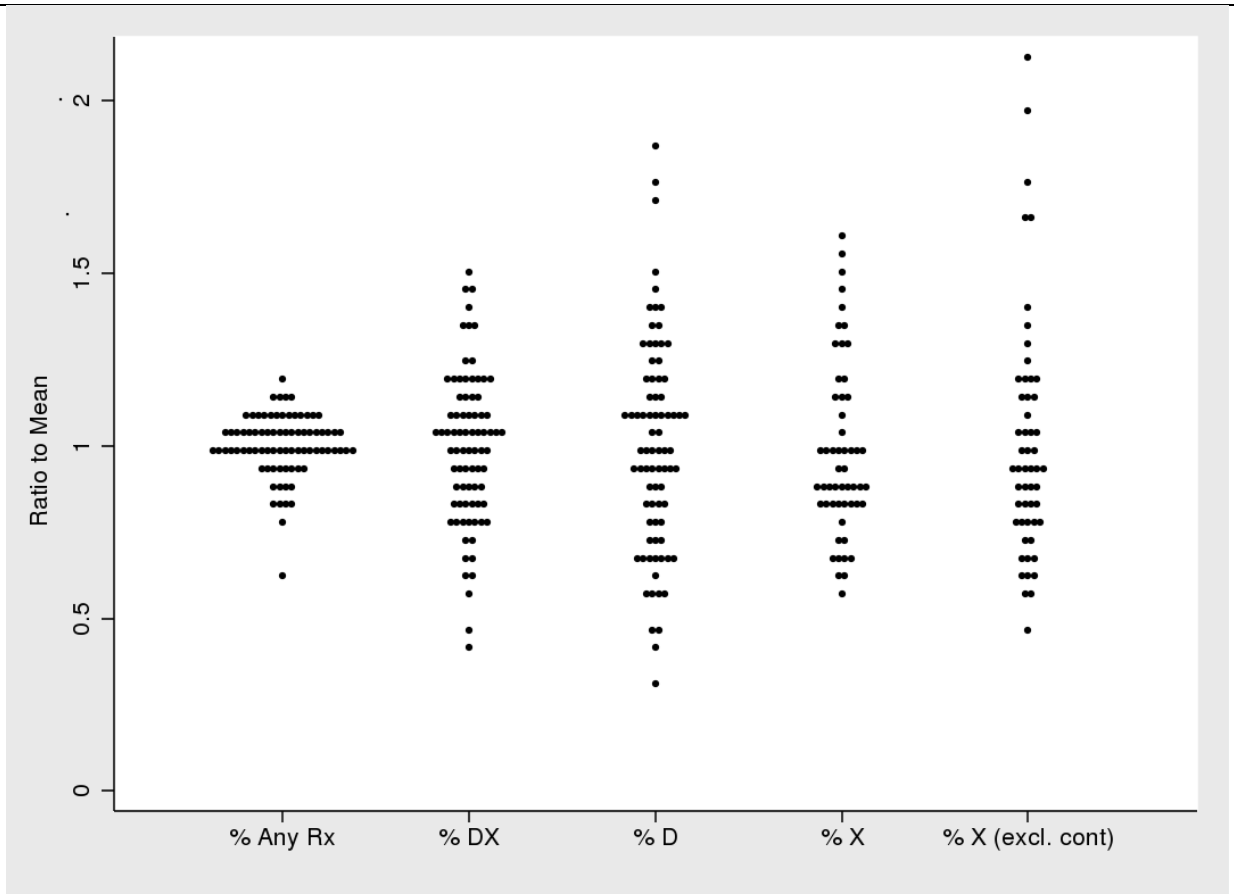
After standardizing for maternal age, women on social assistance had more than double the rate of prescriptions filled with potential for fetal harm (18.2% of pregnant women on social-assistance filled a prescription for a D or X drug, compared to 8.3% for those not on social assistance). However, little difference in the use of category X drugs excluding contraceptives was found based on social assistance status. Multiple pregnancies also had a higher rate of potentially harmful drug purchases compared to singleton pregnancies.

3.3.4 Regional Variations in Overall and Potentially Harmful Prescription Drugs Used In Pregnancy

Figure 3.7 presents the distribution of age-adjusted rates and statistical measures of variation for overall and potentially harmful drugs filled in pregnancy by LHA of maternal residence. After accounting for maternal age at delivery, among the 80 LHAs with at least 125 deliveries in the study period, overall drug use ranged from 39.6% in Arrow Lakes to 72.4% in Prince Rupert (CV% = 8.85). The proportion of pregnancies that filled prescriptions for drugs with potential for harm (category D or X) ranged more than three-fold from 3.3% in Armstrong-Spallumcheen to 12.0% in Summerland. The widest variation was found in the proportion of women who filled at least one category D drug (CV%=30.69) and at least one category X drug excluding contraceptives (CV%=34.62). We found the lowest rates of overall and potentially harmful prescription drug use tended to be among LHAs within the Vancouver Coastal Health Authority. The rates of overall and potentially harmful drug use for all 89 local health areas are presented in Appendix C.

Variation in category X drug use excluding contraceptives is of particular concern as there is no rationale for the use of these medicines in pregnancy. Variations in category D drug use suggest that providers in some regions have a higher propensity to consider maternal benefit to outweigh fetal risks associated with these drugs. Without information on maternal health status or the presence of conditions that may warrant or require treatment with category D drugs in pregnancy, it is not possible to ascertain whether in some regions these variations are based on maternal health need or if they reflect real variations in the appropriateness of care received in pregnancy.

Figure 3.7 Distribution of age-adjusted rates and statistical measures of variation for overall and potentially harmful drugs filled during pregnancy, by local health area of maternal residence (category D, X and X excluding contraceptives).



Mean	0.619	0.079	0.055	0.027	0.012	
Minimum	0.396	0.033	0.018	0.016	0.005	
Maximum	0.724	0.120	0.101	0.043	0.026	
Extremal Ratio	1.83	3.62	5.69	2.71	4.68	
IQ Ratio	1.09	1.37	1.52	1.39	1.52	
CV %	8.85	21.92	30.69	25.44	34.62	

3.4 Discussion

The objective of this population-based study was to describe prescription drug utilization before, during and after pregnancy in the Canadian province of British Columbia. We found the majority of pregnant women filled at least one prescription for any drug and approximately 1 in 12 filled a prescription for a drug with potential risks in pregnancy. The proportion of women filling prescriptions overall, and prescriptions with established risks, differed by maternal

characteristics, namely age, social assistance status and plurality of pregnancy. There was little variation in the use of prescription drugs during pregnancy across local health areas in British Columbia.

3.3.1 Contextualizing our findings: previous drug utilization studies

Overall drug use

The estimate of overall prescription drug utilization found in this study (63%) is higher than two other published estimates of overall prescription drug use in pregnancy in Canadian populations. Our estimated rate is nearly double the rate found in a study of the 2001-02 cycle of the National Longitudinal Survey of Children and Youth, where only 27% of sampled pregnant women reported prescription drug use during their pregnancies, ranging from 22% in Ontario and 26% in British Columbia to 37% in New Brunswick [8]. Given the reliance on self-report and the fact that survey interviews could occur up to one year after pregnancy, these differential rates are likely driven by poor maternal recall of drug exposures and a social desirability bias supporting greater likelihood of under-reporting of drug consumption. In studies comparing medical charts to maternal self-report, distant recall of medical interventions received in past pregnancies, including prescription drugs, has been found to be poor [25, 26].

Our estimates of overall drug use are comparable to what was reported in a recent study in Quebec that found at least one prescription was filled in 56% of pregnancies from 1998 to 2002 [6]. This study analyzed prescription drug claims for women enrolled in Quebec's public insurance program, the RAM-Q, which provides coverage for individuals on social assistance or those who do not have access to a private health insurance plan. It is difficult to compare our findings, based on the entire population of BC, with those from the Quebec study, because the latter includes only the low-income population accounting for 35% of women aged 15-45. A recent study, looking at the differences between the RAM-Q and privately insured populations in Quebec, found differences in reported medication use in the first trimester: 22% of women enrolled in RAM-Q reported use, compared to 30% of privately-insured women. Women enrolled in RAM-Q were also younger, more likely to be primiparous, an immigrant, and of non-Caucasian ethnicity – all factors which may influence the utilization of prescription drugs.

Comparing our findings to international studies of drug utilization in pregnancy using administrative claims databases and excluding vitamins and minerals, the proportion of pregnancies in which at least one prescription was filled in BC (62.8% of pregnancies) is similar to a recent American study that found 64.0% of pregnancies filled at least one prescription (1996-2000) [1], but slightly higher than what has been found in Nordic countries, including estimates of 46.8% of pregnancies in Denmark (1991-1998) [7], 46.2% in Finland (1999) [4] and 57% in Norway (2004-2006) [27]. Our estimates of overall utilization are lower, however, than most findings in Western Europe, including estimates of 69.2% in the Netherlands (1995-2001) [28], 85.2% in Germany (2000-2001) [29] and 93% in France (2004-2005) [3].

This study provides clear evidence of a change in prescription purchases in response to pregnancy. Prescriptions filled for any drug and for drugs with known harms decreased in pregnancy compared to both the period prior to conception and post-partum. This decrease is likely a result of two phenomena: a change in provider's prescribing practices, and/or a form of risk aversion where pregnant women choose not to fill prescriptions. A Canadian study on the perception of risk based on the label of a commonly used anti-nauseant drug found that pregnant women and their partners often believe a drug is harmful to the fetus even after it has been described to them as safe [30]. This perception may lead to a decreased propensity to fill prescriptions in pregnancy.

Some authors have raised concerns that prescription drug use in pregnancy may have been rising in recent years as a result of general population-wide increases in prescription drug use, the rising mean maternal age and the increased incidence of chronic disease in women of childbearing age [6, 31]. However, we did not find a significant increase in the proportion of women filling at least one prescription or in the mean number of drugs used over the study period from 2001 to 2006.

Drug use with potential for harm

Our findings on the use of drugs with potential for fetal harm are similar to previous studies of prescription drug use in pregnancy in Canada using comparable pharmacy claims databases and measurement techniques. We found 7.7% of women used category D and X drugs (5.5% and 2.5%, respectively). In Saskatchewan, 5.2% and 3.9% of pregnant women were found to have used category D or X drugs from 1997-2000 [9]. Of pregnant women enrolled in Quebec's

public drug insurance program, 56% of pregnant women filled at least one prescription drug in pregnancy and 6.3% filled a drug known to pose a risk to the fetus from 1998 to 2002 (based on a list of medications identified by the authors) [6].

Rates of exposure to FDA category D and X drugs in our study and other Canadian studies mentioned above were similar to those described in recent international studies using pharmacy claims databases and the FDA risk classification system. In the United States, from 1996 to 2000, Andrade et al. found 4.8% and 4.6% of women filled a category D and X drug, respectively, in the 270 days prior to delivery, and 3.4% and 1.1%, after the initial prenatal care visit [32]. Malm et al. found 3.5% of pregnant women in Finland were prescribed a drug with clear harms in 1999 (according to three international risk classification systems including the FDA system) [33]. In Italy, Gagne et al. found 2% and 1% of women used a category D and X drug in 2004, respectively (according to the FDA or Australian classification system) [5]. In contrast, a study from France in 2000, found 59% of women used a category D drug and 1.6% received a category X drug [34].

The differences in estimated rates of prescription drug use found between studies should be interpreted with caution. The methods used to study drug utilization in pregnancy, even among those using similar administrative databases, vary widely. For example, studies may use different assumptions about the length of gestation and delivery date, may classify prescription drugs differently or include vitamins and minerals. Estimates are also influenced by the inclusion of prescription drugs in a given claims database, for example, if information is only recorded for reimbursed prescriptions or if drugs commonly available over-the-counter in some jurisdictions are regularly prescribed in others.

3.3.2 The use of drugs with potential for harm during pregnancy in BC

The prescription of drugs that are contraindicated in pregnancy (category X drugs) appears to be minimal in British Columbia. Excluding contraceptives, prescriptions for a category X drug were filled during the second and/or third trimester in only 127 pregnancies over the six-year study period. Given the very low rates in the second and third trimester, the approximately 1% of pregnancies that filled an X drug prescription in the first trimester was likely a result of unknown pregnancy. Our results suggest that once a pregnancy has been identified, providers are rarely

prescribing drugs that are contraindicated in pregnancy (or women are rarely purchasing these prescriptions).

However, some of the utilization of category D drugs in pregnancy in British Columbia may be inappropriate. Category D drugs have known risks, but these risks may be less severe, occur less frequently or the current state of the evidence may be more controversial or less clear than for Category X drugs. Additionally, in light of potential maternal benefit, the risks associated with the use of a given category D drug may be considered acceptable to both a provider and a pregnant woman. We found that category D drug use was largely comprised of prescriptions for anti-depressants (paroxetine and amitryptiline) and benzodiazepines. Interestingly, while the prescription of many category D and X drugs markedly declined across the pregnancy period, the proportion of women filling a prescription for a benzodiazepine or paroxetine stayed relatively stable, and for lorazepam, prescription fills increased in the third trimester. Qualitative inquiry into the counseling process that results in the decision to use these drugs in pregnancy is warranted. Understanding the context of the counseling process would assist in determining whether programs or tools to assist providers and patients in making an informed decision about the use of these drugs are needed.

It appears that drugs considered contraindicated in pregnancy (e.g. classified as category X) are rarely prescribed during pregnancy. For many category D drugs, risks have been found, but it may still be unclear how providers should be incorporating that risk information into practice: when is the use of this drug appropriate? What other options are available (pharmacological and non-pharmacological)? In addition to identifying risks, research on the safety of medicines in pregnancy needs to contextualize those risks, in light of alternatives and probabilities for harm. This may require rigorous comparative safety research of different drug options within a class (for example, within benzodiazepines), compared to placebo and, if available an alternative therapeutic option.

3.3.3 The role of maternal characteristics: age, parity, social assistance and region.

We found that women on social assistance had higher age-adjusted rates of overall and high-risk drug use in pregnancy. These rates should be interpreted with caution given that 9% of pregnancies without a prescription record could not be classified. We cannot determine if these non-users belong to the social assistance or non-social assistance group.

Few studies have examined the socio-economic determinants of overall and potentially harmful prescription drug use in pregnant populations. However, the limited evidence suggests that women of lower socio-economic status may be more likely to use prescription drugs in pregnancy. In Saskatchewan, adjusted for age, parity, and chronic disease score, women on social assistance were 93% more likely to use a category C, D, or X drug than women not on social assistance [35]. Younger women (<25 years) were also more likely to use category C, D, or X drugs compared to women thirty and over (adjusted OR: 1.20; 1.08, 1.34). In Denmark, increased maternal household income and higher maternal and paternal education level were associated with decreasing overall medication use in pregnancy [7]. The strength of this relationship varied by therapeutic categories. Estimates from the US have found higher rates of unintended pregnancies among younger, less-educated and low-income women, suggesting that inadvertent exposure may partly explain these findings [36]. Further research on the determinants of drug use in pregnancy and lactation is needed to identify populations that may be more vulnerable to exposures to drugs with known harms and determine whether maternal socio-demographics are related to the appropriateness of care received in pregnancy.

The small area variations in overall and potentially harmful drug utilization in pregnancy found in this study are larger than those found for overall drug use among LHAs in British Columbia for the general population. In the 2006 British Columbia Rx Atlas, little variation was found in the rates of use of at least one prescription in 2006 after adjusting for age, sex, and health status [21]. Comparing our findings to health services variations literature in the United States, variations in overall use are of similar magnitude to those found in pharmaceutical spending among hospital referral regions for seniors enrolled in Medicare Part D in 2007 after adjusting for individual-level demographics (IQ Ratio: 1.11, CV%: 8.0) [37]. We found five and four-fold differences from the lowest to highest LHA in the proportion of pregnancies exposed to a category D and category X excluding contraceptives, respectively. These extremal ratios are higher than variations found in overall medicare spending in the United States considered to reflect large variations in the quality of health care received across the country (two-fold variations in Medicare spending among hospital referral regions in the United States) [38]. Our findings are also similar findings from the United States that identified high variability among eight common surgical procedures in 1994-95 after controlling for age, race, and sex. (IQ Ratios ranging from 1.21 for colectomy to 1.62 for radical prostatectomy) [39].

The proportion of regional variation in antenatal prescribing practices that are not driven by differences in maternal health needs reflect the magnitude of the opportunity to improve the quality of prescribing during pregnancy. For example if the provincial rate of category X drugs excluding contraceptives was 0.05% (the minimum rate among LHAs), that would translate into 1,142 fewer pregnancies exposed to these medicines over the period of study from April 2001 to June 2006. If the provincial rate of category D drug use was 1.8%, that would translate into 6,035 fewer pregnancies exposed to a category D drug over the study period.

Given our results, further exploration of regional variations in the appropriateness of drug use during pregnancy is warranted. Ideally, such an analysis should take into account maternal health status or diagnoses that may indicate the use of specific drugs with potential for harm in pregnancy. Further, investigation of drug use by therapeutic class may help to elucidate whether differences exist in the content of antenatal prescribing across regions.

3.3.4 Priorities for observational research

We found that many of the most commonly used drugs in pregnancy were categorized as category C by the FDA risk classification system. For example, hydrocortisone, codeine, salbutamol, fluticasone and betamethasone were all among the most frequently used drugs. Category C refers to drugs for which animal studies have shown an adverse effect on the fetus, or there are no adequate well-controlled studies in humans. Indeed, because most marketed drugs have not been studied in pregnant populations, nearly half of classified prescription drugs are assigned to category C (Table 3.10). Clarifying the risks associated with frequently used category C drugs and communicating those risks in context with potential benefits and a consideration of alternative therapies (both pharmacological and non-pharmacological) should be a priority for observational research. Ideally, no drug that is widely used by pregnant women should be categorized as having unknown risks.

Table 3.10 Drugs classified by the US Food and Drug Administration according to risk category, 2000 [40].

Pregnancy Risk Category	Number of Drugs (%)
A	27 (4)
B	148 (23)
C	291 (45)
D	143 (22)
X	36 (6)

3.5 Conclusion

The widespread use of prescription drugs found in our study highlights the need to further understand the risk profiles of medications used during the pregnancy period. The use of drugs that are contraindicated in pregnancy appears to be minimal in British Columbia. However, the use of some medicines with potential for harm (category D) may be of concern. Further study of the appropriateness of the use of these medicines in pregnancy, including their safety and effectiveness compared to safer therapeutic equivalents should be pursued. Drugs that are most commonly used in pregnancy but for which safety has not yet been established may have unknown public health impacts. Clarifying the risks associated with these drugs should be a priority for pharmacoepidemiological research.

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4 Conclusions

4.1 Summary of Findings

This thesis had two primary aims: to synthesize published antenatal drug utilization studies, and to provide comprehensive information on drug utilization during pregnancy in a Canadian population. These aims were pursued through two distinct studies: 1) a systematic review of drug utilization studies published from 1989 to 2010, and 2) a population-based study of prescription drug utilization using administrative datasets in the province of British Columbia.

In the systematic review, we reviewed 17 published studies reporting prescription drug exposures in pregnancy among women residing in OECD countries. We found that estimates of prescription drug use in pregnancy vary widely. Differing data sources for exposure ascertainment (e.g. maternal self report compared to administrative pharmacy claims databases) and the inclusion of vitamins and minerals appear to be the primary methodological sources of heterogeneity among reported estimates of drug utilization in pregnancy. Comparisons among estimates should be done with caution and only among studies using similar methodologies and classification of prescription drugs.

Comparing studies with similar measurement techniques and excluding vitamins and minerals, estimates of exposure ranged from 44.2% to 93.0% of pregnancies. Exposure estimates varied across countries. Nordic countries (including Denmark, Finland and Norway) had the lowest range of estimated use from 44.2% to 57%. Similar studies in the US and Canada found that prescriptions were used in 64% and 56% of pregnancies, respectively. Studies in Germany and France reported the highest prevalence of prescription drug use in pregnancy, with 85.2% in Germany and 93% in France. Among comparable studies, the most commonly used drug classes in pregnancy were systemic antibiotics, analgesics, anti-emetics and anti-asthmatics. The most commonly reported drugs with potential for harm used by pregnant women included benzodiazepines, tetracyclines, NSAIDs in the third trimester, older anti-epileptics, statins, contraceptives, ovulation stimulants, estradiol and retinoids.

The systematic review highlighted the need to establish ‘gold standard’ methods and a consistent reporting framework for antenatal drug utilization studies. To stimulate discussion, we provided suggestions for both of these purposes, including a list of components to be considered in

designing a high-quality antenatal drug utilization study and a checklist for methods reporting. Establishing consistency in the methods used to ascertain drug use and discipline in reporting exposure estimates is essential to ensuring drug utilization studies provide information that is relevant to policymakers, health care providers and other researchers.

In the second study, we analyzed prescription drugs purchased by pregnant women in the community setting for all pregnancies ending in a live birth in a British Columbia hospital from 2001 to 2006. We found that prescriptions were filled in 63% of pregnancies. This finding is comparable to two similar studies conducted in Quebec and the United States. We did not find a significant increase in the use of drugs in pregnancy over the study period.

The most commonly used medicines in pregnancy were systemic anti-infectives, respiratory drugs, dermatologicals and drugs acting on the nervous system. Many of the most commonly used drugs in pregnancy were categorized as category C by the FDA risk classification system, for example, hydrocortisone, codeine, salbutamol and fluticasone. Investigation of the risks associated with frequently used category C drugs identified in this study should be a priority for future observational research.

We found that at least one drug classified as FDA category D or X was filled in 7.8% of pregnancies (5.5% and 2.5% category D and X, respectively). The most frequently prescribed category D and X drugs were benzodiazepines, anti-depressants, oral contraceptives, and drugs related to fertility treatment. Excluding oral contraceptives, the prescription of category X drugs in pregnancy was minimal. However, there may be room for improvement in relation to the prescription of category D drugs in pregnancy in BC – the majority of these were for benzodiazepines and antidepressants.

We found that the use of any prescription drug and the use of drugs with potential for fetal harm varied by maternal age, social assistance status and plurality of pregnancy. We identified levels of variation in utilization rates across local health areas in BC that deserve further exploration.

4.2 Strengths and Limitations

4.2.1 Systematic Review

The systematic review reported in this thesis is, to our knowledge, the only review of antenatal drug utilization studies since the one published in 1990 by Bonati and colleagues. Our review provides an updated synthesis of the literature in this field. We draw meaningful comparisons across studies by taking into account differences in methodologies and suggest recommendations for future antenatal drug utilization studies.

Our review is the first true review of antenatal *prescription* drug utilization studies. Unlike the previous review by Bonati and colleagues, we excluded studies that did not provide estimates that differentiated between prescribed and over-the-counter medications. The lack of stratification of prescription and non-prescription drugs makes it difficult to compare studies and limits the usefulness of the study findings to decision makers. Programs aimed at improving the rational use of over-the-counter medicines may be designed differently than those for prescription medicines. For example, high-risk over-the-counter use may be best targeted through improved product labeling, whereas high-risk prescription use may be addressed through improved information tools to assist health care providers counsel pregnant women on medications. We designed our systematic review so as to ensure that exposure estimates included only prescription medicines.

Our systematic approach to reviewing the literature had several strengths. We developed a review protocol *a priori* and conducted the review accordingly. The protocol outlined the research question, inclusion and exclusion criteria and search strategy. A Master's trained information specialist conducted and documented literature searches of relevant databases. Two independent reviewers completed the study selection process. The data abstraction form was developed and piloted on three studies prior to being applied to all included studies. A minimum of two independent reviewers completed data abstraction for each study and any discrepancies were resolved by consensus. We reported the methods of the review according to the PRISMA statement for reporting systematic reviews [1].

Our approach was not without limitations. In this review, we limited our search strategy to studies published in English. In doing so we may have excluded relevant drug utilization studies

published in other languages. In addition, we limited searches to published peer-reviewed literature. This may have resulted in the exclusion of non-published reports, book or theses. The rationale for including non-published material in reviews is usually based on concerns of publication bias – the bias towards the publication of positive findings. However, because drug utilization studies are descriptive and do not test a hypothesis, we did not suspect that publication bias would be a significant concern in this context. Rather, the greater concern was that unpublished findings not subject to peer-review may use less-rigorous methods and be more prone to bias. Finally, we chose not to calculate pooled estimates of exposure across studies due to the considerable heterogeneity in study methodologies. Our synthesis of research findings was thus limited to reporting the range of estimates among similar studies.

4.2.2 Population-based study

The empirical component of this thesis comprises the first study of antenatal drug use by trimester and therapeutic category in Canada. We provided comprehensive information on drugs prescribed overall, by therapeutic category, and by fetal risk classification before, during, and after pregnancy. Our approach had several strengths. In this study, we captured all prescription drugs dispensed in the community setting over the study period, irrespective of reimbursement. We relied on prescription drug claims, rather than maternal self-report, avoiding maternal recall and social-desirability biases. The population-based design avoided potential selection bias introduced by sampling from a single centre, small geographical area or based on enrolment in a specific health insurance plan. By using the gestational age recorded on hospital birth records, we avoided making assumptions about the length of pregnancy (i.e. assuming a 270-day full-term gestation). By examining trends before and after pregnancy, we could identify changes in drug utilization patterns across the pregnancy period.

This study also has limitations that should be considered when interpreting the results. Like all studies using administrative databases, records may be subject to some degree of coding error. In addition, we excluded women with a maternal length of stay greater than 7 days. While this was necessary to ensure accurate construction of the pregnancy period and only applied to a small proportion of pregnant women (1.8%), it may bias our sample towards healthy pregnancies. In turn, we may underestimate drug exposures, given that women with long hospital stays may be more likely to have chronic health conditions or to have experienced other complications in pregnancy that may have required medication.

The exclusion of pregnancies not ending in a live birth, including stillbirths, spontaneous and therapeutic abortions is common in many studies of drug use in pregnancy. This is primarily due to the limited data available for the study of these pregnancies. However, this approach is not ideal and may result in the underestimation of exposures, particularly for potential teratogens. This an especially important consideration for pharmacoepidemiological studies, which risk failing to detect important safety concerns by excluding women with what may be an outcome of interest. In Canada, the development of pregnancy registries for all pregnant women regardless of outcome, similar to the registries in Quebec or various European countries, would expand the research possibilities in this field, and could allow for the identification of risk modifiers and longer-term effects. For example, the Swedish Medical Birth Registry, a national population based registry, continually monitors drug exposure data and maternal-infant health outcomes for the entire pregnant population of Sweden [2].

To classify the risks of drugs used in pregnancy, we used the FDA risk categories, one of several international risk classification systems for drugs in pregnancy and lactation. This system has been criticized for simplifying risk statements limiting the usefulness of the risk categories to prescribers who must treat a diverse patient population [3-5]. Because of the crude nature of these categories, not all use of drugs classified as category D and X identified in this study can be considered inappropriate. In some cases, these drugs may have been appropriately used in pregnancy after consideration of the potential benefits of treatment relative to the potential risks.

Despite these limitations, the use of a risk classification system has advantages and is common practice in antenatal drug utilization studies. In addition to product labeling, these systems are the prevailing means used to communicate risk information to providers. The FDA categories are explained and referred to in Canadian clinical practice guidelines related to prescribing in pregnancy [6]. These systems allow researchers to easily identify and monitor the use of prescription of drugs with known risks and improve comparability across drug utilization studies.

It is important to differentiate between prescribing, dispensing, and utilization of medications [7]. In our study, we used data on prescriptions filled by women during the study period. Because women may not purchase all prescriptions for drugs they are prescribed and may not consume all drugs they purchase, our study results will underestimate prescribing and

overestimate utilization. The extent to which we overestimate utilization is likely to vary across therapeutic categories. In a Danish study of drug compliance in pregnancy, the majority of women who filled a prescription for a drug indicated for the treatment of a chronic condition reported actually consuming the medicine in pregnancy (ranging from 80% for antidepressants to 100% for insulin), however, lower rates of reported use were found for medications indicated for acute conditions (ranging from 12% for opthalmologicals to 77% for analgesics) [8].

4.3 Recommendations for future research and initiatives to improve the rational use of medicines in pregnancy

The health of mothers is of critical importance, both as a reflection of the current health status of the Canadian population and the health of future generations. Delivering the evidence required to ensure that medicines are used to maximize health during this period and ensuring that women are not unnecessarily exposed to medicines that may cause harm is a public health imperative. Below, we provide recommendations for future research, and considerations for initiatives aimed to improve the rational use of medicines in pregnancy.

4.3.1 Recommendations for drug utilization research

Methods development and statement on reporting in antenatal drug utilization studies

Several antenatal drug utilization studies have been conducted over the past fifty years and while these studies aim to answer the same research question (what drugs are being used during pregnancy?), no standard framework for conducting these studies or reporting methods and results has emerged. In section 2.3 of this thesis, we provide suggestions for issues that should be considered in developing a gold-standard method for antenatal drug utilization studies. In addition, we provide a list of reporting items that could be used to formulate a statement on reporting of antenatal drug utilization studies, similar to statements that exist for other types of observational research (for example, the STROBE guidelines). Researchers in this field should consider collaborating on the development of these guidelines, ideally involving relevant knowledge users, so as to ensure that drug utilization research provides consistent, useful information for the research, policy, and clinical communities.

Development of advanced measures of drug utilization

Measurement of drug use in pregnancy using pharmacy claims databases has been limited to counts of the frequency of exposures, usually measured as whether or not a prescription for a drug was filled with a given period. The development of more complex measures of drug use such as adherence, persistence, or consideration of the timing of pregnancy recognition (e.g. after the first prenatal care visit) may allow for a more detailed picture of exposure for drugs of particular interest. Considering prior patterns of drug use and analyzing individuals who stop, switch, or continue prior drug regimes in pregnancy may be useful for measuring the appropriateness of use within particular drug classes or for certain maternal conditions. For example, such an approach would facilitate monitoring of the switch from oral hypoglycemics to insulins (the safer alternative in pregnancy) among diabetic women after pregnancy recognition.

Identification of the determinants of overall and potentially harmful drug use

In this study, we found that rates of overall and potentially harmful drug use varied by age and social assistance status. We had limited available data on maternal characteristics in our database. The linkage of the databases used in this study to BC's Perinatal Registry, which contains detailed information on maternal socio-demographic characteristics, prenatal care, health status and history of previous pregnancy complications and outcomes, could allow for a more detailed exploration of the determinants of pharmaceutical use in pregnancy than was possible in this study [9]. An analysis of variations in prescription drug utilization in relation to the characteristics of the prescribing provider (e.g. provider age and specialty) may also provide useful information for targeting programs aimed to improve appropriate prescribing.

4.3.2 Recommendations for pharmacoepidemiological research

Observational study of commonly used drugs with unknown risks in pregnancy

Maternal-fetal pharmacoepidemiology is an orphan field [10, 11]. Given the limited number of studies conducted and scarce research dollars – the priorities for this research should be informed by drug utilization studies such as the one presented in this thesis. We identified several drugs that are frequently used by pregnant women but yet are categorized as having unknown harms in pregnancy or having only animal evidence suggesting risk in humans. If harms were identified,

these are the drugs that would have the most significant public health impact. Thus, the establishment of the short and long-term safety of these medicines should be a priority for observational research. Because the most commonly used medicines may change over time, drug utilization in pregnancy should continue to be monitored in order to identify new drugs with inadequate safety information that may be increasingly used in pregnancy.

Observational study to compare therapeutic equivalents for specific maternal conditions

For some maternal conditions, the use of medicines cannot be avoided. In these cases, observational research may help to identify the therapeutic option (pharmacological or non-pharmacological) that is most effective and carries the least potential for harm if used in pregnancy. The use of drugs with known risks is currently driven by a few specific therapeutic classes (e.g. benzodiazepines and antidepressants). The number of women who are taking these medicines suggests that women and providers are considering maternal benefit to be greater than the potential risks to the fetus; however, this decision may not be based on high-quality evidence. Observational research should attempt to clarify both the safety *and* effectiveness of these medicines, including comparative studies within a given class. Comparison to non-pharmacological alternatives, if available, should also be pursued.

4.3.3 Recommendations for initiatives to promote the rational use of medicines in pregnancy

Reducing exposures to potentially harmful drugs is of critical importance for everyone, but of particular salience for pregnant women. The use of these drugs may lead to termination of wanted pregnancy and short or long-term health effects for mother and/or child. When considering interventions to reduce exposure to drugs with known potential for harm, it is useful to consider the clinical contexts in which they may be prescribed. These contexts may be described as the following:

1) Inadvertent exposure: When the woman and provider are unaware of the pregnancy and a potentially harmful drug is prescribed and/or consumed inadvertently.

2) No safe, therapeutic equivalent is available: When therapy is deemed medically necessary for the health of the pregnancy and the unsafe drug is the only therapeutic option available.

3) A safe, pharmacological equivalent is available but not prescribed: When there are therapeutic alternatives deemed safe in pregnancy, yet the potentially unsafe drug continues to be prescribed.

4) A safe, non-pharmacological equivalent is available but not provided: When prescription drug treatment may represent one of a range of effective treatment options available, yet the potentially unsafe drug continues to be prescribed.

The development of initiatives to improve rational prescribing requires unique considerations in each of these contexts:

1) Inadvertent exposure: Planned parenthood programs and contraceptive counseling may reduce inadvertent exposures to harmful drugs in pregnancy. A study of a national US survey found that 49% of pregnancies are unintended [12]. Women of childbearing age taking any medication considered to be potentially harmful in pregnancy should be counseled regarding risks and contraception, regardless of intention to conceive. While no estimates are available for the current extent of this type of counseling in the Canadian context, in the US, an estimated 1 out of every 13 visits to ambulatory practices by women of childbearing age ends in the prescription of a potentially teratogenic medication, with contraceptive counseling provided in less than 20% of visits [13].

2) No safe, therapeutic equivalent is available: Unless a medicine is deemed necessary to ensure the health of the mother or infant, any drug with potential risks should be avoided in pregnancy. In the case where treatment is the only option, the medicine with the least potential for harm among therapeutic equivalents should be selected. Comparative safety information for drugs used to treat conditions known to require therapy in pregnancy should be made available in a format accessible to providers and pregnant women. If possible, a hierarchical treatment algorithm illustrating the first-line treatment (the treatment with the highest benefit to risk ratio) and subsequent treatment choices if the

first-line is ineffective should be portrayed. One example of such a guideline that has been developed for a commonly treated maternal condition in pregnancy is The Society of Obstetricians and Gynaecologists of Canada's clinical guideline for the treatment of nausea and vomiting in pregnancy [14]. This guideline provides a clear summary of the evidence for available treatment options, first-line treatment recommendations, information on appropriate dosing, and advises on treatment alterations based on different clinical presentations (e.g. the presence of dehydration).

3) A safe, pharmacological **or** non-pharmacological equivalent is available but not prescribed: If a provider has knowledge of a pregnancy and prescribes a drug with potential risks even when a safe alternative is available, we must presume this is a result of insufficient communication to providers as to the risk profile of a given medication or the presence of appropriate alternatives. Finding innovative ways to support the transfer of that knowledge to physicians and women of childbearing age would improve the evidentiary inputs into clinical decision-making processes. The current methods used to accomplish this goal are teratogen information services and risk classification systems. Risk classification systems have been widely criticized [3, 4, 15]. Many argue that these systems simplify risk information, fail to offer advice on treatment alternatives or how to alter treatment when a patient has co morbid conditions, and are not adequately updated when new data becomes available. Risk classification systems are currently managed by national regulatory agencies. Different systems have been found to be inconsistent and sometimes provide contradictory information [4]. These differences are not due to the definitions of the categorizations – but rather in the interpretation of original research evidence [4].

There is no rationale for the existence of national risk classification systems. Ideally, one pan-national risk classification system would exist, applicable to all contexts, based on best evidence and informed by consensus among clinical experts. Such a system should attempt to address the criticisms of current systems that have been put forth by the research and clinical community, in order to convey information in a way that is relevant and useful for providers and their patients. An international risk system could be managed by the World Health Organization or through a collaboration of government regulatory departments and/or teratology information services (e.g. the North American

Organization of Teratology Information Specialists and European Network of Teratology Information Services). As 2009 marked the elimination of the Swedish system and the formation of the new European Medicines Agency system, and as the FDA prepares to make changes to its risk classification system, there is a unique window of opportunity for collaboration among these regulatory agencies [2, 3].

Ultimately, the quality of any information tool developed to communicate the risk profiles of medicines in pregnancy will be measured by the quality of the evidence it comprises. The benefits of having reliable information that clinicians and women can use to make confident treatment decisions in pregnancy are immeasurable. Thus, the priority still must be to continue to advance the state of knowledge surrounding drug safety and effectiveness in pregnancy.

4.4 References

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Appendices

Appendix A: Search Strategy for Systematic Review

Database: CINAHL (Ebsco)
Search Date: 2 June, 2010
Results: 178
Search Terms:
1. (MH "Pregnancy+") AND (MH "Prescriptions, Drug") or (MH "Drugs, Prescription") or (MH "Drug Utilization")
Limit: female
Limit: Scholarly (Peer Reviewed) Journals

Database: EMBASE (Ovid)
Search Date: 31 May, 2010
Results: 1858
Search Terms:
1. exp pregnancy/
2. "drug use"/ or prescription/ or prescription drugs.mp.
3. drug therapy/
4. 2 or 3
5. exp drug utilization/
6. 4 or 5
7. 1 and 6
8. limit 7 to (human and english language and yr="1989 -Current")
9. limit 8 to (article or letter or report or "review")
10. prescription/
11. "drug use"/
12. exp "drug use"/
13. exp prescription/
14. prescription drugs.mp.
15. medication.mp. or exp drug therapy/

16. 12 or 13 or 14 or 15

17. 1 and 16

18. limit 17 to (human and english language and yr="1989 -Current")

19. limit 18 to female

20. limit 19 to (article or letter or report or "review")

n.b. fully exploded search resulted in 7170 citations, which was deemed too unwieldy

Database: International Pharmaceutical Abstracts (Ovid)

Search Date: 27 May, 2010

Results: 122

Search Terms:

1. pregnancy.sh.
2. prescribing.sh.
3. "Physicians (prescribing)".sh.
4. Drug utilization.sh.
5. 2 or 3 or 4
6. 1 and 5
7. limit 6 to (english language and human and yr="1989 -Current")
8. limit 7 to (journal articles or letters or reviews)

Database: MEDLINE (Ovid)

Search Date: 27 May, 2010

Results: 672

Search Terms:

1. Pregnancy/
2. Drug Prescriptions/ or Prescription Drugs/ or Pharmaceutical Preparations/ or Drug Utilization/
3. 1 and 2
4. limit 3 to (english language and humans and yr="1989 -Current")
5. limit 4 to (comparative study or "corrected and republished article" or evaluation studies or journal article or letter or meta analysis or multicenter study or "review" or technical report or validation studies)

Database: Web of Science (Science Citation Index Expanded, 1899-present & Social Sciences Citation Index, 1956-present) (ISI/Thompson)

Search date: 31 May 2010

Results: 992

Search Terms:

1. TS="pregnan*" AND Language=(English) AND Document Type=(Article OR Letter OR Review)
2. TS=drug utili?ation AND Language=(English) AND Document Type=(Article OR Letter OR Review)
3. TS=prescribing AND Language=(English) AND Document Type=(Article OR Letter OR Review)
4. TS=medication use AND Language=(English) AND Document Type=(Article OR Letter OR Review)
5. (2 or 3 or 4) and 1

Refined by: [excluding] Subject Areas=(TROPICAL MEDICINE OR MEDICAL INFORMATICS OR COMPUTER SCIENCE, INFORMATION SYSTEMS OR EDUCATION, SPECIAL OR INFORMATION SCIENCE & LIBRARY SCIENCE OR SPORT SCIENCES OR SUBSTANCE ABUSE OR AGRICULTURE, DAIRY & ANIMAL SCIENCE OR BIOCHEMICAL RESEARCH METHODS OR BIOTECHNOLOGY & APPLIED MICROBIOLOGY OR EDUCATION & EDUCATIONAL RESEARCH OR ENGINEERING, CHEMICAL OR VETERINARY SCIENCES OR FOOD SCIENCE & TECHNOLOGY OR GERIATRICS & GERONTOLOGY OR HISTORY & PHILOSOPHY OF SCIENCE OR MEDICAL LABORATORY TECHNOLOGY OR NUTRITION & DIETETICS OR COMPUTER SCIENCE, INTERDISCIPLINARY APPLICATIONS OR PLANT SCIENCES OR ZOOLOGY) Databases=SCI-EXPANDED, SSCI Timespan=1989-2010

Database: POPLINE

Search Date: 27 May, 2010

Results: 46 records, 0 exported

Search Terms:

Pregnancy & Medicine / Pregnancy & Prescriptions AND Language: English

Appendix B: Data Abstraction Form for Systematic Review

1. Study and Reviewer:

Reviewer:

First Author	Journal	Year Published

2. Study Characteristics

Dates of data collection	
Location of data collection (country)	
Location (city, region, state)	
Study design	▪ Retrospective cohort ▪ Prospective cohort ▪ Other:

3. Participants - Characteristics

Sample size (pregnant women)	n =
Sample size (pregnancies) i.e. in the case where women may have multiple pregnancies within the study period	n =
Sampling frame	▪ Population (national) ▪ Population (region/state/province) ▪ Health care organization/insurance ▪ Multi-centre (hospitals/clinics) ▪ Single centre (hospital/clinic)
Sampling method (within above frame)	▪ Population-based ▪ Random ▪ Convenience ▪ Other:
Was the sample defined by demographics, ethnicity or insurance status?	▪ No: general population. ▪ Yes: subpopulation defined by demographics ▪ Yes: subpopulation defined by insurance status ▪ Yes: subpopulation defined by ethnicity
Other relevant information on participant characteristics, eligibility or study enrollment (e.g. participation rate, timing of enrollment)	

4. Participants - Pregnancy Characteristics

Identification of pregnancies	▪ Hospital records ▪ Vital statistics/birth registrations ▪ Pregnancy registry ▪ Self-report/survey ▪ Other:
Pregnancies included (outcomes)	▪ Live births only ▪ Live and stillbirths ▪ Live, stillbirths, and spontaneous abortions ▪ Live, stillbirths and therapeutic abortions ▪ Live, stillbirths, spontaneous and therapeutic abortions ▪ No exclusion based on outcome of birth was indicated

Pregnancies included (location)	▪ Hospital births only ▪ Hospital and home births ▪ No exclusion based on birth location was indicated
Pregnancies included (plurality)	▪ Singletons only ▪ Singletons and multiples ▪ No exclusion based on plurality was indicated
Pregnancies included (parity)	▪ Primiparous only ▪ No exclusion based on parity was indicated
Comments on the representativeness of the sample (e.g. the sample represents 80% of pregnancies in this region)	
Other relevant inclusion/exclusion criteria for pregnancies	

5. Intervention - Exposure Ascertainment

Estimation of delivery date	▪ Exact ▪ Maternal admission (proxy) ▪ Maternal discharge (proxy) ▪ Self-report/survey ▪ Other: ▪ Not indicated
Gestational age assumption	▪ No: birth record ▪ Yes: estimated. Specify: ▪ Yes: self-report/survey ▪ Not indicated
Exposure data source (name)	
Exposure data source (type)	▪ Administrative data (all prescriptions) ▪ Administrative data (based on insurance formulary) ▪ Medical chart review ▪ Self-report: survey and/or interview ▪ Other:
Measurement of Exposure	▪ Count of prescriptions with date of dispense within defined period ▪ Count of prescriptions with days dispensed overlapping defined period ▪ Medical chart review (prescriptions, not dispensing data) ▪ Self-reported drug use ▪ Other:

6. Intervention - Prescription Drug Inclusions and Classification

Drug classification	▪ WHO ATC system. Levels reported: ▪ Other, specify: ▪ No classification
Risk classification system	▪ Not applicable. ▪ FDA system ▪ Australian (ADEC) system ▪ Swedish (FASS) system ▪ Other system, specify: ▪ Authors identified their own list of teratogenic medications Other comments:

Vitamin and/or iron preparations included?	▪ Yes (both) ▪ Yes (vitamins only) ▪ Yes (iron only) ▪ No ▪ Not indicated.
Other relevant inclusion/exclusion criteria or classification of drugs	

7. Outcome - Outcomes Relevant to Review

1. Proportion filled/used ≥1 prescription

Please indicate the proportion and 95% CI if provided.

All		**Excluding vitamins and minerals (if reported)**	
Pregnancy period		Pregnancy period	
1st trimester		1st trimester	
2nd trimester		2nd trimester	
3rd trimester		3rd trimester	

Comments:

2. Mean number of different drugs used among women using ≥1 prescription drugs

a. Entire pregnancy period (mean/median)	
b. Level at which 'different' drugs were defined	

3. Frequency and proportion of pregnancies using ≥1 prescription by ATC LEVEL ONE categories. Only complete this section if authors report results at **ATC level one.**

Therapeutic Category (ATC L1)	**Frequency (%)**
ALIMENTARY TRACT AND METABOLISM	
BLOOD AND BLOOD FORMING ORGANS	
CARDIOVASCULAR SYSTEM	
DERMATOLOGICALS	
GENITO URINARY SYSTEM AND SEX HORMONES	
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	
ANTIINFECTIVES FOR SYSTEMIC USE	
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	
MUSCULO-SKELETAL SYSTEM	
NERVOUS SYSTEM	
ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS	
RESPIRATORY SYSTEM	
SENSORY ORGANS	
VARIOUS	

4. Top ten most frequently used therapeutic classes at the most detailed level reported in the study and proportion used ≥1 prescription within each category

Entire pregnancy period, lowest level reported. Ideally, this information will be at the generic name or chemical substance level (e.g. ATC level 5).

Drug Name	Frequency (%)

5. Reported drug use with potential for harm

Authors may report results for **specific therapeutic classes of concern** (e.g. isoretinoin) or if they used a risk classification system, they may report utilization according to **risk categories**. Please use the appropriate box below to record these results.

Specific Drugs	
Drug Name	**Frequency (%)**

Risk Categories	
Risk Category	**Frequency (%)**

Comments:

6. Risk of Bias

Indicate one to three sources of bias that you feel are most important for interpreting the results of this study.

Other Relevant Information

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given).

Appendix C: Prescription drug utilization measures by local health area of maternal residence.

No.	Local Health Area	n	Any Drug (%)	D/X (%)	D (%)	X (%)	X (%) (excl. contraceptives)
1	Fernie	539	66.37	7.14	3.80	3.86	1.59
2	Cranbrook	976	67.99	8.68	4.61	4.29	2.35
3	Kimberley	249	55.98	8.29	5.52	2.77	1.66
4	Windermere	304	52.26	7.94	2.28	5.93	2.91
5	Creston	438	63.55	9.23	7.21	2.44	0.82
6	Kootenay Lake	139	47.08	6.20	3.86	2.34	0.00
7	Nelson	806	49.96	6.17	4.06	2.33	1.44
9	Castlegar	390	56.71	8.33	5.87	2.45	1.44
10	Arrow Lakes	132	39.55	3.73	3.13	0.60	0.60
11	Trail	623	62.47	8.13	5.54	2.77	1.45
12	Grand Forks	314	53.58	7.12	3.80	3.32	2.78
13	Kettle Valley	124	47.08	6.04	3.36	3.33	0.89
14	Southern Okanagan	541	63.21	8.45	5.25	3.72	1.99
15	Penticton	1179	63.09	8.34	5.78	2.69	0.99
16	Keremeos	141	60.80	8.42	6.11	2.30	0.98
17	Princeton	131	66.62	10.51	7.16	3.35	0.00
18	Golden	301	63.96	6.24	3.67	2.86	0.67
19	Revelstoke	341	58.06	6.15	3.20	2.95	2.50
20	Salmon Arm	1016	61.19	9.48	7.36	2.67	0.92
21	Armstrong - Spallumcheen	385	52.48	3.33	1.78	1.68	0.41

No.	Local Health Area	n	Any Drug (%)	D/X (%)	D (%)	X (%)	X (%) (excl. contraceptives)
22	Vernon	2226	61.04	8.61	6.44	2.24	0.95
23	Central Okanagan	5602	61.10	8.77	6.47	2.53	1.06
24	Kamloops	3723	61.97	10.70	7.67	3.28	1.44
25	100 Mile House	445	64.11	7.88	4.78	3.53	2.13
26	North Thompson	207	64.48	6.41	3.72	3.08	1.47
27	Cariboo - Chilcotin	980	65.92	11.06	7.13	4.16	2.57
28	Quesnel	990	64.63	6.56	3.59	3.51	1.35
29	Lillooet	127	64.83	4.81	2.53	2.28	0.93
30	South Cariboo	142	61.96	6.35	3.61	2.74	0.00
31	Merritt	353	61.50	10.81	9.82	1.58	0.00
32	Hope	256	65.88	9.73	7.87	1.86	0.53
33	Chilliwack	3736	64.46	9.11	6.63	3.11	1.46
34	Abbotsford	6977	69.84	8.28	6.23	2.34	1.21
35	Langley	5881	61.71	9.56	7.05	2.63	1.23
37	Delta	4270	67.21	7.92	5.99	2.09	1.11
38	Richmond	5630	61.37	5.91	4.35	1.88	0.99
40	New Westminster	2738	63.96	6.88	4.76	2.30	0.99
41	Burnaby	8174	59.80	6.00	4.03	2.20	1.15
42	Maple Ridge	4035	67.88	8.31	5.51	3.14	1.36
43	Coquitlam	9549	64.29	7.26	5.13	2.28	1.05
44	North Vancouver	4968	60.20	9.00	6.93	2.29	1.15
45	West Vancouver - Bowen Island	1065	58.33	8.01	5.20	3.10	1.50
46	Sunshine Coast	782	60.37	8.62	5.49	3.64	2.02

No.	Local Health Area	n	Any Drug (%)	D/X (%)	D (%)	X (%)	X (%) (excl. contraceptives)
47	Powell River	586	60.00	7.25	5.91	1.83	0.90
48	Howe Sound	1535	59.33	6.72	5.15	1.72	0.75
49	Bella Coola	96	64.76	8.95	4.70	5.58	0.64
50	Queen Charlotte	145	53.90	5.87	4.66	1.22	0.66
51	Snow Country	30	72.94	5.74	0.00	5.74	0.00
52	Prince Rupert	389	72.38	9.46	5.86	3.86	1.17
53	Upper Skeena	75	49.71	9.24	6.04	5.04	0.91
54	Smithers	898	68.75	6.54	5.02	1.85	0.55
55	Burns Lake	237	70.43	11.28	8.25	3.03	2.11
56	Nechako	797	58.17	7.12	4.46	2.98	1.25
57	Prince George	4120	64.32	8.34	5.48	3.20	1.26
59	Peace River South	1200	62.09	8.07	4.68	3.69	1.27
60	Peace River North	2144	63.86	9.09	5.91	3.48	1.67
61	Greater Victoria	6422	65.34	9.54	7.61	2.37	1.08
62	Sooke	1962	67.48	11.53	9.52	2.41	1.20
63	Saanich	1573	63.06	9.25	7.29	2.25	0.81
64	Gulf Islands	280	50.69	6.47	6.04	0.83	0.00
65	Cowichan	1643	64.99	9.30	7.18	2.41	0.86
66	Lake Cowichan	170	63.38	7.95	6.21	1.74	0.00
67	Ladysmith	509	69.55	8.65	6.59	2.65	0.69
68	Nanaimo	3093	63.34	9.08	6.72	2.52	1.12
69	Qualicum	949	59.79	7.29	5.23	2.36	0.79
70	Alberni	916	65.70	9.34	7.73	2.23	1.13
71	Courtenay	1708	60.22	8.34	5.80	2.68	1.11

No.	Local Health Area	n	Any Drug (%)	D/X (%)	D (%)	X (%)	X (%) (excl. contraceptives)
72	Campbell River	1322	62.60	7.44	5.16	2.39	1.07
75	Mission	1881	67.64	8.28	5.89	2.70	0.92
76	Agassiz - Harrison	285	61.25	5.96	2.53	3.43	2.09
77	Summerland	324	62.58	12.03	10.14	2.15	1.03
78	Enderby	265	57.50	6.89	5.93	1.56	0.90
80	Kitimat	346	63.64	7.19	4.29	3.86	1.55
81	Fort Nelson	364	68.07	7.57	4.15	3.42	0.92
83	Central Coast	11	35.65	0.00	0.00	0.00	0.00
84	Vancouver Island West	70	64.45	8.09	6.58	1.51	0.00
85	Vancouver Island North	479	67.06	9.72	6.07	4.07	0.97
87	Stikine	33	41.18	7.57	7.57	0.00	0.00
88	Terrace	722	66.50	5.50	3.40	2.22	1.20
92	Nisga'a	5	21.17	0.00	0.00	0.00	0.00
94	Telegraph Creek	2	0.00	0.00	0.00	0.00	0.00
161	Vancouver - City Centre	2744	55.68	7.74	5.29	2.61	0.89
162	Vancouver - Downtown Eastside	1461	59.11	7.62	6.07	1.93	0.69
163	Vancouver - North East	4385	60.22	4.70	3.23	1.58	0.75
164	Vancouver - Westside	3954	58.00	6.63	4.98	1.77	1.32
165	Vancouver - Midtown	3901	59.86	5.42	3.84	1.64	0.75

No.	Local Health Area	n	Any Drug (%)	D/X (%)	D (%)	X (%)	X (%) (excl. contraceptives)
166	Vancouver - South	4633	61.54	5.09	3.20	2.02	1.40
201	Surrey	18631	69.55	7.59	5.12	2.69	1.57
202	South Surrey/White Rock	2255	61.76	8.25	6.15	2.36	0.92
999	Missing	1607	60.60	8.02	5.94	2.15	1.17

Appendix D: UBC Behavioral Research Ethics Board Certificates

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL - MINIMAL RISK

PRINCIPAL INVESTIGATOR:	INSTITUTION / DEPARTMENT:	UBC BREB NUMBER:
Steven G. Morgan	UBC/Medicine, Faculty of/School of Population and Public Health/Centre for Health Services and Policy Research	H09-00625

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Jamie Daw

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:
Variations in Pre-Natal Prescription Drug Use: Evidence from British Columbia

CERTIFICATE EXPIRY DATE: April 16, 2010

DOCUMENTS INCLUDED IN THIS APPROVAL:		DATE APPROVED:
		April 16, 2009
Document Name	**Version**	**Date**
Protocol:		
Daw Study Protocol	N/A	March 31, 2009

The application for ethical review and the document(s) listed above have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board and signed electronically by one of the following:

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL - MINIMAL RISK AMENDMENT

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Steven G. Morgan	UBC/Medicine, Faculty of/School of Population and Public Health/Centre for Health Services and Policy Research	H09-00625

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Jamie Daw

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:

Return on Investment from Pharmaceutical Care - Variations in Pre-Natal Prescription Drug Use: Evidence from British Columbia

Expiry Date - Approval of an amendment does not change the expiry date on the current UBC BREB approval of this study. An application for renewal is required on or before: April 16, 2010

AMENDMENT(S):	AMENDMENT APPROVAL DATE:
Change in Study Title	April 22, 2009

Document Name	Version	Date

The amendment(s) and the document(s) listed above have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair

The University of British Columbia
Office of Research Services
Behavioural Research Ethics Board
Suite 102, 6190 Agronomy Road, Vancouver, B.C. V6T 1Z3

CERTIFICATE OF APPROVAL- MINIMAL RISK RENEWAL

PRINCIPAL INVESTIGATOR:	DEPARTMENT:	UBC BREB NUMBER:
Steven G. Morgan	UBC/Medicine, Faculty of/School of Population and Public Health/Centre for Health Services and Policy Research	H09-00625

INSTITUTION(S) WHERE RESEARCH WILL BE CARRIED OUT:

Institution	Site
UBC	Vancouver (excludes UBC Hospital)

Other locations where the research will be conducted:
N/A

CO-INVESTIGATOR(S):

Jamie Daw

SPONSORING AGENCIES:

Canadian Institutes of Health Research (CIHR)

PROJECT TITLE:
Return on Investment from Pharmaceutical Care - Variations in Pre-Natal Prescription Drug Use: Evidence from British Columbia

EXPIRY DATE OF THIS APPROVAL: March 9, 2011

APPROVAL DATE: March 9, 2010

The Annual Renewal for Study have been reviewed and the procedures were found to be acceptable on ethical grounds for research involving human subjects.

Approval is issued on behalf of the Behavioural Research Ethics Board

Dr. M. Judith Lynam, Chair
Dr. Ken Craig, Chair
Dr. Jim Rupert, Associate Chair
Dr. Laurie Ford, Associate Chair
Dr. Anita Ho, Associate Chair