A thesis submitted in fulfilment of the requirements for the degree of

Doctor of Philosophy (Pharmacy & Medical Sciences)

Feasibility of Using Routinely Collected Health Data to Examine Long-Term Effects of Medication Use During Pregnancy

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Abbreviations

5-HT	Serotonin
5-HTT	Serotonin Transporter
BDNF	Brain Derived Neurotrophic Factor
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CNS	Central Nervous System
DNBC	Danish National Birth Cohort
DOHaD	Developmental Origins of Health and Disease
GR	Glucocorticoid Receptor
HPA	Hypothalamic-Pituitary-Adrenal
LGA	Large-for-Gestational Age
NICU	Neonatal Intensive Care Unit
NPY	Neuropeptide Y
OD	Odds Ratio
PBS	Pharmaceutical Benefits Scheme
POBW	Proportion of Optimal Birthweight
PPHN	Persistent Pulmonary Hypertension of the Newborn
PR	Prevalence Ratio
QUM	Quality Use of Medicines
RR	Relative Risk
SCBU	Special Care Baby Unit
SEIFA	Socio-economic Indexes for Area
SGA	Small-for-Gestational Age
SSRI	Selective Serotonin Reuptake Inhibitor

Summary

The aim of this thesis was to investigate the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy on the health of the offspring in later life. To date, the investigation of teratogenic effects of medications has largely focused on physical alterations (i.e. malformations) as opposed to functional alterations (i.e. neurodevelopment, metabolic function) that may not be apparent at birth but could influence an individual's health and risk of disease in later life. The need for a timely and efficient approach which is capable of generating evidence on the potential long-term effects of medication use during pregnancy provided the impetus to explore the feasibility of using routinely collected health data.

To investigate the feasibility of using routinely collected health data to examine long-term effects of medications used during pregnancy, this thesis utilised data obtained from the Women's and Children's Health Network in South Australia. The decision was made to focus on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) during pregnancy, due to the high level of concern and relative paucity of data surrounding potential long-term effects on the health of the offspring in later life. Initial studies were undertaken to explore and validate the use of available South Australian routinely collected health data. The first study validated the use of hospital pharmacy dispensing records to identify exposure to SSRIs during pregnancy. The second study validated the process of accurately linking available datasets to provide meaningful results by examining the effects of prenatal SSRI exposure on neonatal outcomes and comparing results obtained to existing published literature. Following these validation studies, these data were then used to investigate the long-term effects of prenatal SSRI exposure on growth and body weight in childhood. As a point of comparison to this feasibility study, the effects on growth and body weight in childhood were investigated further using data obtained from the Danish National Birth Cohort. This comparison of research methods enabled a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data to examine long-term effects of medication use during pregnancy.

Studies in this thesis have made a number of original contributions to the literature. The first is by demonstrating the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy on the health of the offspring in later life. The second is by providing a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data. Identified challenges relate to aspects of study design and analysis and include the ability to link data across datasets, how medication exposures and outcomes are ascertained and classified, issues around loss to follow-up and the careful interpretation of results in light of data and study limitations. By

outlining evidence-based strategies for using routinely collected health data this thesis provides a framework for guiding and supporting research in this area. This framework is essential in supporting the appropriate use and interpretation of routinely collected health data, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained.

There is an urgent need to better understand the long-term effects of medication use during pregnancy on the health of the offspring in later life. Not only does this thesis demonstrate the feasibility of using routinely collected health data to achieve that understanding, but it also provides an evidence-based framework for guiding and supporting research in this area. The timely and efficient manner in which long-term outcomes can be examined using routinely collected health data represents a major step forward in improving our understanding of the consequences of medication use in pregnancy.

List of Publications in Support of Thesis

Published Manuscripts

1. Grzeskowiak LE, Gilbert AL, Morrison JL. Conception and Beyond – Using Population-Based Record Linkage to Monitor Long-Term Effects of Medications Used During Pregnancy. *J Pharm Pract Res* 2010; 40(1): 46-49.

2. Grzeskowiak LE, Gilbert AL, Morrison JL. Hospital Pharmacy Dispensing Records for Pharmacoepidemiology Research into Late Gestation Exposure to Antidepressants. *J Pharm Pract Res* 2010; 40(4): 265-268.

3. Grzeskowiak LE, Gilbert AL, Morrison JL. Investigating outcomes following the use of Selective Serotonin Re-Uptake Inhibitors for Treating Depression in Pregnancy - A Focus on Methodological Issues. *Drug Saf* 2011; 34(11): 1027-1048.

4. Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or Not Exposed? Exploring Exposure Classification in Studies Using Administrative Data to Investigate Outcomes Following Medication Use During Pregnancy, *Eur J Clin Pharmacol* 2012; 68(5): 459-467.

5. Grzeskowiak LE, Gilbert AL, Morrison JL. Prenatal Exposure to Selective Serotonin Reuptake Inhibitors and Risk of Childhood Overweight*, J Dev Orig Health Dis* 2012; 3(4): 253-261.

6. Grzeskowiak LE, Gilbert AL, Morrison JL. Investigating Outcomes Associated with Medication Use During Pregnancy: a review of methodological challenges and observational study designs, *Reprod Toxicol* 2012; 33(3): 280-289.

7. Grzeskowiak LE, Gilbert AL, Morrison JL. Long term impact of prenatal exposure to SSRIs on growth and body weight in childhood: Evidence from Animal and Human Studies, *Reprod Toxicol* 2012; 34(1): 101-109.

8. Grzeskowiak LE, Gilbert AL, Morrison JL. Neonatal Outcomes Following Late Gestation Exposure to SSRIs, *J Clin Psychopharmacol;* In press.

Submitted Manuscripts

9. Grzeskowiak LE, Gilbert AL, Morrison JL. Using Linked Healthcare and Administrative Data to Investigate Long-Term Effects of Medication Use During Pregnancy – Opportunities and Challenges, *Ther Adv Drug Saf*; Submitted.

10. Grzeskowiak LE, Gilbert AL, Sørensen TIA, Olsen J, Sørensen HT, Pedersen LH, Morrison JL. Childhood Overweight Following Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Maternal Psychiatric Illness. *PLoS One*; Submitted.

Conference Presentations

Invited Presentations

1. Grzeskowiak LE, Gilbert AL, Morrison JL. *Challenges in Using Routinely Collected Healthcare and Administrative Data to Investigate Long-Term Effects of Medication Use During Pregnancy*, Sansom Institute Research Symposium: Drug Use During Pregnancy: Drugs, Nutrition and Fetal Physiology, July 2011: Adelaide, Australia.

2. Grzeskowiak LE**.** *Long-term effects on child growth following prenatal exposure to Selective Serotonin Reuptake Inhibitors (SSRIs),* Australian Birth Defects Society Annual Meeting, March 2012: Melbourne, Australia.

Oral Presentations

3. Grzeskowiak LE, Gilbert AL. *To Conception and Beyond – Using Population-Based Record Linkage to Monitor Long-Term Effects of Medication Use During Pregnancy on Child Health and Development*. State Population Health Conference: Challenges and Successes in Population Health, October 2009: Adelaide, Australia.

4. Grzeskowiak LE, Gilbert AL. *Monitoring Long-Term Effects of Medication Use During Pregnancy on Child Health and Development*. Medicines Management 2009: The 35th Society of Hospital Pharmacists of Australia (SHPA) National Conference, November 2009: Perth, Australia.

5. Grzeskowiak LE, Gilbert AL, Morrison JL. *A Validation Study of Hospital Pharmacy Dispensing Records for Pharmacoepidemiology Research into Medication Safety in Pregnancy – The Example of Antidepressants*, Australasian Pharmaceutical Science Association (APSA) Annual Scientific Meeting, December 2010: Brisbane, Australia.

6. Grzeskowiak LE, Gilbert AL, Morrison JL. *Neonatal Outcomes Following Late Gestation Exposure to Selective Serotonin Reuptake Inhibitors*, Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) Conference, November 2011: Brisbane, Australia.

7. Grzeskowiak LE, Gilbert AL, Morrison JL. *Prenatal Exposure to SSRIs and Neonatal Outcomes*, Medicines Management 2011: The 37th Society of Hospital Pharmacists of Australia (SHPA) National Conference, November 2011: Hobart, Australia.

8. Grzeskowiak LE, Gilbert AL, Sørensen TIA, Olsen J, Sørensen HT, Pedersen LH, Morrison JL. *Childhood Overweight Following Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Maternal Psychiatric Illness*, 28th ICPE: International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 2012: Barcelona, Spain.

Poster Presentations

9. Grzeskowiak LE, Gilbert AL, Morrison JL. *Long-Term Effects of Prenatal Exposure to Selective Serotonin Re-Uptake Inhibitors on Childhood Weight Gain*. Australasian Pharmaceutical Science Association (APSA) Annual Scientific Meeting, December 2009: Hobart, Australia.

10. Grzeskowiak LE, Gilbert AL, Morrison JL. *To Conception and Beyond – Improving Quality Use of Medicines in Pregnancy Using Population-Based Record-Linkage*. National Medicines Symposium (NMS), May 2010: Melbourne, Australia.

11. Grzeskowiak LE, Gilbert AL, Morrison JL. *Prenatal Exposure to SSRIs and Risk of Childhood Overweight*, Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) Conference, November 2011: Brisbane, Australia.

12. Grzeskowiak LE, Gilbert AL, Morrison JL. *Using Routinely Collected Health Data to Investigate Long-Term Effects of Medication Use During Pregnancy – Challenges and Opportunities,* 52nd Annual Meeting of the Teratology Society, June 2012: Baltimore, USA.

13. Grzeskowiak L, Gilbert A, Morrison J. *Neonatal Outcomes Following Late Gestation SSRI Exposure*, 28th ICPE: International Conference on Pharmacoepidemiology & Therapeutic Risk Management, August 2012: Barcelona, Spain.

Declaration

I declare that this thesis presents work carried out by myself and does not incorporate without acknowledgement any material previously Submitted for a degree or diploma in any university. To the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including joint authored publications, is clearly acknowledged.



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Luke Edward GRZESKOWIAK

16 February 2012

Acknowledgements

My PhD journey started back in 2007 when I commenced my internship in the pharmacy department at the Women's and Children's Hospital in Adelaide. As a fresh-faced intern pharmacist I was eager to learn and I was greeted with numerous opportunities. What I experienced was inspiring and life-changing. Whether by chance or fate, within 6 months I knew not only that I wanted to do my PhD, but that I had found my muse. Not only had I become inspired by those working around me and their unwavering dedication towards improving the safe and effective use of medications during pregnancy, but I had also experienced first-hand the real positive difference that I could make to the lives of others. From this point in time I developed a burning passion for making my own contribution, however big or small, towards improving health outcomes for pregnant women and their children. In particular I would like to thank pharmacists Neil Hotham and Lynn Costi, who have always been happy to share their clinical expertise with me. I am sincerely thankful for being given the opportunity to work alongside such passionate and knowledgeable individuals and I thank them for the role that they have played in helping shape my career. Furthermore, I would like to thank Kingsley Coulthard, who was director of the department at that time, for encouraging and supporting me in making the transition into the realm of research.

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Preface

This doctoral thesis is presented as a Thesis by Publication, in accordance with the University of South Australia Academic Regulations for Higher Degrees Research (Clause 16.1.1.b). Specifically, a thesis presented purely by publications typically includes at least 2-3 published works, depending on the convention for each discipline and depending on the quality of the work and the international standing of the publication outlet. The publications included in a thesis containing published research must be part of an integrated project such that the publications presented in the thesis constitute elements of a connected whole.

The aim of this thesis was to investigate the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy and answer the following research question;

> *"Can we use routinely collected health data to examine long-term effects of medication use during pregnancy."*

To investigate the feasibility of using routinely collected health data to examine long-term effects of medications used during pregnancy, this thesis utilised data obtained from the Women's and Children's Health Network in South Australia. The decision was made to focus on the use of Selective Serotonin Reuptake Inhibitors (SSRIs) during pregnancy, due to the high level of concern and relative paucity of data surrounding potential long-term effects on the health of the offspring in later life. Together, this provided a suitable illustrative example to investigate the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy. While the consistent focus and reference to SSRI use during pregnancy provides a theme to this thesis, the findings and discussion are of relevance to the broader aspect of medication use during pregnancy and the general feasibility of using routinely collected health data to examine long-term outcomes.

The body of knowledge that constitutes this thesis is a series of studies presented as ten manuscripts (See Figure 0.1). Each of these manuscripts forms a chapter within this thesis, which are presented within three primary themes.

- **Section I** is separated into two parts. The first part provides an overview of the conceptual frameworks drawn upon throughout this thesis (Chapters 2 & 3). The second part presents a thorough literature review of the safety and potential long-term effects of SSRI use during pregnancy, which forms the basis for subsequent studies (Chapters 4 & 5).
- **Section II** validates and examines the use of local routinely collected health data. The first study in this section validates the use of hospital pharmacy

dispensing records to identify exposure to SSRIs during pregnancy (Chapter 6). The second study examines challenges in using routinely collected health data to classify medication exposure during pregnancy (Chapter 7). The third study validates the process of accurately linking available datasets to provide meaningful results by examining the effects of prenatal SSRI exposure on neonatal outcomes and comparing results obtained to existing published literature (Chapter 8).

- **Section III** evaluates the use of routinely collected health data. This involved using routinely collected health data to investigating the long-term effects of prenatal SSRI exposure on growth and body weight in childhood (Chapter 9). As a point of comparison to this feasibility study, the effects on growth and body weight in childhood were investigated further using data obtained from the Danish National Birth Cohort (Chapter 10). This section culminates in a review of the opportunities and challenges associated with using routinely collected health data to examine long-term effects of medication use during pregnancy (Chapter 11).

Within this structured and themed approach, each chapter builds the argument that routinely collected health data is a necessary and feasible approach for investigating long-term effects of medication use during pregnancy. As a whole, this thesis provides a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data. By outlining evidence-based strategies for using routinely collected health data this thesis provides a framework for guiding and supporting research in this area.

The text within each thesis chapter is identical to that contained within the respective manuscript; however, for the purposes of presentation within this thesis, the manuscripts have been reformatted and the sections, tables and figures have been renumbered for continuity throughout the thesis. As such, due to the format of this thesis, the reader is advised that some aspects of the respective chapters may appear repetitive. Each chapter is referenced individually and all references, tables and figures appear at the end of each chapter.

Figure 0.1 Thesis outline

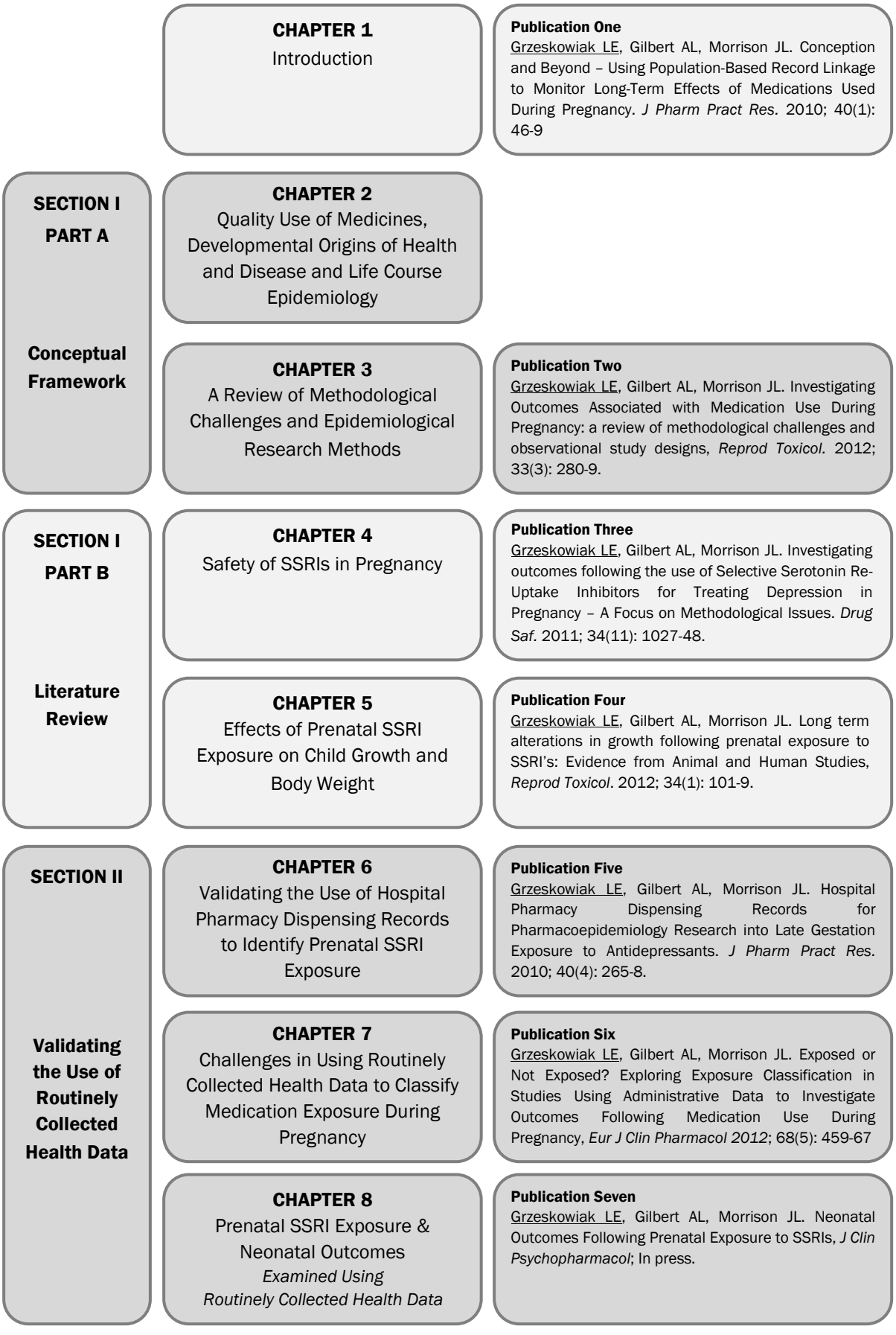
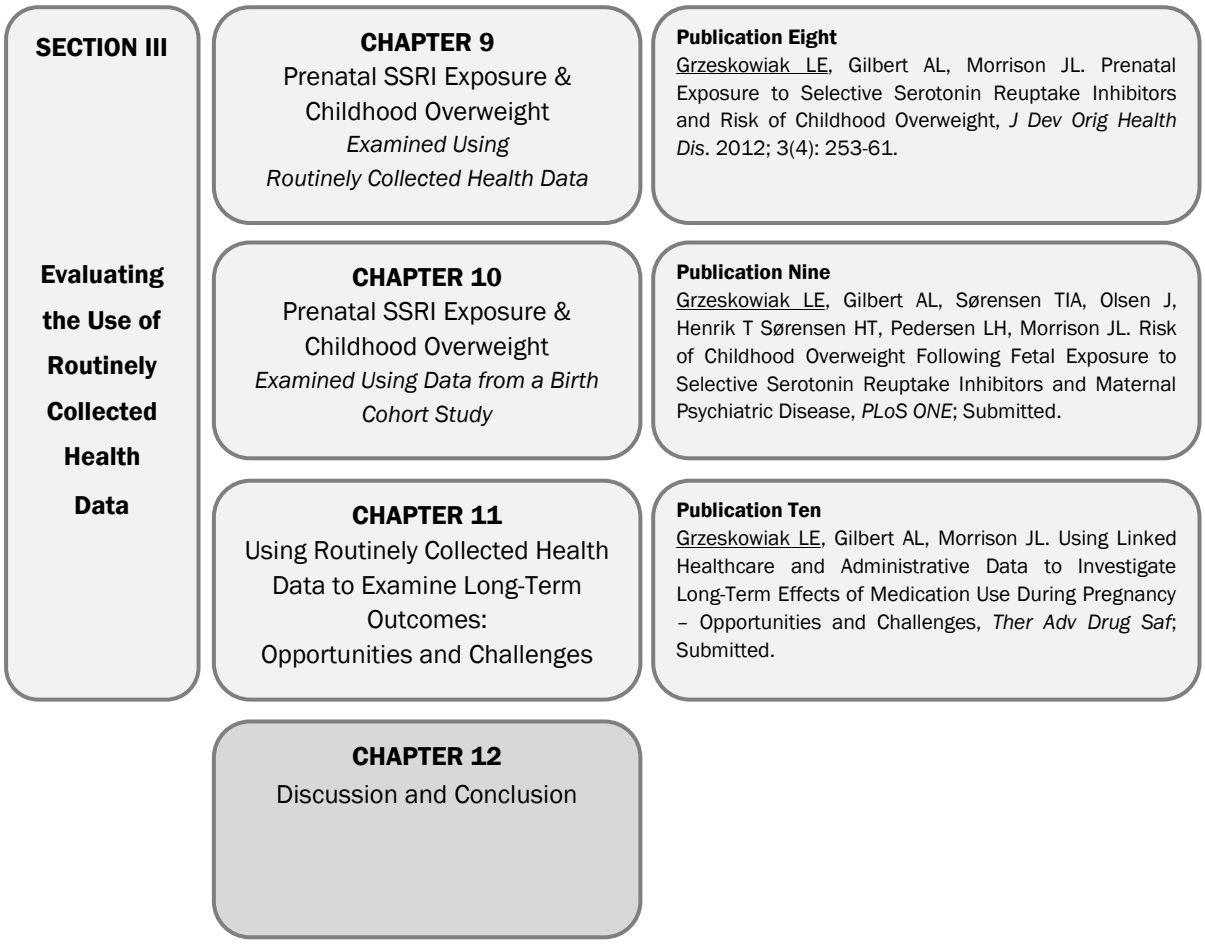


Figure 0.1 Thesis outline



CHAPTER 1

Introduction

Manuscript

Luke E Grzeskowiak, Andrew L Gilbert, Janna L Morrison

Conception and Beyond: Using Population-Based Record Linkage to Monitor Long-Term Effects of Medications Used During Pregnancy

Journal of Pharmacy Practice and Research. 2010; 40(1): 46-49

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	CHAPTER 10 Prenatal SSRI Exposure & Childhood Overweight *Examined Using Data from a Birth Cohort Study*	**Publication Nine** Grzeskowiak LE et al. *PLoS ONE*; Submitted.
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1.1 Abstract

One of the biggest challenges health professionals face when counselling patients about medication use in pregnancy is accessibility to evidence-based information on the risks or benefits associated with treatment. There is inadequate information available regarding the immediate and long-term effects of medications used by pregnant women on the mother and the fetus. Novel surveillance techniques using population-based record linkage could enable better identification, quantification and understanding of long-term risks or benefits of medications used during pregnancy. The technology, data and expertise are available to make it happen.

1.2 Introduction

Although as a society we have more access to information than ever before, women often get mixed messages about medication use during pregnancy. Consider the following scenario of a pregnant female making a medicines information enquiry through a drug information service: *'My friends and family tell me that I shouldn't take my usual medication while I am pregnant because of the risks. My local pharmacist told me that I need to keep taking my medication because my medical condition may get worse and harm my baby if I don't. My doctor says that the medication doesn't appear to cause birth defects but no long-term studies have been undertaken to investigate concerns about potential long-term adverse effects. I have looked it up on the Internet and found lots of web sites where people have written that it can be really harmful. I don't know who to trust and listen to. I just want my baby to be healthy. Please tell me what to do.'*

1.3 Risks and Benefits of Medication use During Pregnancy

Determination of the risks and benefits of medication use in pregnancy is a longstanding issue that urgently needs renewed focus and novel strategic planning.[1] Women are generally advised not to take medications during pregnancy unless the potential benefits justify or outweigh the potential risks to the mother and fetus.[2]

When it comes to medication use in pregnancy, evidence regarding the risks and benefits of the medications is often lacking, contradictory or difficult to interpret and apply in practice.[3,4] In addition, the objective evaluation of the risks and benefits may be clouded by the sensitivities associated with the potential for medications to cause teratogenic effects such as birth defects.[5] Medication use in pregnancy presents a major challenge in balancing optimal management of maternal health with possible harm to the fetus.

There is concern that when adequate evidence-based information on medicine safety is lacking, pregnant women may avoid using essential medications, resulting in suboptimal management of their chronic or acute illnesses. Without the availability of evidenced-based data to reassure them, pregnant women and their health professionals may cease essential medications, which may lead to greater risks to both mother and fetus than continuing with the treatment.[4] Alternatively, women may continue to take medicines during their pregnancy that could adversely affect fetal development.[6]

1.4 Evidence on Medication Safety in Pregnancy

For ethical reasons, clinical trials for new medications usually exclude pregnant women. Once the new medications have gained regulatory approval and marketing, judgements on their safety in pregnancy are usually made on the basis of preclinical animal studies alone.[1]

1.4.1 Animal Studies

1.4.1.1 The Legacy of Thalidomide

Initial reproductive studies with thalidomide failed to show an increased rate of birth defects among pregnant rats and mice, leading many to erroneously believe that human teratogenicity could not be predicted by animal studies.[3] More than 10,000 children were born worldwide with major limb reduction and other defects following exposure to thalidomide during early pregnancy, sensitising manufacturers, governments, health professionals and the public to the issue of human teratogens.[3] This led to the introduction of new regulatory preclinical guidelines around the world to ensure specific studies for evaluating teratogenicity are conducted before medications are marketed.

1.4.1.2 Identification of Teratogens

To this point in time all known human teratogens have demonstrated similar teratogenicity in appropriately designed and conducted animal studies. Indeed, the value of animal studies has been well demonstrated in the example of isotretinoin, where evidence of teratogenicity from preclinical animal studies contributed to a significant reduction of human exposures and

possibly prevented a disaster similar to that of thalidomide. However, there remain over 1000 chemicals that have been shown to demonstrate some measure of teratogenicity in animal studies, but as yet no evidence exists that they produce teratogenic effects in humans.[7] Is this because our systems are not sensitive enough to detect their teratogenic effects in humans? Was it because these animal studies were poorly designed or due to important developmental differences between species? Whatever the reason, it is clear that the interpretation of results from animal studies and their application to human exposure is a complex area of practice and research.

1.4.2 Human Exposure

Despite these challenges and the sometimes limited information on the risks and benefits of medication use in pregnancy, Australian data suggest that 97% of pregnant women use prescription and non-prescription medications across all trimesters.[8] Some women enter pregnancy with chronic medical conditions, such as asthma, epilepsy, hypertension, depression, that require continued pharmacotherapy. Other women may require treatment for acute or pregnancy-induced medical conditions, such as gestational diabetes, migraine headache, nausea and vomiting.[9] The frequent usage of medications during pregnancy highlights the need for the availability of adequate evidence regarding their risks and benefits.

While animal studies may be the first line of investigation for determining medication safety during pregnancy, they should not be the only approach. There is a need to study outcomes following human exposures to determine both the risks and benefits of medication use during pregnancy. While ethical issues make it difficult to justify exposing pregnant women to medications of unknown safety in randomised controlled trials, unintentional or unavoidable medication exposures during pregnancy do occur. These exposures provide a significant opportunity to gather evidence on resultant pregnancy outcomes, both in the short and long-term, but only if outcomes are followed. This places a heavy reliance upon ongoing data collection to generate this evidence.

1.4.3 Data Collection

At present in Australia, there is no routine, mandatory, systematic approach to the collection of data to enable a better understanding of the consequences of medication use in pregnancy. Worldwide, methods for such data collection and analysis vary but include case reports, pregnancy registries, cohort studies and case-control studies.[9] Each approach has its associated strengths and weaknesses. Some approaches are heavily reliant on voluntary reporting while others lack the required sample sizes to ascertain truly significant associations. Most methods tend to focus only on the immediate adverse effects such as major malformations at birth.[9]

1.5 Population-Based Record Linkage

While it is recognised that no single approach is sufficient for delineating the complete spectrum of risks or benefits of medication use in pregnancy, we must continue to explore and develop novel approaches to gathering evidence, especially regarding the potential long-term effects of medication use in pregnancy.[1] Population-based record linkage, which involves bringing together records relating to the same individual from different sources, represents a novel approach to data collection and analysis of medication use during pregnancy in Australia.[10]

1.5.1 Advantages

The use of population-based record linkage has several advantages over other more labour intensive data collection efforts.[11] The most significant advantage lies in the ability of population-based record linkage to generate evidence in a rapid and systematic manner. Health professionals are constantly confronted with having to provide timely answers to questions regarding the safety of medications used during pregnancy. These questions could either be answered by constructing prospective birth cohort studies and waiting years to generate the evidence, or by utilising existing data to provide immediate answers.

1.5.1.1 Datasets

The linkage of existing health and administrative datasets would also enable the establishment of very large cohorts of women and their children. This aspect would be a significant advantage as very large samples are often required in observational studies in order

to obtain adequate power to detect a low to moderate increased risk of an adverse outcome associated with medication use during pregnancy. The data would be usually collected in a consistent fashion and could include information on potential confounders of interest. There would effectively be no loss to follow-up, only potential failures in the linkage of records. The data collection costs would also be low as the data has already been collected and would often be available in electronic format.[10] The routine and prospective manner in which data are collected and recorded in these datasets would eliminate recall bias, which is often an issue in traditional retrospective cohort studies.[12,13]

1.5.2 Limitations

Population-based record linkage is, however, not without its limitations. While linkage of existing records would be unobtrusive, there is a need to carefully consider participant confidentiality. These issues and concerns can be addressed, and appropriate protocols and procedures put in place to ensure this type of research can be undertaken in an ethical manner.

As the data have already been collected, the researchers can only work with the available data. It can be difficult to go back and collect further data if required. Potential confounders may not be accounted for in the datasets and the inability to account for these confounders needs to be acknowledged when interpreting results.[11] Health and administrative datasets were never designed to be used for research purposes and so it is crucial that the quality and accuracy of the data are assessed together with an evaluation validity for use in record linkage projects.[10] The lack of truly national health and administrative datasets places a significant restriction on Australia-wide population-based record linkage research. Individual states and territories and local institutions such as hospitals often boast rich data collections, but often these same data are not collected consistently across institutions and jurisdictions, making the compilation of national datasets impractical.

Lastly, the lack of unique personal identifiers across each of the datasets presents difficulties when linking records related to the same individual or when linking maternal and child records to enable longitudinal assessment of outcomes.

1.5.3 Australian Scenario

Despite these limitations, population-based record linkage offers a complementary approach to data collection and analysis of medication use in pregnancy. Australia is in an excellent position to undertake strong data linkage projects due to its long-term, comprehensive and stable population datasets.

Within Australia, although data relating to medication use, pregnancies and their outcomes are routinely collected through a myriad of data collection systems, they remains hidden and under-utilised. Examples of data collection systems that contain useful and relevant data include pharmacy dispensing records, Pharmaceutical Benefits Scheme claims data, hospital records, midwives notification records, birth defects registries, mental health records, cancer registries, Medicare Benefits Scheme data, private and public hospital admissions and discharges, emergency department presentations and child and adolescent health and development records. While the usefulness of these data are limited in isolation, linking the datasets could allow medications use to be tracked before and during pregnancy and enable immediate and long-term assessment according to pregnancy outcomes.

Evidence is growing that population-based record linkage is a practical approach to investigating medication safety in pregnancy. Researchers in Western Australia have recently demonstrated the potential for combining various data sources through population-based record linkage.[14] By linking medication dispensing data from the Pharmaceutical Benefits Scheme with other population-based health datasets in Western Australia, such as the birth defects register and midwives' notification records, Colvin et al.[14] were able to study how medicines are used during pregnancy and assess the impact on pregnancy outcomes. This novel approach proved to be a feasible and relatively cost-effective means of investigating the effects of medication use in pregnancy.

Existing facilities such as the Western Australian Data Linkage System, Centre for Health Record Linkage and SA/NT DataLink, have the expertise and facilities required to assist researchers in undertaking population-based record linkage projects. These centres have undertaken many, and somewhat varied, linkage projects utilising existing routinely collected data, with more than 600 projects undertaken through the Western Australian Data Linkage System alone. While displaying the significant advantages of population-based record

linkage, these projects also highlight a significant gap that exists in the literature with regards to research on medication safety in pregnancy. This presents a challenge for researchers to build and expand on this type of research to incorporate the ability to investigate unknown long-term effects of medication use during pregnancy.

1.6 Long-Term Effects of Medication Use During Pregnancy

Strong associations between influences on fetal growth during pregnancy and subsequent development of chronic diseases during adulthood have sparked interest in the early origins of adult health.[15] The growing body of literature associating, for example fetal and postnatal growth with the development of cardiovascular disease, diabetes and reduced cognitive function in later life, raises concerns about the potential long-term effects of exposure to medications *in utero*.[16-19]

It is not known what role medications used during pregnancy play in the early origins of adult health, but evidence exists regarding the potential long-term effects. The discovery of an association between the use of diethylstilbestrol during pregnancy and an increased rate of vaginal adenocarcinomas in young women exposed *in utero* is a pertinent reminder that we must ensure adequate follow-up of all medication exposures during pregnancy.[20] In more recent examples, there is evidence that *in utero* exposure to sodium valproate is associated with an increased risk of impaired cognitive function in children aged 3 years and paracetamol use during pregnancy is associated with an increased risk of asthma and wheezing in childhood.[21,22]

These examples add strength to the debate that childhood conditions such as obesity, diabetes, asthma, atopy, behavioural disorders and impaired cognitive function may be linked to medication use during pregnancy. However, until systems are established for long-term follow-up of medication use during pregnancy, knowledge on this subject will remain inadequate. The many unanswered questions about the long-term effects of medication use in pregnancy demand that more time and effort be devoted towards answering them. It would be wasteful to continue to allow useful and already routinely collected state and national data to languish in administrative or statistical archives. Privacy, security and confidentiality are paramount considerations in all areas of research, but these concerns can be addressed and should not prevent valuable public health research opportunities using record linkage. High-level security arrangements can be utilised, compliant with relevant privacy laws, regulations and codes, to ensure data are securely protected during linkage and only provided to researchers in a de-identified format. By linking records across databases we can investigate medication use during

pregnancy and their resultant positive or negative effects on the mother and the offspring as children, adolescents and adults.

1.7 Current and Future Directions

Research is currently under way in South Australia to explore the practicalities of using population-based record linkage as a method to investigate the long-term effects of medication use during pregnancy. The research team has expertise in the use and linkage of large datasets for use in pharmacoepidemiological research and in understanding the effects of medications used during pregnancy with regards to fetal development and the long-term effects on the children. A framework has been established for further research investigating long-term effects of medication use during pregnancy by combining routinely collected healthcare and administrative data. Expanding this work to include population data from other jurisdictions is a future priority.

1.8 Conclusion

Receiving a query from a worried and distressed pregnant woman looking for answers and certainty regarding use of a specific medication is not an infrequent occurrence for many health professionals, especially pharmacists working in drug information centres. Pharmacists play an integral role in achieving quality use of medicines by providing evidence-based information to support informed decision making, but they also play an important role in undertaking and supporting research which builds on, and fills significant gaps that exist in, available evidence.

The improved collection and evaluation of data on medication use and pregnancy outcomes in the long-term using population-based record linkage will strengthen safety data, support medication use during pregnancy and allow health professionals and women to be adequately informed of the risks and benefits associated with medication use. The technology and expertise are available to make it happen, now is the time for action.

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Section I: Part A -
Conceptual Framework

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SECTION I **PART A** **Conceptual Framework**	**CHAPTER 2** Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology	
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	CHAPTER 12 Discussion and Conclusion	

Preamble

This thesis draws and expands upon the theoretical constructs of quality use of medicines, the developmental origins of health and disease hypothesis, life-course epidemiology and epidemiological research methods to answer the overall research question of whether it is feasible to use routinely collected health data to examine long-term effects of medication use during pregnancy.

Discussed first are the conceptual frameworks provided from three areas of research; Australia's National Strategy for achieving Quality Use of Medicines (QUM), the Developmental Origins of Health and Disease (DOHaD) and life-course epidemiology (Chapter 2).

The National Strategy for QUM describes the principles, building blocks and approaches required to improve health outcomes through improved medicines use. An essential component of QUM involves obtaining adequate evidence regarding the risks and benefits of medication use during pregnancy, especially long-term outcomes.

In turn, the DOHaD hypothesis provides a framework for understanding and investigating the potential role that prenatal exposure to various medications could play in determining the health of the offspring in later life. While the DOHaD hypothesis postulates that programming of the long-term structure and function of body systems can be influenced and altered by environmental exposures *in utero*,[2-4] most research has focused on the role of nutrition and fetal growth during pregnancy and subsequent development of chronic diseases in adulthood. At present, there has been little regard for the role that medication exposures during pregnancy could play in influencing susceptibility towards disease in later life. Therefore, an overview of DOHaD serves two purposes;

- The first is that, based on fundamental sciences including biology, genetics, embryology, teratology, epigenetics and epidemiology, there is biological plausibility and a mechanism for the relationship between early life influences and the health of the offspring in later life.

- The second is that it highlights the importance of investigating potential long-term effects of medication use during pregnancy and the role that they may play in influencing the health of the offspring in later life.

This chapter concludes with a brief overview of life-course epidemiology. This serves to highlight the importance of conceptualising disease aetiology within a life course framework, as well as recognising that the aetiology of many later-life conditions may rest with prenatal

and early-life biological and social factors, in addition to, or in synergism with, those of well-established adult exposures or risk factors.

After establishing the need to examine long-term outcomes following medication use during pregnancy, Chapter 3 explores various epidemiological research methods available to examine such outcomes; in particular the relatively novel approach of using routinely collected health data. Given the focus of this thesis is on investigating the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy, it is critical to understand the strengths and limitations of this approach in relation to other epidemiological research methods. In addition, this Chapter provides an overview of methodological challenges associated with investigating the effects of medication use during pregnancy, which is important in informing the work of subsequent chapters exploring the utility of routinely collected health data.

CHAPTER 2

Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology

2.1 Introduction

This chapter draws on the conceptual frameworks provided from three areas of research; Australia's National Strategy for achieving Quality Use of Medicines (QUM) the Developmental Origins of Health and Disease (DOHaD) hypothesis and life-course epidemiology.

The National Strategy for QUM describes the principles, building blocks and approach required to improve health outcomes through improved medicines use. An essential component of QUM involves obtaining adequate evidence on the risks and benefits of medication use during pregnancy.

In turn, the DOHaD hypothesis provides a theoretical framework for understanding and investigating the potential role that prenatal exposure to various medications could play in influencing the health of the offspring in later life. There is an ever expanding body of research based on the theoretical framework provided by the DOHaD hypothesis. This not only provides clues as to the potential long-term effects of medication use during pregnancy on the health of the offspring in later life, but also provides a framework to guide and support research in this area. As such, the knowledge that this conceptual framework provides is not only essential in achieving a greater understanding of the feasibility of using routinely collected health data to investigate long-term effects of medication use during pregnancy, but also in supporting its ability to investigate such outcomes.

Furthermore, this chapter provides an overview of life-course epidemiology. This serves to highlight the importance of conceptualising disease aetiology within a life course framework, as well as recognising that the aetiology of many later-life conditions may rest with prenatal and early-life biological and social factors, in addition to, or in synergism with, those of well-established adult exposures or risk factors. This enables the more thorough investigation and improved evidence of potential long-term effects of medication use during pregnancy.

2.2 Quality Use of Medicines

QUM is defined as the[1];

> Judicious selection of management options[1]: This involves considering the place of medicines in treating illness and maintaining health, only using them when appropriate and recognising that a non-drug option, or no treatment, may be the appropriate management choice;

Appropriate selection of medicines[1]: This involves choosing the most appropriate medicine when a medicine is deemed necessary, by taking into account factors such as the individual, the clinical condition being treated, the potential risks and benefits of treatment, the required dosage, length of treatment and the cost;

Safe and effective use of medicines[1]: This involves ensuring medicines achieve the goals of therapy by ensuring adequate levels of knowledge and skills exist amongst consumers and healthcare professionals to adequately monitor and manage medication use.

The overall goal of the National Strategy for QUM is;

> "…to make the best possible use of medicines to improve health outcomes for all Australians."[1(p 5)]

Importantly, the National Strategy for QUM forms a key element of Australia's National Medicines Policy (Figure 2.1)[1]. The aim of the National Medicines Policy is;

> "…to meet medication and related service needs, so that both optimal health outcomes and economic objectives are achieved for Australians"[1(p 3)]

Obtaining adequate evidence on the judicious, appropriate, safe and effective use of medicines is essential, but not sufficient, to achieving QUM. Even with adequate evidence, studies have demonstrated that many patients may, in fact, not receive care that is in line with current scientific evidence, and the care that they do receive may not be needed or could even be harmful.[2] Strategies directed at improving health outcomes through the improved use of medicines face many challenges and barriers. In recognition of this, the authors of the National Strategy for QUM developed a strong theoretical framework to ensure an evidence-based approach to the translation of research findings into national activities directed at achieving QUM.[1] This evidence-based approach is based on principles derived from education, behaviour change, community development, health promotion, public health and social advocacy literature.[1] Theoretical models used to inform the development of the National Strategy for Quality Use of Medicines include: Social Cognitive Theory[3]; the Transtheoretical Model[4]; PRECEDE-PROCEDE[5]; and the integrative approach to health psychology and public health suggested by Winett, King and Altman[6]. These models apply to consumers, healthcare professionals and policy makers, all of which play an integral role in achieving QUM. More recently, researchers concerned with the gaps that often exist between evidence and clinical practice, have moved to formalise the field of Implementation Research.[2,7,8] They have further defined the conceptual framework for

this area of research, but the research base relies on the same theories of behaviour change as those utilized in structuring the QUM strategy.

The QUM framework is a multi-strategic, multi-level, systems approach to health system change, as it appreciates the need to include the perspectives of all stakeholders in developing, executing and assessing initiatives to improve medicines use.[1] The framework is based on an understanding that the activities of stakeholder groups (i.e. consumers, healthcare professionals, pharmaceutical industry, and governments) influence QUM, with partnership and cooperation between these groups essential if quality use of medicines is to be achieved.

Also considered essential to the success of any QUM endeavour are six key building blocks (Figure 2.2). These building blocks are based on evidence and expert opinion about interventions, regulatory efforts and programs to improve medication use.[1] Evidence and experience in implementing QUM activities over 20 years has firmly established these building blocks as essential components of any initiative towards achieving QUM.[9]

2.2.1 Quality Use of Medicines in Pregnancy

The tenets of QUM are the same regardless of the patient population or condition being treated. The use of medications during pregnancy, however, is made more difficult by the need to balance the risks and benefits associated with their use to both the mother and her unborn child.

When treating medical conditions in women who are pregnant, or are planning to become pregnant, the judicious selection of management options is essential and must address a number of key questions including: Is her condition best managed by pharmacological or non-pharmacological treatment options? How important is it to effectively treat the medical condition during pregnancy? Are there risks to the unborn child if a medical condition is not treated during pregnancy?

If a medication is considered necessary it is important to ensure appropriate selection of medicines. What medication has the most evidence of safe and effective use during pregnancy? What are the risks and benefits associated with using a particular medication? What medications should be avoided during pregnancy? What is the most appropriate dose to use during pregnancy? Are there particular concerns about use in the different stages of pregnancy?

Finally, once a medication has been chosen it is important to ensure all people engaged in prescribing, dispensing, administering or taking of medicines have the knowledge and skills for achieving safe and effective use to achieve the best possible health outcomes.

In order to achieve QUM it is essential to develop, implement, and evaluate resources which guide the judicious selection of management options and appropriate selection of medicines, combined with processes to monitor the safe and effective use of medications against a wide range of health outcomes. There is also a need to develop education and information resources which assist others in adopting and adhering to the appropriate selection and monitoring of treatment options. Underpinning each of these steps is the need for good evidence and effective dissemination of that evidence to all stakeholders to support better informed decision making on medication use during pregnancy.

As outlined in Figure 2.3, there are a number of key steps towards improving quality use of medicines in pregnancy. A key evidence gap identified from clinical practice and existing literature is the potential long-term side effects of prenatal exposure to medications during pregnancy on infant, child, adolescent and adult health and development. Knowledge of long-term side effects is essential for clinical practice and is critical in supporting informed decision making regarding the use of medications during pregnancy. Having identified this evidence gap, the subsequent step involves undertaking research to generate evidence to support the provision of evidence-based information on medication use during pregnancy. It is well recognised that no single approach is sufficient for delineating the complete spectrum of risks or benefits of medication use in pregnancy, especially regarding the potential long-term effects of medication use in pregnancy.[1] However, there is a lack of evidence evaluating the feasibility of using linked health data to assess long-term effects of medication use during pregnancy, providing the focus for this thesis. An evaluation of this approach and other epidemiological research methodologies is presented in Chapter 3.

When considering potential long-term effects of medication use during pregnancy, it is important to have a sound understanding of the way in which environmental influences in early prenatal life can impact on the health of the offspring in later life. The conceptual framework provided by the literature

supporting the Developmental Origins of Health and Disease (DOHaD) hypothesis provides that essential understanding.

2.3 Developmental Origins of Health and Disease

2.3.1 Origins of the Hypothesis

Despite a long latency period between an environmental exposure and the onset of subsequent disease being long recognised in the etiology of certain cancers, it is only in recent years that this phenomenon has been recognised in the etiology of other conditions, such as cardiovascular and metabolic disease.[10] For these conditions, it is well established that adult disease risk is determined by a number of environmental influences and lifestyle factors.[11] However, the scope of the interaction between environment and disease development has been greatly extended over the past 20 years with the introduction of a new paradigm, known as the DOHaD hypothesis.[12] Previously referred to as the Barker or fetal origins of adult disease hypothesis, the DOHaD hypothesis postulates that long-term programming in the structure and function of organs or body systems can be influenced and altered by environmental exposures *in utero*.[13] These alterations in programming of organs and body systems can produce permanent physiological changes that alter disease risk in later life.[12]

A diagrammatical representation of the DOHaD hypothesis is presented in Figure 2.4. The diagram describes the process in which environmental influences at the time of, or following, conception can alter development during the prenatal period. These alterations, potentially combined with postnatal environmental influences, can lead to altered susceptibility to disease in later life.[14] This Figure has been adapted to include the importance of the preconception period in influencing the health of the offspring in later life through alterations in oocyte development prior to conception.[15]

Supporting the DOHaD hypothesis is evidence from fundamental sciences including biology, genetics, embryology, teratology, epigenetics and epidemiology. These sciences provide the biological plausibility and explanation for the relationship between early life influences and phenotypic development and evolution.[16]

2.3.2 The Emergence of the Developmental Origins of Health and Disease Concept

The general concept of the developmental origins hypothesis is not new. The broad idea of a link between early life environmental exposures and health and disease in later life has been around in one form or another since the early 1930s.[17-19] Having observed a reduction in death rates in England, Scotland, Wales and Sweden between 1751 and 1930, Kermack et al.[17] hypothesised that an individual's life expectancy was largely determined by conditions that existed during their early years of childhood, with improved conditions in later adulthood having little direct effect on health outcomes.[17] Using animal studies, Dubos et al.[18] demonstrated that biological characteristics of the adult could be affected in a lasting manner by early life experiences. In 1977, Forsdahl demonstrated, a positive correlation between mortality from coronary heart disease in those aged 40-69 years and infant mortality rates relating to the same cohorts some years earlier in a Norwegian cohort. Differences in infant mortality rates between Norwegian counties was used as an index of the standard of living, suggesting that those born in areas where the infant mortality rate was high were exposed to a low standard of living in early life.[19] Based on these data, it was hypothesised that poor standards of living in the early years could make an individual more vulnerable to a more affluent adult life-style, possibly through permanent alterations caused by early nutritional deficits, and greatly increase an individual's risk towards developing coronary heart disease (CHD) in later life.[19] Similarly, Notkola et al.[20] demonstrated that, in rural Finland, poor living conditions in childhood were associated with an increased risk of CHD mortality and morbidity in adulthood. In the same year, Wadsworth et al.[21] reported that birth weight was inversely associated with blood pressure in both men and women aged 36 in the United Kingdom. However, it was not until a series of studies by Barker et al.[22-27] in the late 1980s and early 1990s that the observations of early life influences affecting disease risk in later life began to be conceptualised into what is now the DOHaD hypothesis.

The first of these studies was published in 1986, with Barker and Ormond demonstrating a positive geographical association between mortality rates for ischaemic heart disease in 1968-78 and neonatal and infant mortality rates in 1921-25.[26] This correlation between mortality rates was interpreted as suggesting a link between adverse environmental influences during early life and future risk of CHD.[26] This initial report led to a number of studies demonstrating a positive relationship between markers of impaired fetal

growth and the incidence of chronic diseases in later life. Anthropomorphic measurements were used as markers of impaired fetal growth, with low birth weight, reduced head and abdominal circumference and low ponderal index found to be associated with an increased incidence of CHD[24,27], hypertension[23,24], type 2 diabetes[22,28] and respiratory disease in adulthood[25]. Notably, the association between birth size and disease risk was continuous across all birth sizes and not just associated with extremes of size.[29] These findings led Barker et al.[30] to conclude that CHD, and other chronic diseases have their origins in early life.

The implications of such findings proved to be highly controversial, with much criticism directed at the hypothesis Barker et al. had proposed and the evidence supporting it. Criticism surrounded the methodological flaws of early epidemiological studies and the emphasis placed on maternal/fetal undernutrition as the underlying causal mechanism.[31,32] Further criticisms have been directed at early epidemiological studies for the level of inconsistencies in results[33], the potential for selection bias due to loss to follow up[34], failures to adjust for important confounders[35] and potentially incorrect statistical interpretation.[36]

In particular, criticisms have been raised regarding the inconsistencies in growth characteristics used. While early studies utilised birth weight as a proxy for fetal growth and development, recognition that this may in fact be a poor marker led many to identify and analyse more detailed growth characteristics at birth.[31] This led to the publication of studies showing associations between birth weight[37], length[38], abdominal circumference[39], head circumference[40], ponderal index at birth (kg/m^3)[41], placental weight[23] and weight at 1 year[42] with later life disease risk.[31] The replication of many of these associations however, has been poor, with birth weight the only characteristic consistently shown to be associated with later life disease risk.[31] The poor replication of results with other characteristics could be explained by the greater difficulty in their measurement at birth as compared to birth weight, and therefore the greater the potential for random error.[31]

An additional area of much debate has been the effect of weight in later life on the associations between birth weight and later disease risk.[31] In some studies, associations between birth weight and later disease risk only emerged after current weight or BMI was adjusted for.[43-46] This led to the suggestion that it is not birth weight itself, but rather the change in weight from birth to current

weight which could be associated with later disease risk.[36] This suggestion has been supported with evidence of associations between rapid weight gain in early life and later disease risk,[38,41,42,47,48] which is discussed in more detail later on in this chapter.

Other criticisms have been directed at the large loss to follow-up in a number of historical cohort studies by Barker et al.[31] Large losses to follow-up are not uncommon in longitudinal studies that span many years, however, it has been shown that membership of some early cohort studies only represented around 37% of eligible births that occurred during the period under study.[35] Other studies (often involving physical examination or laboratory studies) have included an even smaller fraction of the initial birth cohorts (only 5-10%).[34] Therefore, it is not possible to rule out the potential for selection bias.[31,35] Despite these concerns, more recent studies which have managed to generate high follow-up rates of more than 90% have also demonstrated associations between birth weight and later life disease.[37,49,50]

The initial studies by Barker et al. were based on retrospective data from birth cohorts, with limited data available on potential confounders of interest.[31] More recent studies have been able to adjust for potential confounders such as socioeconomic status, ethnicity, maternal medical conditions and age at birth, cigarette smoking, breastfeeding duration and levels of physical activity and still demonstrate the same associations.[37,49,50]

While the initial suggestion was that maternal/fetal undernutrition was responsible for the underlying mechanism, none of the studies provided an actual measure of nutritional intake in mothers or babies.[33] Levels of nutrition are inferred indirectly from fetal and infant growth, with criticism that this is a doubtful surrogate measure.[31,33] Therefore, it is unknown whether nutrition or some other effect is actually being measured.[33] In contrast, studies following up cohorts of individuals exposed to the Dutch famine in 1944-1945 have demonstrated that poor nutrition during early pregnancy, as defined by exposure to famine, is associated with later disease risk, even after controlling for birth weight.[51,52]

While the initial focus of these previously mentioned studies was on the fetal origins of certain diseases in adulthood (i.e. fetal origins hypothesis), it was soon recognised that this only took into account exposures that occurred up until birth, despite the fact that key developmental processes may continue to

be vulnerable to adverse effects even after birth.[53] Therefore, in an effort to recognise the contribution of both the pre- and postnatal environments in the determination of health and disease in later life, the DOHaD hypothesis was formed.[54]

Despite facing numerous criticisms, the DOHaD hypothesis has found a general level of acceptance in the scientific community, with numerous epidemiological investigations supporting the hypothesis that the early environment can influence disease risk in later life.[28,37,38,40-42,48-50,55-66] Notably, these perinatal exposures may exert effects that are relatively independent of environmental risk factors in adults, or may be amplified by other risk factors as is suggested in conceptual life course models.[10] More recently, debate appears to have shifted away from doubts over the existence of early life predictors of future disease risk and instead focused on the public health implications and underlying biological mechanisms which explain this relationship.[31]

The introduction of the DOHaD hypothesis into the medical literature has paved the way for a new field of research investigating the relationship between early life environmental influences and health and disease in later life.

2.3.3 Role of Animal Studies in the Developmental Origins of Health and Disease

Given the noted complexities and difficulties of following up large cohorts of people over long periods of time, animal studies have helped form a critical part of research into the DOHaD hypothesis.[67] These animal studies are critical in advancing the level of understanding about key causal mechanisms underpinning the DOHaD hypothesis, bridging knowledge gaps that would otherwise be unachievable, ethically, in human pregnancies. Various models have been developed using different animal species such as rats,[68] mice,[69] sheep,[70] guinea pigs[71] and pigs,[72] with the rat model most frequently utilised due to its relatively short gestation period and quick postnatal maturation.[70] These models utilise different approaches to investigate long-term impacts of an impaired intrauterine environment. These approaches include models of impaired uteroplacental perfusion to investigate effects of intrauterine growth restriction, maternal nutrient manipulation (i.e. reduction or increase in global nutrient intake or only certain components of the diet such as protein or fat), and maternal exposure to stress and/or glucocorticoids.[73] As a result of these animal studies, a large body of experimental research has now been established to support the biological plausibility of a relationship between early

environmental influences and future disease risk and research continues to further elucidate key mechanisms underlying this relationship.[70,74-78]

2.3.4 Conceptual Models Used to Explain the Developmental Origins Hypothesis

A number of hypotheses have been put forward to describe the biological basis of the associations observed between birth weight and health outcomes in epidemiological studies.[78] These hypotheses include: the thrifty genotype, the thrifty phenotype and the predictive adaptive response model.

2.3.4.1 The Thrifty Genotype

In 1962, Neel proposed the thrifty genotype hypothesis to explain why obesity and type 2 diabetes occurred in such high frequencies within certain populations.[79] The thrifty genotype hypothesis suggests that susceptibility to obesity and type 2 diabetes occurs as a result of a gene-environment interaction.[79] The hypothesis is based on the fact that those who possessed thrifty gene variants are believed to have had an evolutionary advantage in environments characterized by cyclical food shortages and famine.[80-82] These thrifty genes are thought to result in energy-sparing metabolism, ultimately enhancing an individual's ability to store surplus energy as fat.[80,81] However, in circumstances where individuals with a thrifty genotype are exposed to an abundant and stable food supply, it is suggested that their evolutionary advantage begins to work against them, increasing their susceptibility towards the development of obesity and type 2 diabetes.[80,81]

2.3.4.2 The Thrifty Phenotype

The 'thrifty phenotype' hypothesis was first developed by Hales and Barker[64] in 1992 to describe the observed association between poor nutrition *in utero* and insulin resistance and type 2 diabetes in later life.[54] In contrast to the thrifty genotype hypothesis, the thrifty phenotype hypothesis suggests that exposure to adverse prenatal environmental influences can produce a metabolically thrifty phenotype.[64] The hypothesis proposes that a fetus subjected to *in utero* nutrient deficiency becomes thrifty with the available nutrients, adjusting glucose metabolism to maintain high levels of

sugar in the bloodstream required to promote brain development at the expense of muscle growth.[54] It is believed that this induction of a thrifty phenotype is an adaptive response to poor *in utero* conditions, aimed at conserving resources for immediate survival in a sub-optimal environment.[83] It is suggested that once adopted, this thrifty behaviour becomes permanent.[54] If a thrifty phenotype is exposed to a postnatal environment of overnutrition this greatly increases the risk of developing obesity and/or type 2 diabetes as the reduced metabolic capacity of the thrifty phenotype are likely to be overloaded by the excessive nutritional inputs.[64,83]

2.3.4.3 The Predictive Adaptive Response Model

The predictive adaptive response model suggests that the fetus makes predictive developmental responses *in utero* based on early developmental clues.[84] The adoption of various developmental pathways *in utero* are not thought to offer any immediate benefits, but rather form a predictive response that shapes physiological development in expectation of the future postnatal environment.[29] Subsequent disease risk is thought to be related to how well the predictive developmental responses made *in utero* match the actual postnatal environment.[29] The greater the mismatch between the predicted and actual environments, the greater the risk of disease.[29] Such errors in prediction could be made by the fetus due to alterations in the postnatal environment or due to 'faulty' environmental cues on which the prediction was made.[84] These faulty environmental cues could be the result of maternal diabetes or nutrient deficiency and placental dysfunction, for example.[84] Therefore, the fetus exposed to an environment of poor nutrition, undergoes permanent changes to its metabolic functions to optimise survival in a postnatal world of expected food shortage[85] Similarly, a fetus exposed to overnutrition during pregnancy, would be expected to adapt to a postnatal life in which food is plentiful.[85] Problems, such as obesity, occur when there is a difference between fetal programming and postnatal reality.[85]

2.3.5 Mechanisms for the Developmental Origins of Health and Disease

Two overall prenatal mechanisms have been proposed for the DOHaD hypothesis, including developmental disruption and developmental plasticity.[29] An overview of these mechanisms and how they relate to the DOHaD hypothesis is presented in Figure 2.5.

The most striking example of developmental disruption is a physical malformation caused by exposure to a teratogen during a critical period of fetal development.[29] Notably, apart from physical malformations, teratogens can cause a number of other adverse effects including; intrauterine growth restriction, changes in organ programming and functional or developmental alterations (i.e. neurodevelopment, metabolic function).[86,87] While many of these may not necessarily be apparent at birth, they could play an important role in influencing an individual's risk of disease in later life.[86-88]

In contrast to developmental disruption, developmental plasticity is considered to be more regulated, where one particular genotype can give rise to a number of different phenotypes.[29] The concept of developmental plasticity is best described within the thrifty phenotype and genotype hypotheses and the predictive adaptive response model, which have been previously described. In this situation, the developing fetus is able to respond to a number of environmental cues and alter development in a way that is considered to give it an immediate or future adaptive advantage, but which may have adverse consequences in later life.[29]

Three molecular mechanisms are thought to underpin both disruptive and adaptive developmental responses to adverse prenatal environmental stimuli.[67] These include; changes in gene expression, remodelling of tissue development and alterations in the endocrine axis.[67,78]

2.3.5.1 Changes in gene expression

Environmental influences have the capability of influencing gene expression in one of two ways.[29] Firstly, they may cause a transient and reversible effect on gene expression, which represents the normal process of gene promotion and repression.[29] Secondly, they may permanently alter gene expression through chemical modification of DNA in a process referred to as epigenetic

modification.[29] In this situation, expression of a gene becomes fixed in either the 'on' or 'off' position.

Epigenetics refers to the study of mechanisms which modify the structure of DNA, and therefore gene expression, without causing any alterations in the DNA sequence itself.[89,90] The mechanisms by which epigenetic mechanisms can occur include DNA methylation, histone modification and small-interfering RNAs.[90] Epigenetic changes can be inherited mitotically (through the process of cell division), providing an explanation for the long-lasting effects on gene expression observed as cells proliferate throughout life. [91,92]

There is strong evidence that prenatal and postnatal environmental influences such as dietary factors,[93-99] xenobiotic chemicals,[100-102] assisted reproductive technologies[103,104] and low dose radiation,[105] can all lead to epigenetic changes in gene expression, which influence the risk of developing disease in later life.[91] While the majority of this evidence comes from animal models, there is supporting evidence emerging from studies in humans.[106]

For example, there is evidence from animals that periconceptional restriction of maternal folate leads to widespread changes in the fetal epigenome and the development obesity and insulin resistance in later life.[107] This is supported by evidence from humans that adiposity and insulin resistance at 6 years of age is strongly correlated with maternal levels of serum folate during pregnancy.[108]

Further evidence suggesting early-life nutrition can cause persistent changes in the human epigenome is evidence from humans that periconceptual exposure to famine is associated with decreased methylation of insulin like growth factor 2 (IGF2), when measured nearly 6 decades following the exposure.[109] As IGF2 is a key factor involved in human growth and development,[109] this could provide a mechanistic understanding for the increased prevalence of obesity and coronary heart disease observed in adulthood in individuals with periconceptual exposure to famine.[110]

While genes are susceptible to epigenetic modification in the pre- and post-natal periods, the period of most vulnerability is believed to be during embryogenesis.[111] During this time the DNA synthesis rate is high, establishing the elaborate DNA methylation patterning and chromatin structure required for normal tissue development.[112] Notably, the adverse effects of epigenetic modifications that occur during early development may not become apparent until much later in life, especially if they affect genes which modulate response to later environmental challenges.[10] Evidence also suggests that epigenetic modifications may be inherited transgenerationally, meaning early environmental influences may not only have an impact on an individual's health in later life, but also on the health of future generations.[73,91,112]

2.3.5.2 Tissue Remodelling

Tissue remodelling refers to alterations in the characteristics of tissues, through changes in cell number and cell type, which in turn directly influence overall organ structure, size, and function.[67] Critical periods of tissue and organ susceptibility to adverse environmental influences include embryonic and fetal development. Exposure to adverse environmental influences during critical periods of development can permanently alter tissue and organ development through alterations in cellular proliferation and differentiation. This type of response occurs either as a direct reaction to a teratogenic exposure (i.e. thalidomide and limb defects), or as part of a homeostatic adaptation designed to conserve resources and ensure survival in a sub-optimal developmental environment.[67]

There is evidence that adverse prenatal environmental influences can lead to alterations in the structure and function of organs such as the kidney,[113] lung,[77] pancreas,[114] heart[115] and brain[116]. In particular, maternal protein restriction and gestational diabetes have both been shown to induce significant alterations in neuronal density and neuroanatomical structure in the hypothalamus.[68,117] In addition, exposure to glucocorticoids and prenatal stress *in utero* has been demonstrated to alter adult hypothalamic-pituitary-adrenal axis activity and behaviour through alterations in

glucocorticoid receptor gene expression and the development of the serotonergic, noradrenergic and dopaminergic systems.[69,118,119] It is noted that while these alterations in the structure and function of such organs may appear subtle, they could limit their ability to respond adequately to physiological challenges in later life, especially when faced with a decline in function as occurs with age.[120]

2.3.5.3 Alterations in programming of the endocrine axis

Hormones released from the endocrine system closely regulate fetal growth and development.[14] Accordingly, alterations of fetal and/or maternal endocrine function are likely to be key mechanisms in which environmental stimuli can act to influence prenatal growth and development.[14] There is considerable evidence from human and animal studies that early environmental influences can induce permanent changes in the programming of various endocrine systems including the renin-angiotensin system, insulin endocrine axis and hypothalamic-pituitary-adrenal (HPA) axis.[14,67,121-127] For example, low birth weight has been associated with long-term alterations in the function of the hypothalamic-pituitary-adrenal axis, with a subsequent increased risk of hypercortisolemia.[122-124] Similar alterations in HPA axis function have been observed in studies following exposure to prenatal maternal stress,[125,128,129] maternal undernutrition[126,130-132] or glucocorticoids[127,133,134], with offspring displaying alterations of either basal or stimulated HPA axis activity. Exposure to maternal stress during pregnancy, for example, increases circulating levels of glucocorticoids, which can enter the fetal circulation and down-regulate central glucocorticoid receptors in the hippocampus.[135,136] This leads to reduced feedback inhibition and an overactive HPA axis, resulting in increased cortisol secretion in the basal state and in conditions of stress.[135,136] This has a number of important implications for metabolic function in later life, as overactivity of the HPA axis has been associated with a range of cardio-metabolic outcomes in later life, including hypertension, impaired glucose tolerance, insulin resistance and obesity.[137,138]

Given the close relationship between the endocrine system and metabolic function, it is not surprising that prenatal exposure to endogenous and exogenous hormones can disrupt the developing endocrine system and are associated with life-long alterations in metabolic function.[139-144] For example, animal studies have demonstrated that fetal hyperinsulinemia, as a result of maternal diabetes during pregnancy, can produce long-lasting alterations in hypothalamic neurotransmitters involved in the regulation of food intake, body weight and metabolism, thus promoting the development of hyperphagia, overweight and diabetogenic disturbances in later life.[117,145] Furthermore, prenatal exposure to environmental chemicals that have oestrogenic-like activity disrupt complex endocrine signalling pathways and homeostatic control mechanisms, re-setting normal physiological set-points, leading to adverse metabolic consequences in later life such as the development of overweight and obesity.[139,141]

2.3.6 Developmental Origins of Overweight and Obesity

While much of the initial focus was on the developmental origins of diseases such as diabetes and cardiovascular disease, more recently there has been a growing interest in the developmental origins of overweight and obesity.[144] The rapid rise in the prevalence of overweight and obesity worldwide, somewhat unexplainable by factors such as genetic predisposition alone, has led many to question the role of environmental factors *in utero* and susceptibility towards overweight and/or obesity in later life.[140,146] There is now a growing body of literature demonstrating that nutritional and environmental influences *in utero* and early postnatal life could have a significant influence on increasing an individual's susceptibility to becoming overweight or obese in later life.[47,49,51,52,62,147,148]

2.3.6.1 Birth Weight

Numerous studies have demonstrated a positive association between birth weight and subsequent body mass index (BMI) in later life.[149] This association between birth weight and adult BMI has been demonstrated to be J- or U-shaped, with a higher prevalence of adult obesity evident among those individuals with

birth weights which are at the low or high end of the birth weight distribution.[47,49,74,150-154]

A large Danish study involving over 200,000 children born between 1936 and 1983 demonstrated a remarkably stable association between having a high birth weight and being overweight at 6-13 years of age.[155] Furthermore, the association between high birth weight and high BMI in adulthood has been demonstrated to be independent of the rate of childhood growth, but is largely accounted for by maternal weight,[47] suggesting maternal nutrition may play a key role in influencing weight of the offspring in later life.

In recognition of the noted criticism surrounding the use of BMI as an indicator of adiposity, Kensara et al.[62] investigated the association between birth weight and adult body composition using dual-energy X-ray absorptiometry. They observed that, as adults, males with a lower birth weight were more likely to have a greater fat mass, central adiposity and lower muscle mass than those with a high birth weight.[62] The researchers also found that traditional anthropometric measures used in other studies can be misleading, especially when comparing individuals with low and high birth weights.[62] For example, among individuals with the same BMI, percentage body fat was greater in the low birth weight group compared with the high birth weight group.[62] This observation may help to explain the somewhat paradoxical observation among adults of the same BMI, that being of low birth weight is associated with an increased risk of CHD, compared to being of high birth weight. Notably, a limitation of this study was that no control group of men with a normal or average birth weight was included for comparison.

It is important to note that the use of birth weight as an indicator of fetal growth *in utero* represents a relatively crude measure.[156] While a low or high birth weight could be a product of an adverse nutritional environment during pregnancy as is often hypothesised, use of birth weight alone does not adequately reflect the effect of the intrauterine environment on fetal growth. For example, major non-pathological determinants of intrauterine growth include

gestational age, infant sex, maternal weight and parity.[157] In addition, pathological determinants of intrauterine growth include placental function, smoking and the presence of medical conditions (i.e. asthma, diabetes), during pregnancy.[157] Each of these determinants may have a transient or permanent effect on fetal growth, with patterns of growth likely to vary between individuals. Therefore, while the investigation of the association between birth weight and BMI in adulthood may implicate the fetal environment in the development of obesity in later life, additional research has focused on specific determinants of fetal growth and their long-term effects on the health of the offspring in later life.

2.3.6.2 Poor Nutrition During Pregnancy

The most widely recognised approach to investigating the long-term impact of maternal under-nutrition during pregnancy in humans has been to follow-up offspring exposed to the Dutch famine of 1944-5.[52] Initial follow-up of 300,000 males aged 19 years demonstrated that exposure to famine during the first 2 trimesters of pregnancy is associated with an increased risk of overweight and/or obesity in later life.[51] This observation was independent of body size at birth.[51] On the other hand, exposure to the famine in the last trimester of pregnancy and the first 3-5 months of life was associated with a decreased risk of overweight and/or obesity in later life.[51] As the famine lasted for approximately 5 months, no individuals were exposed to famine throughout all of gestation. Ravelli et al.[52] followed up 741 males and females at the age of 50 who were exposed to the famine during pregnancy. They found that exposure to famine during early gestation was associated with higher BMI and waist circumference in women, but not in men. [52] These observations agree with the thrifty phenotype and predicative adaptive response models, where initial adaptations to an environment of nutrient deficiency, followed by exposure to an environment of nutrient excess (once the famine was over) increases the risk of overweight and/or obesity in later life.

In addition to maternal nutritional intake, poor fetal nutrition may also be caused by placental insufficiency.[75] The effects of placental

insufficiency have been investigated in a number of experimental studies, in which fetal growth restriction occurs in response to decreased placental delivery of oxygen and glucose.[75] Placental insufficiency may be a transient or permanent effect and may occur at different time periods during gestation. In line with the predictive adaptive response model previously described, it has been demonstrated that during periods of placental insufficiency the fetus makes a number of neuroendocrine, metabolic and cardiovascular adaptations to prepare themselves for an expected lifetime of continuing adversity. [74,75,158] When this prediction fails, however, due to a mismatch between a poor prenatal and abundant postnatal nutritional environment, the individual is at greater risk of adverse health outcomes in later life, in particular the development of obesity.[75,158]

2.3.6.3 Catch-Up Growth During Early Childhood

The somewhat paradoxical observation that those with a lower birth weight are most likely to have a higher adult BMI is complex. Some of these low birth weight babies experience accelerated growth, with more rapid weight gain during the early postnatal period.[36,159] This rapid weight gain is thought to adversely affect body composition, influencing disease risk in later life.[160]

The definition, and therefore investigation, of accelerated growth is somewhat variable within the literature. In general, it can be defined as growth velocity (height and weight change per year) greater than the median for age and sex.[161] This could be observed, for example, as an infant of low birth weight rapidly crossing weight and height for age centiles on commonly used growth charts. While studies have differed in relation to the definitions of rapid growth and overweight or obesity in childhood and adolescence and the age of subjects at follow-up, there appears to be sound evidence supporting the association between rapid postnatal growth and the development of overweight and/or obesity in later life.[47,160,162,163] These observations are further strengthened by evidence from studies of formula-fed and breastfed infants, which show overweight and/or obesity in later

life is associated with formula feeding and rapid weight gain in early infancy owing to overnutrition during this period.[164-166]

2.3.6.4 Maternal Overnutrition and Diabetes During Pregnancy

In the context of the global obesity epidemic it is also important to consider the impacts of maternal overnutrition during pregnancy.[74,167,168] Women entering pregnancy with a high BMI are at increased risk of developing a number of pregnancy related complications including gestational diabetes and of giving birth to an infant with fetal macrosomia (birth weight > 4000g or birth weight for gestational age > 90 percentile).[169] There is growing evidence from animals that intrauterine overnutrition can induce permanent changes in appetite control, neuroendocrine functioning and metabolic function in the developing fetus, influencing their lifelong risk of obesity.[168] This is supported by evidence from epidemiological studies which demonstrate that children born to obese mothers are twice as likely to be obese by 2 years of age compared to children of mothers whose BMI was in the normal range at the beginning of pregnancy.[153]

A key component of the association between maternal obesity and risk of overweight in the offspring in later life appears to be the impact of maternal diabetes, whether pre-existing or pregnancy induced. The presence of maternal diabetes is a significant risk factor for fetal macrosomia (large for gestational age baby).[170] Unlike maternal glucose, maternal insulin is not able to cross the placenta.[151] In response to this glucose, the developing fetal pancreas produces insulin, which in addition to its hypoglycaemic effects, also acts as a fetal growth hormone.[151] Therefore, maternal hyperglycaemia leads to excess fetal insulin which, through its effects on fetal growth, leads to higher birth weights.[171] As previously mentioned, In addition to this, animal studies have demonstrated that fetal hyperinsulinemia can produce long-lasting alterations in hypothalamic neurotransmitters involved in the regulation of food intake, body weight and metabolism, thus promoting the development of hyperphagia, overweight and diabetogenic disturbances in later life.[117,145] Studies investigating the long-term impacts of fetal hyperinsulinemia have

demonstrated that infants of mothers who had diabetes during pregnancy exhibit a significantly enhanced risk of overweight and/or obesity in later life.[172-176]

2.3.6.5 Maternal Smoking During Pregnancy

The deleterious effects associated with smoking during pregnancy have been well documented.[177] Smoking during pregnancy has been associated with intrauterine growth restriction, with children of smokers more likely to have low birth weights, be shorter and have less fat mass at birth than children of non-smokers.[178,179] Given fetal growth restriction is normally associated with decreased placental delivery of oxygen and glucose to the fetus, any adaptive responses the fetus makes to cope with decreased nutrition supply is likely to place them at increased risk of adverse health outcomes in later life.[75,158]

Indeed, numerous cross-sectional and cohort studies have demonstrated that childhood or adult obesity is associated with maternal smoking during pregnancy.[61,144,148,177,179-188] In addition, a recent systematic review and meta-analysis concluded that there was strong evidence linking maternal smoking with childhood overweight, even after adjustment for potential confounders such as socioeconomic status, parental body size, gestational weight gain, infant feeding and childhood behaviours.[189]

Notably, a study by Power et al.[61] demonstrated an increased risk of overweight and/or obesity at age 33 in men and women whose mothers smoked during pregnancy. Smoking during pregnancy was associated with lower birth weight.[61] However, after adjusting for birth weight, the association between maternal smoking and obesity was not affected, suggesting smoking influences later risk of overweight and/or obesity independently of its effects on fetal growth.[190] This finding supports that of the Dutch famine cohort study, where the association between early *in utero* malnutrition and obesity was independent of its effects on birth weight.[51]

Wideroe et al.[182] also showed that maternal smoking was associated with childhood overweight and/or obesity at 5 years of age. In addition, a linear relationship was observed between the

number of cigarettes smoked and BMI at 5 years of age, suggesting a dose-response effect which has also been observed in other studies.[61,180,182] In contrast to the findings by Power et al.[61] however, they found that adjustment for birth weight increased the observed risk.[182]

No clear mechanisms have been identified to explain the observations between maternal smoking and childhood overweight and/or obesity. Questions have been raised about nicotine, which is known to cross the placenta, and carbon monoxide, which can influence placental vascular function and cause fetal hypoxia.[189] Studies in both humans and animals demonstrate a reduction in appetite and body weight following nicotine administration, while the opposite occurs in nicotine withdrawal, with hyperphagia and weight gain common.[191-196] The underlying mechanism may lie in nicotine's effects on hypothalamic neurotransmitters involved in appetite control and regulation, with animal studies showing that fetal exposure to nicotine can cause long-term alterations in the dopamine and serotonin neurotransmitter systems.[197-199]

2.3.7 Prenatal Medication Exposure and the Developmental Origins of Health and Disease

This chapter outlines the expanding body of research that is being undertaken based on the theoretical framework provided by the DOHaD hypothesis. Using this framework, an extensive body of evidence has been generated linking fetal exposure to a number of environmental influences during pregnancy (i.e. poor nutrition, maternal obesity, diabetes, smoking and exposure to environmental chemicals) and a greater risk of adverse health outcomes in later life, including the development of overweight and obesity. Conceivably, exposures to medications used during pregnancy could also play a significant role in influencing the development of diseases in later life. The challenge now is to further examine the applicability of this theoretical framework for examining potential long-term effects of medications used during pregnancy.

To date, the investigation of teratogenic effects of medications has largely focused on physical alterations (i.e. malformations) as opposed to functional alterations (i.e. neurodevelopment, metabolic function) that may not be

apparent at birth but could influence an individual's health and risk of disease in later life.[88]

The discovery in the early 1970s of an association between the use of diethylstilbestrol during pregnancy and an increased rate of vaginal adenocarcinomas in young women exposed in utero is a pertinent reminder of why we must ensure adequate follow-up of all medication exposures during pregnancy.[200] In more recent years, potential long-term effects following prenatal exposure to other medications have emerged. For example, *in utero* exposure to sodium valproate has been associated with an increased risk of impaired cognitive function in the child at 3 years of age.[201] There is evidence that paracetamol use during pregnancy is associated with an increased risk of asthma and wheezing in the offspring during childhood.[202] Furthermore, antidepressant use during pregnancy has been associated with an increased risk of childhood autism spectrum disorders[203] and the disturbed development of the enteric nervous system[204]. Given the well demonstrated associations between neonatal outcomes, such as birth weight and gestational age, and morbidity and mortality in later life,[62,149,205,206] questions are raised about the potential long-term impacts of prenatal medication exposures. For example, use of phenytoin and phenobarbital during pregnancy has been associated with both intrauterine and postnatal growth restriction[207,208], while the use of atypical antipsychotics[209] and antidepressants[210] has been associated with an increased risk of low birth weight. Whether these adverse effects caused by medication use during pregnancy translate into susceptibility to disease in the offspring in later life is not well investigated.

While these provide examples of potentially negative outcomes associated with medication exposure, in some instances medication use may play a role in positively influencing long-term outcomes. For example, the use of medications in the treatment of maternal diseases such as diabetes and hypertension, which themselves have been associated with long-term adverse outcomes,[173,211] are important in reducing the adverse impact of these diseases on fetal development and subsequent later health outcomes. As such, it is important to consider not only the long-term risks, but also potential long-term benefits, associated with medication use during pregnancy.

Conditions in childhood such as obesity, diabetes, asthma, atopic diseases, behavioural disorders and impaired cognitive function may well be linked to medication use during pregnancy,[212] but until systems are established for

longer-term follow-up of medication exposures during pregnancy, knowledge on this subject will remain inadequate. The importance of assessing the risks and benefits of medication use during pregnancy is beyond dispute, as medications could potentially increase or decrease susceptibility towards disease in later life depending on a number of factors.

2.4 Life Course Epidemiology

Over recent years there has been an increasing interest in conceptualising disease aetiology within a life course framework.[213] With this framework, there has emerged a growing realisation that the aetiology of many later-life conditions may rest with prenatal and early-life biological and social factors, in addition to, or in synergism with, those of well-established adult exposures or risk factors.[214] It is this field of research which is now referred to as life course epidemiology.[213]

By definition, life course epidemiology is the;

> "Study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life."[215]

By taking into account the importance of time and duration of exposures and time in relation to disease development, life course epidemiology seeks to understand causal links between exposures and outcomes.[216] The premise for life course epidemiology lies in the understanding that numerous biological and social factors across an individual's life course can independently, cumulatively and interactively influence health and disease outcomes in later life.[215]

A number of conceptual life course models have been proposed and are listed in Table 2.1. The one of particular interest in the area of medication exposures during pregnancy, and therefore the focus in this thesis, is the critical period model.

The critical period model emphasises the timing at which exposure occurs, where exposures that occur during critical periods of development throughout an individual's life course, could have long-lasting effects on anatomical structure or physiological function that may eventually result in disease.[213] It is this theory of biological programming that forms the basis of the DOHaD hypothesis.[213] Exposures during critical periods of development may have long-lasting effects that are not modified in any dramatic way by later life exposures.[215] Alternatively, the critical period model also recognises that these long-term effects on disease may in fact be influenced by later life

risk factors or effect modifiers.[213] For example, following exposure during the critical period of development, other exposures such as physiological or psychological stressors in later life may either enhance or decrease the risk of subsequent development of chronic disease.[216]

A critical period of exposure is not a new concept when it comes to studying potential teratogens. Taken in its most pure form, this model advocates that an exposure occurring during critical periods can cause permanent and irreversible damage or disease.[213] The most stark example of this would be maternal exposure to thalidomide in pregnancy and it's well recognised adverse effects on limb development.[217] However, it is essential that within the context of chronic disease, a differentiation be made between the effects of exposure on physical alterations (i.e. congenital malformations) as opposed to functional alterations (i.e. neurodevelopment, metabolic function) that may not be apparent at birth but could influence an individual's health and risk of disease in later life. For example, an infant exposed to sodium valproate during pregnancy may show no signs of physical malformations, but may suffer from an intellectual disability or autism spectrum disorder, both of which have been associated with prenatal exposure to valproate.[218]

It is important to note that the risks associated with adverse exposures during fetal life may be modulated by the postnatal environment. This has also been demonstrated to be sex-specific, with quality of maternal care in the early postnatal period shown to influence hippocampal volume in adulthood in females, but not males.[219] Birth weight, used as a measure of a potentially disadvantageous prenatal environment, was shown to predict adult hippocampal volume, but only among female subjects reporting low maternal care. No relationship was observed between birth weight and adult hippocampal volume among those reporting high maternal care, suggesting the postnatal environment can modulate the neurodevelopmental consequences of prenatal risk. Therefore, differences in postnatal maternal care between those with treated and untreated psychiatric illness could play an important role in determining the risk of disease in the offspring in later life. This has important implications as, while low birth weight has been associated with alterations in HPA activity and increased risk of metabolic dysfunction in later life,[220] the considerable variability in outcome measures assessed in follow-up studies of low birth weight infants[221] could be explained by the interaction of postnatal factors with prenatal conditions.

2.5 Summary

Given the potential for environmental influences in early prenatal life to affect the health of the offspring in later life, it is important to investigate methods which can be used to investigate long-term outcomes following exposure to medications during pregnancy. It is recognised that no single approach is sufficient for delineating the complete spectrum of risks or benefits of medication use in pregnancy, especially regarding the potential long-term effects of medication use in pregnancy.[222] In light of this, the next chapter reviews epidemiological research methodologies used to examine outcomes following medication use during pregnancy and discusses their associated strengths and limitations.

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Figure 2.1 Interdependence of the four objectives of Australia's National Medicines Policy

Reproduced from [1(p 4)]



This figure illustrates the interdependence of the four components of Australia's National Medicines Policy. Central to this policy is the optimisation of health outcomes for consumers. Directly supporting this goal is the Quality Use of Medicines component of the policy. Essential in enabling and supporting quality use of medicines are the other three closely interlocked components of the policy: quality, safety and efficacy; equity of access; and a viable pharmaceutical industry. Also depicted in this figure is the concept that public policy on medicines must be integrated with broader health and trade policies.[1]

Figure 2.2 Six key building blocks supporting Quality Use of Medicines

Text reproduced from [1(p 17)]

Objective information and ethical promotion	Quality Use of Medicines				Strategic research, evaluation and routine data collection
	Policy Development and Implementation	Facilitation and coordination	Education and training	Services and Interventions	
i.e. the need for access to information that supports best practice	*i.e. the need for policies and protocols that support QUM*	*i.e. the need for ways to foster and facilitate research into QUM*	*i.e. the need for access to education and training that supports best practice*	*i.e. the need for the ability to access or provide services and interventions that support QUM*	*i.e. the need for routine evaluation of practice to ensure QUM is being achieved.*

Figure 2.3 Cyclical process of improving Quality Use of Medicines in pregnancy

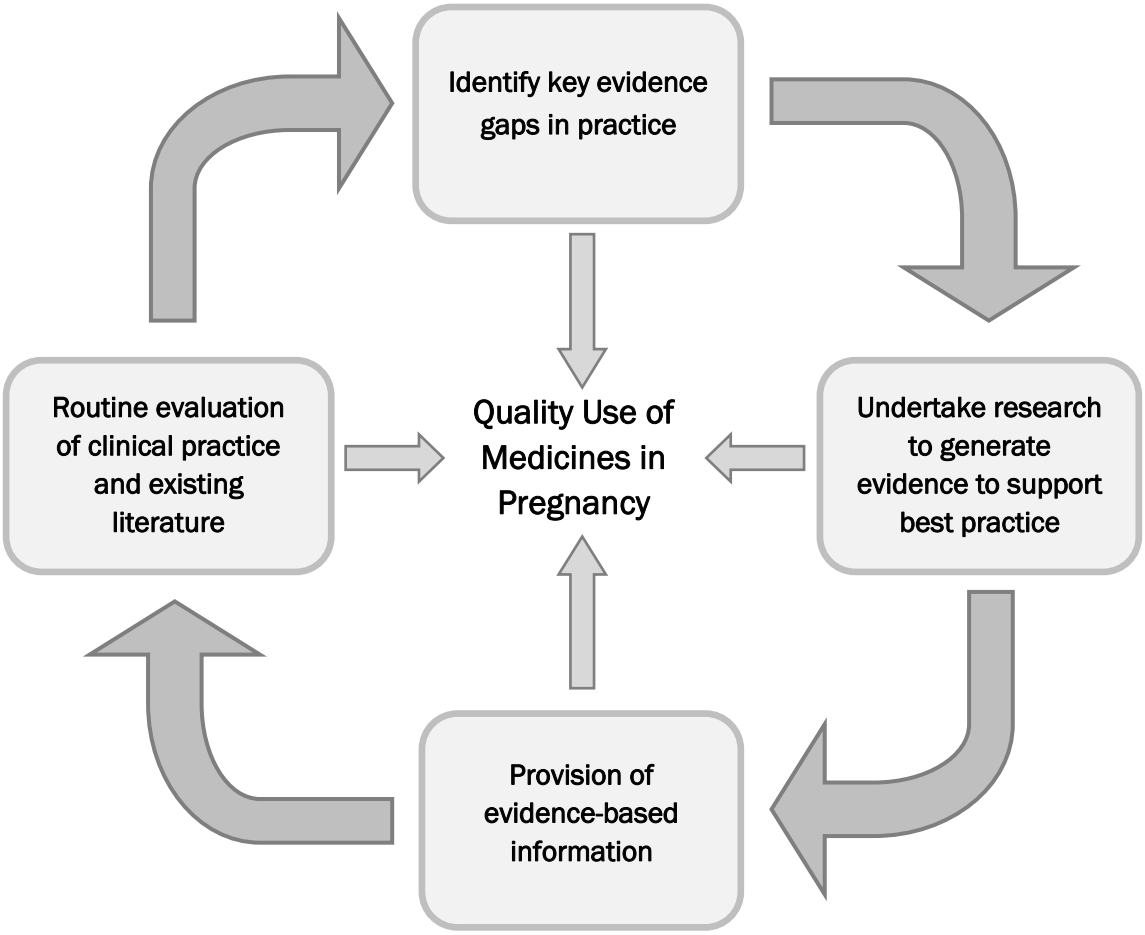


Figure 2.4 Diagrammatical representation of the Developmental Origins of Health and Disease hypothesis (Adapted from [14(p 2),15])

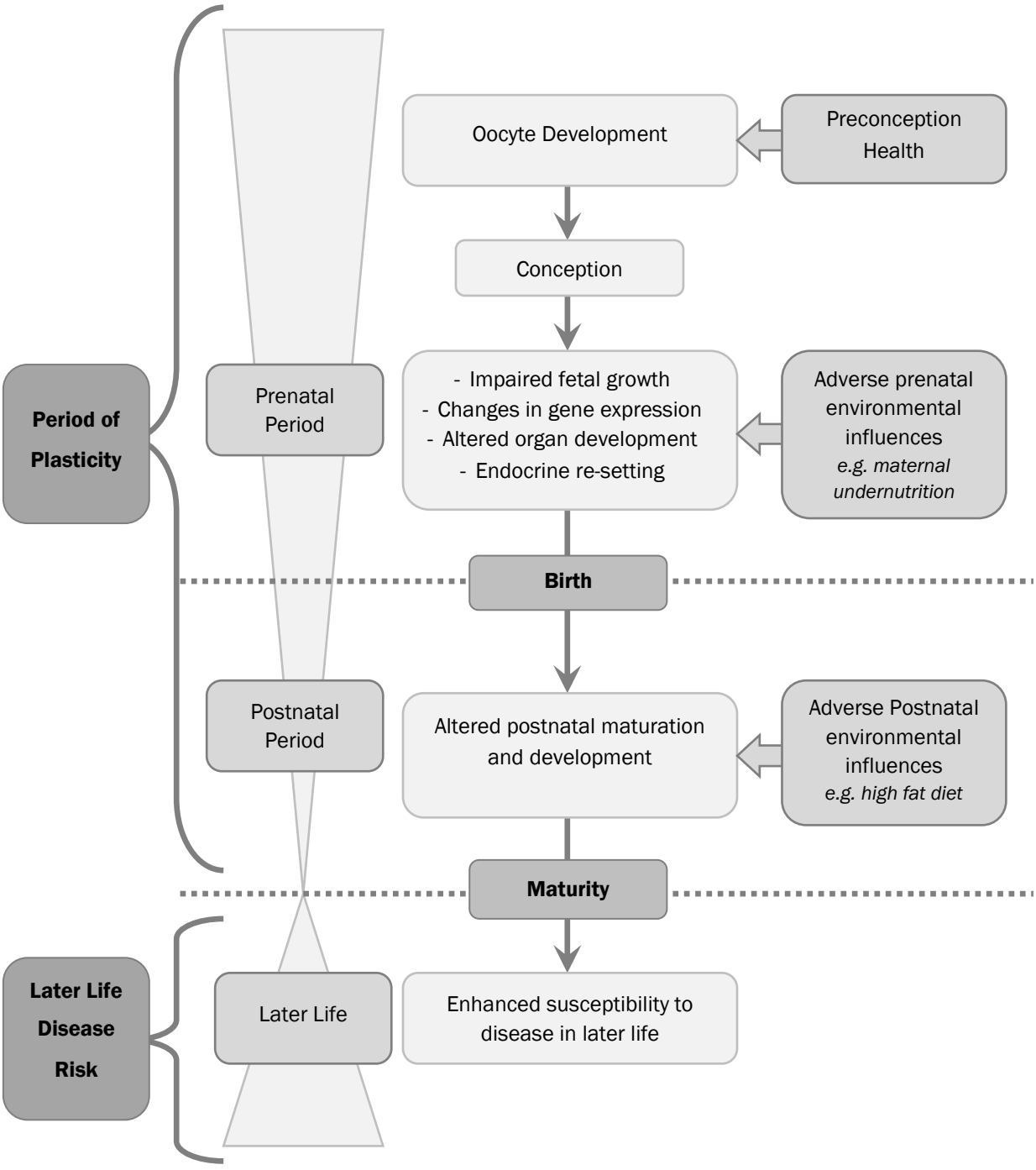
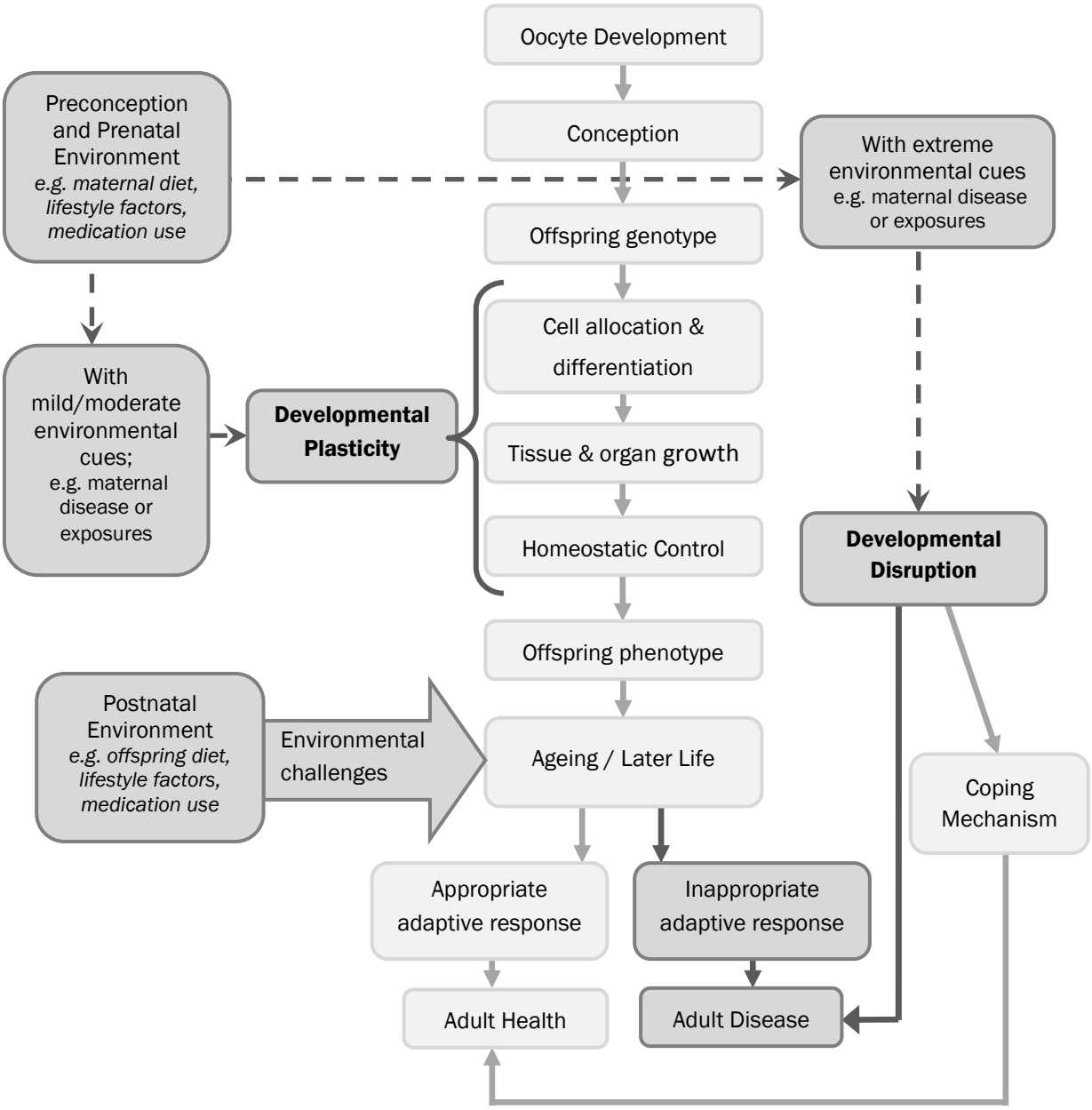


Figure 2.5 Overview of mechanisms proposed in the Developmental Origins of Health and Disease hypothesis (Adapted from [120(p 4)])



This figure provides an overview of the two prenatal mechanisms which have been proposed for the DOHaD hypothesis. These mechanisms include developmental disruption and developmental plasticity. An individual's genome is subjected to a wide range of environmental influences in utero, which help determine its phenotype. In the case of developmental plasticity, the developing fetus is able to respond to a number of environmental cues and alter development in a way that is considered to give it an immediate or future adaptive advantage, but which may have adverse consequences in later life depending on the extent of matching between the prenatal and postnatal environments. In the case of extreme environmental influences (e.g. maternal disease, maternal medication use), a clear disruption of normal development can occur (i.e. equivalent to teratogenesis as shown by the dotted line), in which case the individual is left to cope with the alteration in development and is at immediate and future risk of disease. In addition, this Figure has been adapted to include the importance of the preconception period in influencing the health of the offspring in later life through alterations in oocyte development prior to conception.[15]

Table 2.1 Conceptual life course models[213]

Critical period model
With or without later risk factors
With later life effect modifiers
Accumulation of risk
With independent and uncorrelated insults
With correlated insults
‘risk clustering’
‘chains of risk’ with additive or trigger effects

CHAPTER 3

A Review of Epidemiological Research Methods and Methodological Challenges

Manuscript

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Investigating Outcomes Associated with Medication Use During Pregnancy: a review of methodological challenges and observational study designs

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3.1 Abstract

In the absence of randomised controlled trials, knowledge of outcomes associated with medication use during pregnancy is dependent on observational studies. Numerous observational study designs exist, with the decision on which is most appropriate depending on a number of factors, including the exposure and outcome under investigation and knowledge of key methodological issues. This review provides an overview of the key methodological issues involved in undertaking observational studies to investigate medication use during pregnancy, including selection bias, exposure and outcome classification, information bias, confounding and statistical analysis. This review also discusses observational study types used to investigate outcomes associated with medication use during pregnancy and summarises their relative strengths and weaknesses. Knowledge of the strengths, weaknesses and methodological issues associated with observational studies can assist clinicians in making assessments about the validity and applicability of results presented in order to provide the best recommendations to patients.

3.2 Introduction

Women are generally advised not to take medications during pregnancy unless the potential benefits of treating an illness outweigh the potential risks of the medication to both the mother and fetus. Unfortunately, when it comes to medication use in pregnancy, evidence regarding the risks and benefits is often lacking, contradictory or difficult to interpret and apply to clinical practice. While randomised controlled trials (RCTs) are seen as the gold standard for assessing safety and efficacy of medications, pregnant women are usually excluded from RCTs for ethical and medical reasons. In addition, RCTs tend to have short-term follow-up, limiting the potential to investigate long-term outcomes. Therefore, this places a heavy reliance on observational studies to provide evidence to support informed decision making on medication use during pregnancy.[1,2] While ethical issues, for example, may make it difficult to justify exposing pregnant women to medications of unknown safety in RCTs, unintentional or unavoidable medication exposures during pregnancy are common. These exposures provide a significant opportunity to undertake observational studies to gather evidence on resultant pregnancy outcomes, both short and long-term. The most important difference between an observational study and a RCT is the non random allocation of exposures between individuals. This presents challenges in the design and analysis of observational studies and the ability to separate causal from non-causal explanations of observed associations.[3,4] Despite these challenges, observational studies can generate

credible evidence on outcomes associated with medication use during pregnancy, as long as they are appropriately designed, evaluated and reported. The importance of good design, evaluation and reporting of observational studies is highlighted in the recently published "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement".[5] While medication use during pregnancy can be evaluated using a number of different observational study designs, the decision on which study design is most appropriate depends on a number of factors, including the exposure and outcome under investigation and the study's ability to address key methodological issues.

The aim of this review is to provide an overview of the key methodological issues involved in undertaking observational studies to investigate outcomes associated with medication use during pregnancy. This review will also discuss observational study types used to investigate outcomes associated with medication use during pregnancy and discuss their relative strengths and weaknesses. This will assist in facilitating an understanding and appraisal of their validity and applicability in clinical practice. A guide is also provided to assist healthcare professionals in critically evaluating observational studies which is essential in making assessments about the validity and applicability of results presented in order to provide the best recommendations to patients.

3.3 Methodological Challenges

In many ways, depending on the outcomes being investigated, the epidemiological challenges involved in studying outcomes following medication use during pregnancy are similar to those of other epidemiological studies. There are, however, a number of key challenges that are either unique to this field of research, or are sufficiently important to demand particular attention and these will be discussed further. Epidemiological challenges include: selection bias, exposure and outcome classification, information bias, confounding, statistical analysis, interpretation of results and sample size considerations.[6] These methodological challenges can threaten the validity of a study and should be considered when interpreting reported outcomes associated with medication use during pregnancy. Key factors to consider when evaluating observational studies are summarised in Table 1, and will be discussed further individually

3.3.1 Selection Bias

Selection bias is a systematic error due to differences in characteristics between those who are selected for a study and those who are not. Selection bias leads to differences in measured or unmeasured baseline characteristics

between study groups as a result of design and execution errors in sampling, selection or allocation methods.[7] Certain aspects of the selection of patients for a study can influence the generalisability of the results (i.e. external validity) to other populations. For example, studies undertaken using records collected from teratogen information services suffer from the limitation that the sample population is only representative of those who call the teratogen information service (TIS). Women who utilise these services, however, may not be reflective of the general population.[8] For example, women who contact a TIS are more likely to be of higher socioeconomic status and have a greater educational background. As such, women who call a TIS may be at a lower risk of adverse pregnancy outcomes than those that do not call.[9] However, as long as the exposed and control group is derived from the same population of women calling the TIS, this will not affect the validity of any findings, only their generalisability.

Studies which rely heavily on voluntary reporting (e.g. pregnancy exposure registries) or require consent from subjects to take part in the study can also suffer from selection bias.

The degree to which voluntary reporting can bias results is well demonstrated in a study comparing the rate of major birth defects among women taking itraconazole during pregnancy who were either identified prospectively (i.e. during pregnancy) or retrospectively (i.e. after pregnancy) in a pregnancy exposure registry.[10] They observed that among the children of women retrospectively identified, 13.0% had major birth defects, compared with 3.2% in those prospectively identified (RR 4.04; 95% CI 1.50–10.9).[10] This meant that the chance of a major birth defect being reported after first-trimester exposure to itraconazole was four times higher if the report was made after the pregnancy outcome was known, highlighting the impact of voluntary reporting bias.

The inclusion of only live-born infants in a study can represent an important form of selection bias. With improvements in ultrasound and antenatal care many malformations can be detected at an earlier stage during pregnancy, meaning women have the opportunity to terminate the pregnancy in the case of major malformations. Furthermore, even if these pregnancies are not terminated, they may result in a spontaneous abortion or stillbirth. Therefore, the investigation of malformations only among live-born infants may

significantly underestimate any increased risk of malformations associated with medication exposure.[11]

Selection bias can also be an issue if there are differences between those who consent and do not consent to participate in a study. While it is not uncommon to see consent rates between 60-80%,[12-15] the exact difference in consent rates between groups should be reported and compared as well as any potential differences in maternal and/or neonatal differences that could help assess the potential for selection bias.

Another aspect of selection bias that is prevalent in prospective cohort studies, especially those that extend over long periods of time, is loss to follow-up. This is important if there are systematic differences between those who are and who are not lost to follow-up. Therefore, all longitudinal studies should outline and compare the number of participants lost to follow-up and examine potential differences in underlying characteristics between those lost and not lost to follow up.

Confounding by indication is another key challenge in observational studies and represents a form of selection bias. Confounding by indication can occur where there is an underlying difference in the risk profiles (which can include clinical and non-clinical patient factors) amongst those exposed and not exposed to a medication of interest.[16] For example, when comparing outcomes between women exposed and not exposed to antidepressants during pregnancy, it is difficult to separate the direct effect of the antidepressant exposure from that of the underlying maternal psychiatric illness, especially when maternal psychiatric illness is associated with a range of maternal characteristics (e.g. smoking, substance abuse) which could influence the underlying risk profile for the outcome under investigation.[4] In the absence of data on underlying maternal illness, one approach to dealing with this issue is to compare outcomes between women using different medications for the same condition. However, this also has its limitations as there may be underlying differences between subjects (i.e. disease or disease severity) which influenced the decision on whether they were prescribed one particular medication over another. For example, a recent study by Bar-Oz et al. demonstrated that significantly more women reported using paroxetine for anxiety or panic disorders (49.3%) than women taking other SSRIs (19.9%) (OR 4.11 95% CI 2.39, 7.08).[17]

Therefore, it is critically important that all studies address the potential for confounding by indication and attempt to delineate any potential negative effects of an underlying disease from that of the medications used in their management. This approach is essential in ensuring any teratogenic potential of a medication is not falsely exaggerated at the expense of important advice regarding the appropriate management of maternal illness during pregnancy.

3.3.2 Exposure Classification

The accurate identification and assessment of medication exposures during pregnancy is a critical methodological challenge. Key factors including timing, dose and duration of medication use are all likely to play an important role in influencing outcomes.[18]

Before discussing each of these factors, it is important to highlight the limitation associated with the common approach of evaluating outcomes for a class of medications together, rather than individually. While sample size may be improved by analysing medication as a class, it relies on the potentially flawed assumption that all medication within that class have the same teratogenic risk.[19] Differences in chemical structure, therapeutic indication, pharmacology (i.e. receptor specificity) and pharmacokinetics (i.e. half-life) could all have a significant effect on influencing teratogenic risk. For example, thalidomide and glutethimide are structurally related, but there is no evidence that glutethimide is teratogenic, even at large doses.[4,20] Therefore it is important that a class of medications be assessed separately, and only grouped if there is no apparent heterogeneity.[9,19]

3.3.2.1 Timing of Medication Use

It is essential that studies investigating outcomes associated with medication use during pregnancy carefully consider and identify exposure occurring during relevant periods of fetal development.[19] For outcomes such as intrauterine growth restriction or neurodevelopment the exposure interval of interest may be wide, but for malformations this exposure interval is relatively narrow. Traditionally, studies investigating associations with malformations have focussed on exposures occurring during the first trimester of pregnancy.[19] Given the period of greatest susceptibility for most major malformations is during the second and third month of

pregnancy, the first trimester concept could be considered outdated.[19] In light of this, evaluation of outcomes should be undertaken according to exposures occurring only during known critical periods of development, rather than the first trimester as a whole.[21] This, however, would require international consensus on the critical periods of exposure for different malformations and may not always produce reliable results if there are concerns around the accuracy of data on the exact timing of medication exposures during pregnancy. For example, one factor influencing the accuracy of data on timing of exposure is the accuracy of reported gestational age. As such, it is important to consider how gestational age is determined. Gestational age based solely on the estimated date of the last menstrual period may be inaccurate, while gestational age confirmed by antenatal ultrasound is likely to be more reliable.[19] Furthermore, timing of exposure will not only depend on the date when the medication was taken, but will also differ according to its pharmacokinetics (i.e. half-life). For example, a medication with a long-half life, such as fluoxetine,[22] may remain in the fetal circulation for a number of days before being completely eliminated. Therefore it is important to take into account the pharmacokinetics of the medication under investigation before deciding on relevant exposure periods during pregnancy, and is some cases exposures occurring a number of days or weeks prior to the critical period of development may still be important.[19] In addition, it is important to comment on the increasing use of administrative database studies to investigate outcomes associated with medication use during pregnancy. A major limitation associated with these studies are uncertainties regarding the exact timing and duration of medication use, which have been well described elsewhere.[23] The major limitation is the underlying assumption that all women dispensed a medication take that medication at the time the medication was dispensed during pregnancy.

Therefore, while the first trimester concept could be considered outdated, in situations where there is a degree of uncertainty as to the exact timing and duration of medication use we need to question how confident we can be in focusing on narrow intervals

of medication exposure. While wider windows of exposure may be necessary to counter uncertainty of exposure, narrow windows are necessary to ensure validity of outcomes.

3.3.2.2 Dose Taken

In addition to data on timing, the inclusion of data on the dose taken during pregnancy is useful as it enables investigation of a dose-response relationship. That is, whether outcomes are more likely to occur as dose increases. It is also important to consider the difference between a dose-response relationship and dose-threshold effect. For example, does a medication cause a proportional increased risk of malformations at all doses, or is there a clear dose-threshold effect where only doses above a certain level are considered teratogenic. Dose-threshold effects have been demonstrated in a number of studies. For example, according to data collected in an anti-epileptic use in pregnancy registry the incidence of malformations following prenatal exposure to sodium valproate was 30.2% in those taking doses greater than 1100mg compared to just 3.2% (similar to background rate) in those taking doses less than 1100mg.[24] Additional studies have also demonstrated an increased risk of malformations at doses higher than 1000mg per day.[25, 26] In an additional example, one study demonstrated that paroxetine was only associated with an increased risk of cardiac malformations among women taking an average daily dose >25 mg/day.[27] In this study, 25% of women had an average daily dose >25 mg/day. In this situation the average daily dose was estimated based on the total cumulative dose of paroxetine dispensed (mg) divided by the estimated total duration of paroxetine use (days) during the first trimester. This approach has obvious limitations and the use of dispensing data to estimate dose has not yet been validated. Notably, additional studies have failed to demonstrate the same dose-threshold effect.[28,29]

A unique approach towards studying the teratogenicity of medications is the investigation of outcomes among women who attempt suicide by taking large doses of medication.[19] Assessing these outcomes is useful, as if no increased risk of malformations is observed following exposure to very large doses of medications

then it serves as a strong argument against teratogenicity. The difficulty lies in interpreting results where an increased risk of malformations is observed. Given the doses consumed by women attempting suicide are often much higher than doses used clinically, translating results from these studies into clinical practice is challenging. Additional important limitations include the fact that the number of women who attempt suicide while pregnant, specifically during the second or third month of pregnancy, is low and only a small number of certain medications tend to be used.[19] Furthermore, outcomes could be confounded by concurrent use of other medications, alcohol and/or illicit substances. Despite these limitations, in situations where outcomes are assessed following exposure to different doses, these could be used to investigate dose-response relationships and potential dose-thresholds, which would be useful for clinical practice. For example, knowledge of these outcomes would provide guidance following subsequent deliberate or inadvertent exposure to high doses of medications. As such, calls to establish an international monitoring system of self-poisoned women could be justified.[19]

Finally, while evidence of a dose-response relationship strengthens arguments for establishing causality, relying on estimates of dose may not provide the complete picture. For example, key factors such as individual differences in pharmacokinetics and pharmacogenomics play important roles in influencing the concentration and effects of fetal exposure to particular medications. As such, the same dose administered to two different individuals may elicit different responses.

3.3.2.3 Duration of Medication Exposure

Duration of exposure may play an important role in determining the teratogenic potential of a medication. For example, Oberlander et al., investigated the effect of timing and duration of exposure to SSRI's on neonatal outcomes.[30] They observed an increased risk of intrauterine growth restriction and a reduction in mean gestational age according to duration of SSRI exposure during pregnancy.[30] In many cases the importance of duration of exposure may depend

on the underlying mechanism suspected of causing the observed outcome. For example, if a medication is associated with intrauterine growth restriction, is this due to a permanent or transient effect on uteroplacental blood flow and fetal haemodynamics? Understanding such mechanisms can assist in determining whether intrauterine growth restriction is more likely after short or prolonged exposure to the medication during pregnancy.

Other outcomes such as long-term effects on child neurodevelopment may also be associated with duration of exposure. Given brain development occurs over a substantial period of the pregnancy and even continues into postnatal life the question of interest may be whether this occurs following exposure during a particular time point in pregnancy, or after prolonged exposure during brain development?

While it's important to consider the clinical relevance of short compared to prolonged exposure to medication during pregnancy, when considering duration of exposure it is important to consider its relationship with underlying maternal illness. As discussed previously in relation to confounding by indication, there may be systematic differences between women who take a medication for only a short period during pregnancy compared to women who take a medication throughout pregnancy.

In addition, a major challenge in studying relationships between duration of exposure and pregnancy outcomes lies in the fact that the two are interrelated.[30] For example, length of gestation can affect duration of exposure and duration of exposure can affect length of gestation. This requires careful assessment and use of appropriate statistical methods, such as time-varying covariate models, which are capable of generating effect estimates which vary over the course of gestation.[31] Importantly, the data required for these models are complex and necessitate the need for accurate and complete data on dose, duration and timing of exposure, which are not always available in sufficient detail.

3.3.3 Outcome Classification

A major methodological issue when investigating the safety of medications used during pregnancy is classification of outcomes, especially malformations.[32] Not all studies report on major and minor malformations and there is a lack of consistency across studies as to what is classified as major and minor.[32] Accordingly, statistical significance of major malformations may depend on the classification of a single malformation as major or minor.[19] As such, there are strong arguments surrounding the need for consensus regarding the definition of major malformations and how these should be investigated or reported.[9] Equally strong is the argument against reporting on all major malformations as a composite end-point.[19] If a medication was only associated with an increased risk of a specific malformation, evaluating risk according to all malformations combined could mask the increased risk associated with that specific malformation. As teratogens generally increase rates of specific defects or a spectrum of defects it would make intuitive sense to evaluate the risk of isolated (non-syndromic) and multiple (syndromic) forms of malformations separately.[19,32]

3.3.4 Incomplete ascertainment of outcomes or exposures

The incomplete ascertainment of data on either exposures or outcomes is usually a minor problem, as long as data are obtained without bias.[23, 33] For example, women may be misclassified as not exposed to a medication during pregnancy, when they were actually exposed, based on incomplete data. Similarly, some infants may be misclassified as not having the outcome of interest based on incomplete or missing data. Incomplete ascertainment can affect all study types and has been previously demonstrated to have little effect on risk estimates, but will decrease the power of a study (as evident by an increased width of associated confidence intervals).[33] Incomplete ascertainment of exposures or outcomes becomes an issue when they are not obtained without bias, as discussed below.

3.3.5 Information Bias

Information bias is said to occur when there are systematic differences in the completeness and/or accuracy of data that leads to a differential misclassification of individuals regarding the exposure or outcome under investigation.[9]

This can be introduced if offspring of mothers exposed to a medication thought to be a teratogen are subjected to more detailed pre- or post- natal investigations then offspring who were not exposed.[9] In some situations blinding of researchers and/or clinicians to the exposure of interest can eliminate or reduce this bias. For example, there is much controversy regarding the potential association with prenatal SSRI exposure and cardiovascular malformations. It has been demonstrated that women who use SSRIs are more likely to have an ultrasound or echocardiogram procedure during pregnancy and their children are more likely to be taken to the emergency department and receive an echocardiogram procedure during the first year of life compared to others not exposed to SSRIs medications during pregnancy.[34] Differences such as these between exposed and unexposed groups can introduce bias, as there is a higher chance of identifying malformations amongst those who are exposed compared to healthy controls.[34]

Furthermore, recall bias can have a significant impact on studies relying on maternal recall of medication use during pregnancy. For example, reporting of medication use during pregnancy may be more complete among women who gave birth to an infant with the outcome of interest compared to women who gave birth to normal infants. Conversely, reporting bias could occur if participants give answers that they consider to be in the direction of interest to the researcher or under-report socially unacceptable or embarrassing behaviours. For example, some women may not wish to admit that they were taking particular medications, such as antidepressants, during pregnancy. Espnes et al. compared recorded medication use in the Medical Birth Registry of Norway (MBRN) with prescribed medicines registered in the Norwegian Prescription Database (NorPD).[35] They found that medication use recorded in the MBRN was poor compared with prescribed medicines in NorPD. For SSRIs in particular, the sensitivity of the MBRN in identifying women who received a dispensing for a SSRI during pregnancy was 41% (95% CI; 39-43), suggesting that a large amount of SSRI use was underreported.[35] These results were similar to those obtained by Stephansson et al. who compared reported medication use in the Swedish Medical Birth Register (SMBR) with prescribed medicines registered in the Prescribed Drugs Register (PDR).[36] They also found that reporting of antidepressant use during pregnancy was poor, with a sensitivity of 59.8% (95% CI: 57.7-61.9).[36]

Duration of postnatal follow-up could also be regarded as detection bias if there are differences in the length of follow-up between the groups that may

impact on the detection of the outcome under investigation. For example, some birth defects may remain undetected in infants with only short-term follow-up, while others may have resolved spontaneously by the time of later follow-up. In addition, long-term effects of medications used during pregnancy on child health and development may not become apparent until many years later. Therefore, ideally, only cohorts with the same duration of follow-up should be compared to eliminate potential bias.[9]

3.3.6 Confounding

If significant differences exist between study group characteristics, and these characteristics are independently associated with the outcome of interest, this can confound the observed association as differences in observed outcomes between study groups may be due to other factors apart from the exposure under investigation.[37] Importantly, by definition, a factor can only be considered as a confounder if it differs between the exposed and unexposed groups.[7] In addition, for a factor to confound an association it must be associated with both the exposure and outcome and its relation to the outcome should be independent of its association with the exposure[7] For example, if we know that smoking during pregnancy is associated with adverse pregnancy outcomes and there is an uneven distribution of smokers in the exposed and unexposed study groups, then this could confound any observed association between the medication used in pregnancy and the outcome under investigation. Unfortunately, in many studies, data on important confounders may be incomplete or absent, limiting our ability to account for confounding.

Approaches during the design phase of a study to improve comparability of exposed and unexposed groups include restricting subjects based on inclusion or exclusion criteria and matching of controls to cases. It is important to note that while adjustments can be made for confounding in the data analysis phase of a study, these represent only a statistical adjustment and some degree of residual confounding may remain, usually due to unmeasured variables. Matching of controls to cases using either frequency or one-to-one matching can enhance equal representation of subjects with certain confounders among study groups.[7]

When interpreting the results of any study it is important to know what confounders have been measured, how well they have been measured and to consider the role of unmeasured or unknown confounders.[37] Confounding can

cause an over- or under-estimation of the true relationship and can even change the direction of the observed effect.[7]

3.3.7 Impact of Medical Interventions and Use of Folic Acid

The assessment of pregnancy outcomes associated with medication use during pregnancy is made even more complex as a result of the numerous medical interventions aimed at improving pregnancy outcomes. For example, tocolytics are regularly used among women at risk of preterm delivery and can result in a significant prolongation of pregnancy up to 7 days.[38] Therefore, if a medication is suspected of being associated with a reduction in gestational age, it would be informative to consider the influence of medical intervention with tocolytics. A higher incidence of tocolytic use in the exposed group would not only be clinically relevant in highlighting the increased need to intervene among women taking that medication, but would also highlight the potential for tocolytic use to significantly influence the assessment of outcomes such as preterm delivery and mean gestational age. Furthermore, it would be important to consider whether differences in pregnancy outcomes could be due to differences in access to medical services and the level of medical care provided (i.e. differences in local protocols for managing preterm labour). This is an important form of bias if medical interventions differ between those exposed and not exposed to the medication of interest.

An additional intervention aimed at improving pregnancy outcomes is the use of folic acid. Folic acid supplementation during pregnancy has been demonstrated to reduce the risk of neural tube defects[39] and cardiac malformations,[40] and has been demonstrated to significantly influence outcomes associated with medication use during pregnancy. For example, among women taking dihydrofolate reductase inhibitors during the second or third month of pregnancy an increased risk of cardiovascular malformations was observed among those women who were not taking a folic acid supplement (RR 7.7; 95% CI 2.8-21.7), but not among those women who reported taking a folic acid supplement (RR 1.5; 95% 0.6-3.8).[41] Therefore in assessing outcomes such as malformations it would be informative to know how many women were taking folic acid supplements and at what dose, as this could have an effect on the risk of the outcome associated with the medication exposure. This is particularly important if there are systematic differences between women who do and do not take folic acid, and if this is associated with exposure to the medication under investigation.

3.3.8 Statistical Analysis and Interpretation

While a detailed description of statistical limitations is beyond the scope of this review, there are particular issues worth discussing. The first is that we must be cautious in the interpretation of statistically significant results, given the large number of comparisons and statistical tests that are often undertaken. Multiple testing, as occurs with subgroup analyses and the assessment of many outcomes such as individual malformations, increases the potential for 'chance' findings. At the frequently utilized 5% significance level (95% confidence interval) there is a 5% chance of obtaining a statistically significant result that is false (i.e. due to chance alone). With studies performing 20–40 individual tests, there is a possibility that 1–2 will be statistically significant by chance alone. Therefore it is important that studies adjust for multiple testing using appropriate statistical methods, such as the Bonferroni correction.[19]

To assist in the interpretation of the clinical significance of research findings, studies should report the absolute risk, rather than just relative risk of outcomes associated with medication use during pregnancy. For many malformations which are rare, the relative risk may appear high, but the absolute risk increase is usually low. The absolute risk is critical in the implementation of findings into clinical practice as it is a more informative way of describing the potential risks and benefits associated with treatment. For example, prenatal SSRI exposure has been associated with an approximate 6-fold increase in the relative risk of PPHN [42]. Notably, the absolute risk is relatively small, given the low prevalence of PPHN in the general population (increased from 0.1% to 0.5%).[43]

Despite past obstetric history having a strong relationship to future pregnancy outcomes,[44] many studies include multiple pregnancies related to the same woman. This is only appropriate if statistical methods are utilised which address the potential for clustering associated with repeated pregnancy outcomes. Other approaches to address this issue include the restriction of only the first, last or a random pregnancy for each woman. For a more in depth review of this issue see Louis et al.[44] Similar to the inclusion of multiple pregnancies, many studies include the assessment of outcomes among multiple infants belonging to the same pregnancy. This creates similar issues in relation to clustering as described previously, and can significantly influence results given the well-known differences in growth rates and pregnancy outcomes compared to singleton births.

3.3.9 Sample size considerations

Obtaining an adequate sample size represents a major challenge for many observational studies.[2] Adequate sample sizes are required to ensure sufficient statistical power, both for estimating risk and for providing assurances of safety. While a study may report no association between medication use and a particular outcome, it is important to assess what the study was powered to detect. The sample size required varies dramatically according to how commonly the medication is used during pregnancy, the prevalence of the outcome under examination and the estimated increase in risk associated with the exposure.[2] Many studies, for example, only have sufficient power to detect very large increases in risk. For example, Andrade et al. investigated the association between prenatal SSRI exposure and persistent pulmonary hypertension of the newborn (PPHN).[45] Due to the very rare occurrence of PPHN and the associated small sample size, the study was only powered to detect a 6-fold difference in the prevalence of PPHN among infants exposed prenatally to SSRIs. While studies with low statistical power are still useful in ruling out large increases in risk, studies with much larger sample sizes are required to more accurately define smaller, but still clinically relevant, differences.

3.3.10 Consistency of literature

An important issue when considering the teratogenicity of medications is the consistency of the literature. An observed association is more likely to be causal if it is found in multiple studies undertaken using different study populations and/or research methods.[46] Therefore, it is always important to consider the totality of the evidence, rather than single reports, when considering potential associations. In addition to considering consistency of the literature it is important to consider biological plausibility.[46] Is the observed outcome plausible? Biological plausibility may be based on evidence generated from experimental studies or from a sound understanding of sciences such as physiology, embryology and/or pharmacology. Importantly, the lack of a biologically plausible argument does not rule out causality, as in some cases the exact mechanism of effect may be unknown.

3.4 Observational Study Types Used to Investigate Outcomes Associated with Medication Use During Pregnancy

Given the wide range of potential outcomes under investigation in both the mother and child, no single methodological approach is sufficient for delineating the complete spectrum of risks or benefits of medication use in pregnancy. Each approach has its own strengths and limitations that need to be taken into account when interpreting evidence and applying it to clinical practice. Table 2 presents an overview of the advantages and disadvantages of observational and other study designs used in determining risks and benefits of medication use during pregnancy.

3.4.1 Case Reports

Case reports describe one or a series of clinical observations on medication exposure during pregnancy and subsequent outcomes. Case reports frequently provide the first accounts of adverse fetal outcomes following exposure to a particular medication during pregnancy. Relying purely on case reports, however, can create bias in safety data collected as adverse outcomes are over-represented with little information frequently available on the number of pregnancies with normal outcomes.[47] Therefore it is important to be cautious and objective when evaluating isolated case reports. If a medication in question is taken by a relatively small number of pregnant women or causes rare malformations, then a small number of case reports can establish a strong association. Alternatively, if the medication is taken by a large number of pregnant women, a small number of case reports of abnormalities may simply reflect the background rate of birth defects in the general population.[48]

Initial concerns regarding commonly known teratogens, such as thalidomide, were first raised through case reports.[49] On their own, however, they cannot distinguish coincidence from causality or assess teratogenic risk, but, reports of distinct abnormalities or groups of abnormalities related to medication exposures in pregnancy can suggest an association, serving as an important warning signal and providing a stimulus for further observational studies.[32]

3.4.2 Cohort Studies

Cohort studies can be retrospective, prospective, or a combination of both. The main characteristic of a cohort study is that it begins by identifying a group of women who are exposed to a medication of interest and follows these individuals over time to assess a range of outcomes. A challenge associated

with cohort studies is the correct identification of women who are exposed to the medication of interest and the appropriate identification of a suitable control group of women who are not exposed to the medication of interest.

3.4.2.1 Prospective Cohort Studies

The strength of the prospective cohort design is the prospective, systematic collection of data, including exposures, confounders, and outcome information. As a result, recall bias can be avoided.[2]

To date the majority of prospective cohort studies have been carried out by teratogen information services (e.g. Canadian Motherisk organisation,[50] Californian Teratogen Information Service,[51] European Network of Teratogen Information Services (ENTIS)[52]), where women are identified while requesting information about the safety of a medication during pregnancy, and then followed to determine the outcome of their pregnancy. Information is often gathered prospectively through maternal interviews, questionnaires and clinical assessments and in some cases this information is confirmed by reviewing medical records.[53,54] Selection bias is a concern with studies undertaken using teratogen information services, as women who utilise these services may not be reflective of the general population.[8] The identification of a suitable control group of women who are not exposed to the medication of interest is also a challenge, with researchers developing a control group comprising women who contacted the centre regarding exposures to other medications during pregnancy which are not considered likely to be associated with the outcome under investigation. These studies commonly have small sample sizes, limiting their statistical power to detect clinically important differences and provide adequate reassurance about the safety of medications. This can be due to the overall low prevalence of exposure to the particular medication of interest or the investigation of rare outcomes.[6] Researchers may try to overcome this limitation by using a multicentre approach.[2] This, however, presents additional challenges with concerns regarding heterogeneity of women enrolled from different centres. This may be due to differences in ethnic backgrounds, prescribing behaviours, varying local guidelines, access to teratogen

information counselling services and the way data are collected.[9] As such, multi-centre studies should ensure each exposed woman has a suitable control subject identified from the same centre and that all centres contribute adequate numbers of subjects to the study.[9] In addition, data should be assessed to ensure that it is appropriate to pool the data in a multicentre study.[52]

Medical birth registers which contain prospectively collected data on medication exposure during pregnancy (e.g. Swedish Medical Birth Register) have also been used to identify cohorts of women for prospective cohort studies.[33] While a major strength of these registers is that they are population-based and contain prospectively collected data, there is potential for incomplete data on medication exposures during pregnancy due to non-reporting of medication use.[36]

An alternative approach to examining a wide range of outcomes following medication use during pregnancy are prospective birth cohort studies (e.g. Danish National Birth Cohort Study,[55] Norwegian Mother and Child Cohort[56]). The major difference between birth cohort studies and traditional prospective cohort studies is that birth cohort studies are not designed based on a single hypothesis or set of hypotheses. Instead, the aim is to collect data on as many relevant exposures and health outcomes as feasible to assist in answering various research questions that may emerge over time.[56] As such, a major advantage of these studies is the collection of pre-specified detailed data on a range of factors including exposures, confounders and outcomes of interest across large cohorts of women and their children over long-periods of time.[32] This broad approach, however, can sometimes be a limitation. These studies are extremely expensive and despite an initial large sample size (up to 100,000 mothers enrolled in the cohort), the numbers of women exposed to particular medications of interest, or the number of children with outcomes of interest may still be small.[2] It is also impossible to foresee all potential research questions when designing a birth cohort study. This means that data on certain exposures, confounders and/or outcomes of interest may not always be collected, or data may not be collected in the same manner as they would have been if the

research question had been identified prior to the development of a purpose-built prospective cohort study.

A further limitation affecting these and other prospective studies, however, is the extent of loss to follow-up, where information on outcome variables for some subjects may not be obtained, especially if the study spans several years.[2]

3.4.2.2 Pregnancy Exposure Registries

Pregnancy registries are increasingly being used to monitor medication safety in pregnancy.[57] Pregnancy exposure registries usually enrol pregnant or non-pregnant women following exposure to one or more specific medications of interest and then prospectively follow that pregnancy or future pregnancy over time to assess outcomes.[58] The strength of this approach lies in the ability to enrol women early in pregnancy and to ensure data on medication exposures and other potential confounders are collected prospectively, before outcomes are known.[58] Adverse pregnancy outcomes in the exposed cohort are then compared to rates in unexposed women identified either from the study itself or from population data. As much as possible the control group should consist of women with similar underlying characteristics to those in the exposed group, to minimise the potential for selection bias. This makes the use of population data as a control group a significant limitation, as there may be systematic differences between women in each group and also in the way in which the outcome is ascertained or classified. In addition, it is important to note situations where retrospective data is reported to pregnancy registries as this may introduce bias if pregnancies with negative outcomes are more likely to be reported than those with normal outcomes. Therefore it is essential that any prospective and retrospective data collected in pregnancy registries be analysed separately to limit any bias.[57] Due to voluntary reporting, pregnancy registries also tend to be small.[58] Examples of pregnancy exposure registries include the Australian antiepileptic pregnancy register[59], and the National Register of Antipsychotic Medication in Pregnancy[60].

3.4.2.3 Administrative Database Studies

Existing healthcare and administrative datasets are increasingly being used to identify and establish large cohorts of pregnant women for cohort studies.[61-64] The major advantage of these studies is that data are collected prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and the data can be linked at the individual patient level.[65]

Use of linked datasets enables the identification of very large cohorts of women and their offspring, which is particularly useful in assessing rare outcomes such as malformations.[66] Compared with resource intensive prospective cohort studies, there is effectively no loss to follow-up, only potential failures in the identification and linkage of relevant data on outcomes. Furthermore, these studies are more efficient than prospective cohort studies for investigating outcomes with a long-latency period (i.e. teratogenic effects in an infant that may not become apparent until many years later). Linkage of existing records is unobtrusive to patients and their children and the routine and prospective manner in which data is collected and recorded in these datasets eliminates recall bias.[66] In addition, as data have already been collected, studies can be undertaken in a more timely and cost efficient manner than is possible with other research design methods.

The greatest limitation, however, associated with studies relying on healthcare and administrative data is the fact that these data were not collected with the original intention of being used for research purposes. Thus the data may lack the necessary detail for investigating associations between medication exposures and pregnancy outcomes, especially in relation to potential confounders.[66] In addition, a drawback associated with very large sample sizes is the potential for chance findings, especially given the large number of statistical tests often undertaken. Furthermore, studies utilising electronic prescriptions records rely on the assumption that the date of dispensing and amount of medication supplied is the same as the time and duration the medication was actually taken, which may not be accurate. As

such, these studies are probably more accurate in investigating outcomes associated with medications used in the management of chronic medical conditions (e.g. diabetes, epilepsy, hypertension, depression), than for medications used for the treatment of acute medical conditions (e.g. migraine, nausea, insomnia).

3.4.3 Case-Control Studies

Case-control studies are usually retrospective and consist of a group of patients with the outcome being investigated (e.g. those with a malformation as cases) who are compared to another group who do not have the outcome of interest (e.g. those without a malformation as controls). These two groups are then compared according to the frequency of exposure to a particular medication. The proportion of cases with the exposure of interest is compared with the proportion of controls with the same exposure and used to calculate an odds ratio. This is used to determine the relative importance of the exposure with respect to the presence or absence of the outcome.[7,48] A major benefit of case-control studies is that, due to the higher percentage of cases per study, obtaining an adequate number of cases to provide sufficient statistical power to assess medication safety during pregnancy is often easier than alternative study designs, even when the association under investigation is uncommon.[2] Therefore, when investigating rare outcomes such as malformations, the case-control study design is often the method of choice. In addition, the smaller sample sizes and avoidance of lengthy times to follow-up means case-control studies are often more cost-effective than cohort studies. Interviews, questionnaires, or a review of medical records are commonly used to retrospectively collect information on medication exposures during pregnancy. While the outcome under investigation is limited (i.e. presence or absence of an outcome), a large number of exposures as potential risk factors can be studied at one time using the same cases and controls. A limitation of many case-control studies is that information is often collected in a retrospective fashion, which can be subject to recall bias.[6] In some situations recall bias can be addressed through the use of prospectively collected data in hospital, pregnancy, or pharmacy records to validate exposures or outcomes, however, this relies on the assumption that these data sources contain complete and accurate information, which may not always be the true. For example, does the absence of data in medical records on whether someone used a medication during pregnancy mean that they did not use that medication, or does it mean

that the record is incomplete or that the data are missing? Furthermore, the period of recall can also differ substantially between studies, with some concluding within 6 months of delivery[14,67] and others including women up to 2 years following delivery[13,28]. In addition, there is also the potential for response bias, with up to 30-40% of women declining to participate in some case-control studies and consent rates differing between those exposed and non-exposed to the medication of interest.[13,14]

3.4.4 Nested Case-Control Studies

A nested case-control study consists of subjects sampled from within a cohort study. For this reason, the case-control study is said to be 'nested' within the cohort study.[68] Nested case-control studies are convenient and cost-efficient to construct within a cohort once a sufficient number of cases have accumulated. They are particularly useful in situations where the outcome of interest is rare, as they improve the statistical power of the subsequent analysis. Analysis of nested case-control studies is undertaken in the same manner as for case-control studies and allows the computation of an odds ratio of a particular exposure being associated with a certain observed outcome. An advantage of a nested case-control design over the standard cohort design includes improved control for confounding, as the group with the outcome of interest can be matched to a group that is similar in most respects except for the outcome of interest.[68]

3.5 Conclusion

In the absence of randomised controlled trials, observational studies provide the best means of evaluating medication safety during pregnancy. These studies can be used to identify associations between medication exposure and outcomes, both immediate and long-term, while also quantifying the strength of such an association.[6] Although it may be impossible to demonstrate absolute safety in observational studies, they can provide some level of reassurance if the risks associated with medication use during pregnancy are not elevated. This level of reassurance, much like evidence of risk, can be quantified to allow and support evidence based decision making on medication use in pregnancy.

There are a number of challenges in using observational studies to investigate medication safety during pregnancy but these can be overcome with good research design and careful analysis and interpretation of study results. Some challenges can be

overcome in the design phase of a study, while others can be addressed in the data analysis phase.

It is imperative that clinicians caring for pregnant women are able to critically evaluate studies investigating outcomes associated with medication use during pregnancy as this assists them in making assessments about the validity and applicability of results presented in order to provide the best recommendations to patients.

3.6 References

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Table 3.1 Guide for evaluating observational studies investigating outcomes associated with medication use during pregnancy[2,4,5]

Introduction/Background

- Are there clear objectives for undertaking the study? Is there a clear hypothesis?

Study Population

- What were the inclusion and exclusion criteria?
- How generalisable are the results likely to be to your patients?
- How and where were subjects recruited (Are there differences in consent rates between groups)?
- What type of comparison group was used? How comparable are the groups? Were they matched according to any characteristics?
- Is an additional suitable control group of women with the same underlying illness included?

Medication Exposure Ascertainment

- Was data on dose, duration and timing of exposure collected?
- How were data on exposures reported and/or confirmed (e.g. patient report, health care professional report, medical/pharmacy records)? How reliable are data on exposures?
- How accurate are data on timing of exposure?
- Was there a significant time lag between the time when the exposure was likely to have occurred and when it was assessed (e.g. women asked about exposures that occurred during pregnancy 2 years ago)?

Outcome Ascertainment

- What outcomes were evaluated and how were these defined?
- Was the length of follow-up on the infant appropriate for the outcome under investigation?
- Were outcomes investigated in the same manner in both groups (e.g. no difference in follow-up between case and control groups)?
- Who or what was the source of outcome information (e.g. mother, paediatrician, birth defects registry or hospital database)?
- Were medical records used to confirm reported outcomes?
- Is there any assessment of the potential for recall bias between the groups?
- What is the proportion lost to follow-up? Was this accounted for during analysis?

Confounding

- What confounders were assessed and how well were they measured (e.g. smoking status)?
- What is the potential for confounding due to underlying maternal illness?

Analysis and Interpretation

- Does the crude estimate differ substantially from the adjusted estimate?
- Is analysis based on timing of exposure (e.g. first trimester exposure vs. second or third month of pregnancy)?
- Is the background rate of the outcome under investigation stated? What is the absolute increase in risk associated with medication exposure?
- How many statistical tests were undertaken? What is the possibility of chance findings?

Statistical Power

- What level of risk is the study powered to evaluate?
- Are confidence intervals provided? If yes, are these intervals wide or narrow?

Consistency of Literature

- Is the same observation seen in other studies?
- Is the observed association biologically plausible based on experimental studies?

Table 3.2 Advantages and disadvantages of study designs used to investigate outcomes associated with medication use during pregnancy[2,6]

Study Type	Advantages	Disadvantages
Case Reports	• Cheap and easy method for generating hypotheses	• No control group • No denominator to calculate incidence rate • Potential under-reporting • Retrospective reporting
Case-Control Study	• Cost efficient and fast • Can study multiple exposures and rare or uncommon outcomes	• Selection of control group problematic • Potential for recall bias with retrospective exposure assessment
Prospective Cohort Study	• Prospective exposure and outcome assessment • Can study multiple outcomes • Can study uncommon exposures • Unbiased exposure data • No recall bias	• More time consuming and expensive then case-control studies • Often small number of women exposed identified • Possibly biased outcome data as a result of loss to follow-up, especially if investigating long-term outcomes • Potential for detection bias
Pregnancy Exposure Registries	• Majority collect data prospectively beginning early on in pregnancy • Can study multiple outcomes • Can study uncommon exposures	• Voluntary reporting; potential for selection bias • Difficulties recruiting large sample sizes • Identification of suitable control group can be difficult
Administrative Database Studies	• Able to generate very large sample sizes • Commonly population-based, improving generalisability of findings and reducing potential for selection bias • Eliminates potential for recall bias • Cost efficient and fast compared to labour intensive prospective cohort studies • Allows timely investigation of long-term outcomes using existing data	• As data already collected relevant data of interest (i.e. confounders) may be missing • Assumptions regarding dose, timing and duration of medication exposure based on dispensing data • Restricted to investigating outcomes routinely recorded in the data • Large sample size can lead to increased likelihood of chance findings

Section I: Part B –
Literature Review

	CHAPTER 1 Introduction	**Publication One** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(1): 46-9.
SECTION I **PART A** **Conceptual Framework**	**CHAPTER 2** Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology	
	CHAPTER 3 A Review of Methodological Challenges and Epidemiological Research Methods	**Publication Two** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 33(3): 280-9.
SECTION I **PART B** **Literature Review**	**CHAPTER 4** Safety of SSRIs in Pregnancy	**Publication Three** Grzeskowiak LE et al. *Drug Saf.* 2011; 34(11): 1027-48.
	CHAPTER 5 Effects of Prenatal SSRI Exposure on Child Growth and Body Weight	**Publication Four** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 34(1): 101-9.
SECTION II **Validating the Use of Routinely Collected Health Data**	**CHAPTER 6** Validating the Use of Hospital Pharmacy Dispensing Records to Identify Prenatal SSRI Exposure	**Publication Five** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(4): 265-8.
	CHAPTER 7 Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy	**Publication Six** Grzeskowiak LE et al. *Eur J Clin Pharmacol*. 2012; 68(5): 459-67.
	CHAPTER 8 Prenatal SSRI Exposure & Neonatal Outcomes *Examined Using Routinely Collected Health Data*	**Publication Seven** Grzeskowiak LE et al. *J Clin Psychopharmacol*; In press.
SECTION III **Evaluating the Use of Routinely Collected Health Data**	**CHAPTER 9** Prenatal SSRI Exposure & Childhood Overweight *Examined Using Routinely Collected Health Data*	**Publication Eight** Grzeskowiak LE et al. *J Dev Orig Health Dis*;. 2012; 3(4): 253-61.
	CHAPTER 10 Prenatal SSRI Exposure & Childhood Overweight *Examined Using Data from a Birth Cohort Study*	**Publication Nine** Grzeskowiak LE et al. *PLoS ONE*; Submitted.
	CHAPTER 11 Using Routinely Collected Health Data to Examine Long-Term Outcomes: Opportunities and Challenges	**Publication Ten** Grzeskowiak LE et al. *Ther Adv Drug Saf*; Submitted.
	CHAPTER 12 Discussion and Conclusion	

Preamble

Given a sound understanding of the conceptual frameworks used to inform this thesis it is necessary to focus attention towards the subject of the illustrative example which has been chosen to achieve a greater understanding of the opportunities and challenges associated with using routinely collected health data to examine long-term effects of medication use during pregnancy. The subsequent literature reviews help to establish why SSRIs are a suitable focus for a feasibility study, highlighting the high level of concern, conflicting results, and relative paucity of data on neonatal and childhood outcomes, associated with their use during pregnancy.

Furthermore, the review of the safety of SSRIs in pregnancy (Chapter 4) is particularly unique as it focuses on the methodological limitations associated with studies undertaken to assess the safety of SSRIs in pregnancy. This review serves a number of purposes;

- The first is that it thoroughly explores and details various methodological challenges associated with observational study designs. This plays an important role in informing the design and analysis of subsequent studies within this thesis. Furthermore, this review highlights the importance of having accurate data on medication exposures during pregnancy, the importance of which is discussed further in subsequent chapters (Chapter 6 & 7).

- The second is that it provides an in depth assessment of the effects of prenatal SSRI exposure on neonatal outcomes, which informs a subsequent validation study assessing neonatal outcomes following late gestation exposure to SSRIs using routinely collected health data (Chapter 8).

- The third is that it highlights the relative paucity of data that exists surrounding long-term effects of prenatal SSRI exposure on the offspring, supporting the need for improved assessment of long-term effects using routinely collected health data.

The subsequent chapter (Chapter 5) focuses on the potential long-term effects of prenatal SSRI exposure on child growth and body weight. This review of animal and human studies provides the rationale and biological plausibility for investigating the association between prenatal SSRI exposure and child overweight in subsequent studies (Chapters 9 & 10).

CHAPTER 4

Safety of SSRIs in Pregnancy

Manuscript

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Investigating Outcomes Following the Use of SSRIs for Treating Depression in Pregnancy: A Focus on Methodological Issues

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4.1 Abstract

The aim of this review was to critically appraise the existing literature with a particular focus on identifying methodological issues associated with studying outcomes following the use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy.

Existing studies evaluating outcomes following prenatal SSRI exposure suffer from a number of important methodological limitations that should be taken into account when interpreting their results. The contradictory results obtained from prospective and retrospective cohort studies and case-control studies could be accounted for by dissimilarity between study populations, selection bias, detection bias, confounding, or differences in underlying maternal illness, data sources used, exposure classification, follow-up and statistical power/analysis. Only a small number of studies actually account for underlying maternal illness and how this may lead to adverse pregnancy outcomes. Even when such information is available, studies that include data on maternal illness have small sample sizes, limiting the statistical power to identify statistically and clinically relevant associations. Pregnancy outcomes may be confounded by the higher incidence of smoking, alcohol consumption and substance abuse frequently encountered amongst those suffering from depression, factors that are often insufficiently controlled for.

While evidence of associations between prenatal SSRI exposure and adverse pregnancy outcomes are conflicting, there is an urgent need to evaluate how the particular SSRI used, the dose, timing and duration of use, genetics (maternal, paternal and/or fetal), concomitant medication use, maternal characteristics and underlying maternal illness all interact to alter pregnancy outcomes.

4.2 Introduction

As depression affects 10–25% of women aged between 25 and 44 years,[1] many women enter pregnancy with either a history of, or existing, depressive symptoms. In addition, a number of women develop depressive symptoms during pregnancy, with up to 13% of women estimated to suffer from depressive symptoms at some stage during pregnancy.[2] Therefore, women and healthcare professionals are often faced with difficult decisions regarding the initiation or continuation of antidepressant use during pregnancy, with any decisions to interrupt or withhold treatment requiring a complex assessment of the risks and benefits associated with treatment.[3]

Over recent years, there has been a growing awareness of the importance of identifying and effectively managing depression during pregnancy, given the strong associations

between prenatal and subsequent postnatal depression,[4-6] and the negative impact depression has on pregnancy outcomes and subsequent child health and development.[7-18] In the US, use of antidepressant medications has increased from 2% of pregnancies in 1996 to 7.6% of pregnancies in 2005.[19] Of particular interest is the use of selective serotonin reuptake inhibitors (SSRIs), which increased from 1.5% of all pregnancies in 1996 to 6.4% in 2005, making them the most used antidepressant during pregnancy.[19]

SSRIs exert their pharmacological effects by selectively inhibiting the reuptake of serotonin (5-HT) at the presynaptic junction, resulting in an increased concentration of serotonin in the synaptic cleft and thus enhanced serotonergic neurotransmission.[20] Since their introduction into clinical practice in the 1980s, SSRIs quickly replaced tricyclic antidepressants as the treatment of choice for many psychiatric disorders, due largely to their more favourable safety profile and reduced toxicity in overdose.[3,21,22] Consequently, there has been an increase in the number of women of childbearing age taking SSRIs, many of whom continue to take SSRIs throughout pregnancy, despite limited evidence of their safety in pregnancy.

While numerous studies have been undertaken to assess outcomes following SSRI use during pregnancy, evidence generated is inconclusive. In light of this, we have attempted to critically appraise the existing literature with a particular focus on identifying methodological issues associated with studying outcomes following the use of SSRIs during pregnancy. Outcomes covered include congenital malformations, spontaneous abortions, neonatal outcomes and child neurodevelopment.

To address these issues, MEDLINE and EMBASE were searched from their inception to 31 November 2010 using the search terms ‘SSRI’, ‘fluoxetine’, ‘citalopram’, ‘paroxetine’, ‘sertraline’, ‘fluvoxamine’ and ‘escitalopram’ in association with ‘pregnancy’, ‘prenatal exposure’, ‘depression’, ‘malformation’, ‘birth defect’, ‘miscarriage’, ‘spontaneous abortion’, ‘neonatal complications’, ‘child/ infant development/neurodevelopment’. Papers were limited to the English language and studies in humans. The reference lists of identified articles were examined for additional relevant publications.

4.3 Depression During Pregnancy

A challenge in investigating outcomes following SSRI use during pregnancy is that of differentiating the effects of exposure to the drug itself from that of the underlying

maternal illness. For the purposes of this review, the focus will be on SSRI use for depression.

Depression during pregnancy has been associated with numerous adverse pregnancy outcomes, including miscarriage,[7,23] preterm delivery,[10,14-17] low birthweight,[9-13] intrauterine growth restriction[17,24,25] and increased admissions to neonatal care units.[25] In addition, depression has been associated with an increased risk of gestational hypertension[9] and subsequent pre-eclampsia.[26] Depressed mothers may also be less likely to obtain prenatal care and attend prenatal clinics, further augmenting the potential for adverse pregnancy outcomes.[5] These adverse pregnancy outcomes, however, may be confounded by the higher incidence of smoking, alcohol consumption and substance abuse frequently reported amongst those suffering from depression.[5] The lack of control for confounding, and issues related to small sample sizes, infrequent adjustment or consideration of medication use (including antidepressant use), as well as other methodological limitations, preclude definitive conclusions regarding the association between depressive symptoms and adverse pregnancy outcomes.

One concern of poorly managed prenatal depression is the risk of worsening depression, which may lead to suicidal ideation or attempts.[5] Women with major depression who discontinue antidepressant therapy prior to pregnancy have a significantly increased risk of depression relapse (68%) compared with women who maintain their antidepressant therapy (26%), with that risk related to length of illness and the number of past depressive episodes.[27] Studies have shown that prenatal depression is associated with postpartum depression,[4-6] worsening of depressive symptoms[27] and increased suicide attempts.[28] Postpartum depression is of significant concern because of its well demonstrated negative impact on mother-infant attachment and cognitive, emotional and behavioural development in the offspring.[18,29]

4.4 A Critique of Study Designs

Ethical, medical and medico-legal concerns limit our ability to study the risks and benefits associated with SSRI use during pregnancy through randomized controlled trials. This limits our investigations to the use of observational study designs such as prospective and retrospective cohort studies and case-control studies, each with their own strengths and limitations.

4.4.1 Cohort Studies

Cohort studies can be retrospective or prospective in nature, or a combination of both. The main characteristic of a cohort study is that it begins with a group of women who are exposed to a medication of interest and follows these individuals over time to enable the assessment of a range of outcomes. A challenge associated with cohort studies involves the correct identification of women who are exposed to the medication of interest and the appropriate identification of a suitable control group of women who are not exposed to the medication of interest.

To date, the majority of prospective cohort studies have been carried out by teratogen information services[30-35] where women are identified while requesting information about the safety of a medication during pregnancy and then followed to determine the outcome of their pregnancy. Information is often gathered prospectively through maternal interviews, questionnaires and clinical assessments, and in some cases this information is confirmed by reviewing medical records.[33,35] Selection bias is a concern with studies undertaken using teratogen information services, as women who utilize these services may not be reflective of the general population.[36] The identification of a suitable control group of women who are not exposed to the medication of interest is also a challenge, with researchers often having to rely on a control group comprising of women who contacted the centre regarding other exposures during pregnancy that are considered not likely to be associated with the outcome under investigation.

Pregnancy exposure registries are also utilized to prospectively identify cohorts of women with an exposure of interest.[37] Most pregnancy exposure registries, however, rely on voluntary reporting of medication exposures, which may introduce bias if pregnancies that are more likely to be associated with adverse pregnancy outcomes are more likely to be those that are reported. In particular, it is important to note situations where data are reported to pregnancy registries after the outcome has occurred as this may be introduce reporting bias, with negative outcomes more likely to be reported than normal outcomes.

The strength of the prospective cohort design is the prospective, systematic collection of data, including exposures, confounders and outcome information. In addition, as ascertainment of exposure takes place before the outcome is known, recall bias can be avoided.[38] Medical birth registers that contain

prospectively collected data on medication exposure during pregnancy (e.g. Swedish Medical Birth Register) have also been used to identify cohorts of women for prospective cohort studies.[39] While a major strength of these registers is that they are population-based, there is potential for incomplete data on medication exposures during pregnancy due to non-reporting of medication use.[40] Finally, purpose-built prospective birth cohort studies (e.g. Danish National Birth Cohort Study) are increasingly being used to investigate a wide range of outcomes following medication exposures during pregnancy.[41] These come at considerable expense but have the major advantage of collecting detailed data on many exposures, confounders and outcomes of interest across large cohorts of women and their children over long periods of time. A limitation affecting these and other prospective studies, however, is the extent of loss to follow-up, where information on outcome variables for some subjects may not be obtained.[38] This issue is particularly important in situations where loss to follow-up may differ between study groups. In addition, any study that relies on patient consent to participate can be subject to response bias if there are differences in characteristics between those who choose to participate in a study and those who do not.[42]

In contrast to prospective cohort studies, retrospective cohort studies are often less resource intensive and less time consuming, making them an increasingly popular alternative, with the major difference to the prospective cohort design being that exposure and outcome ascertainment occurs at the time that the retrospective cohort study begins. Traditional retrospective cohort studies have relied on data obtained from interviews or questionnaires and therefore can be affected by recall bias where, compared with mothers of healthy children, mothers of affected children may be more likely to recall medication exposures during pregnancy.[43] More recently, researchers are beginning to construct large retrospective cohort studies utilizing linked healthcare and administrative datasets.[44-53] The major advantage of these studies is that data are collected prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and the data can be linked at the individual patient level. The prospective collection of data eliminates the potential for recall bias. Use of linked datasets enables the identification of very large cohorts of women and their offspring, which is particularly useful in assessing rare outcomes such as congenital malformations. In addition, as data have already been collected, it enables studies to be undertaken in a more timely and cost-efficient manner than is possible with other research

methods. This, however, is also the greatest limitation associated with studies relying on healthcare administrative data, as these data were not collected with the intention of being used for research purposes. Thus, the data may lack the necessary detail for investigating associations between medication exposures and pregnancy outcomes, especially in relation to potential confounders. Furthermore, studies utilizing linked prescription records rely on the assumption that the date of dispensing and amount of medication supplied coincides with the time and duration the medication was actually taken, which may not be completely accurate.

4.4.2 Case-Control Studies

Case-control studies are usually retrospective and consist of a group of patients, the 'cases', with the outcome being investigated (e.g. those with a congenital malformation) who are compared with another group, the 'controls', who do not have the outcome of interest (e.g. those without a congenital malformation). Case-control studies are particularly useful for generating sufficient statistical power to investigate rare outcomes associated with prenatal SSRI exposure.[38] As information is often collected in a retrospective fashion, case-control studies can be subject to recall bias. While recall bias can be addressed through the use of hospital, pregnancy or pharmacy records to validate exposures or outcomes, this relies on the assumption that these data sources contain complete and accurate information, which is not always the case. For example, does the absence of data on whether someone used a medication during pregnancy mean that they did not use that medication, or could it just be incomplete? Furthermore, the period of recall can also differ substantially between studies, with some concluding within 6 months of delivery[32,54] and others including women up to 2 years following delivery.[34,55] In addition, there is also the potential for response bias, with up to 30–40% of women declining to participate in some case-control studies and consent rates differing between those exposed and not exposed to SSRIs.[54,55]

4.5 Congenital Malformations

Prospective cohort studies,[30-35,56] retrospective cohort studies[44-53,57,58] and case-control studies[4,55,59-6] have been undertaken to investigate the relationship between congenital malformations and prenatal exposure to SSRIs.

Studies either report on major[30-34,45-47,50-55,59,60] or minor[31,45,47,51] malformations, or a combination of both,[44,48,49] while a number focus purely on cardiovascular malformations.[35,56,58,61] Major malformations are classified as structural or functional abnormalities that have significant medical or social consequences,[32] while minor malformations are classified as structural defects that have no cosmetic or functional importance.[31]

4.5.1 Focus on Paroxetine

In late 2005, GlaxoSmithKline® (GSK), the manufacturer of paroxetine, together with regulatory bodies from around the world, including Australia, the US, Canada and the UK, issued media releases concerning the safety of paroxetine during pregnancy. This decision was made primarily on the basis of results from two studies, one sponsored by GSK[62] and another independently undertaken by Kallen and Olausson.[50] Preliminary unpublished results from the GSK study suggested that, compared with other antidepressants (including SSRIs and other classes of antidepressants), paroxetine use during the first trimester was associated with an increased risk of congenital malformations (odds ratio [OR] 2.2; 95% CI 1.34, 3.63) and cardiovascular malformations (OR 2.08; 95% CI 1.03, 4.23).[62] The most commonly reported cardiovascular malformations were ventricular septal defects.[62] These preliminary results were based on retrospective analysis of data from two large US insurance healthcare databases, which included births from 1995 through 2002, of which 591 infants were exposed to paroxetine alone.[62]

Following the inclusion of births from January 2003 through September 2004 (an extra 224 infants), an updated analysis of the GSK study demonstrated an association between paroxetine and congenital malformations (OR 2.03; 95% CI 1.26, 3.25), but not cardiovascular malformations (OR 1.47; 95% CI 0.74, 2.89).[44]

In contrast, Kallen and Olausson[50] utilized data from three Swedish health registers to identify 6555 infants with first trimester exposure to an SSRI. When compared with the remainder of the population who were not exposed to an SSRI (n = 873 876), SSRI exposure was not associated with an increased risk of congenital malformations (OR 0.89; 95% CI 0.79, 1.07).[50] Further subgroup analysis, however, showed a significantly increased risk for cardiovascular malformations following exposure to paroxetine (OR 1.63; 95% CI 1.05, 2.53), but not other SSRIs.[50] Following exclusion of women with a high body mass

index (BMI), women born outside of Sweden, women who previously had difficulties getting pregnant and women who were exposed to certain other medications (antipsychotics, sedatives, hypnosedatives, folic acid, non-steroidal anti-inflammatories and antiepileptic drugs), there was nearly a 3-fold increase in the risk of cardiovascular malformations following exposure to paroxetine (OR 2.93; 95% CI 1.52, 5.13) and an even greater increase in the risk of septal defects (ventricular and atrial) (OR 3.23; 95% CI 1.30, 6.65).[50]

Three subsequent studies have found an increased risk of congenital malformations following prenatal exposure to paroxetine,[34,44,59] while no other studies have found an association with cardiovascular malformations overall. Individually though, studies have demonstrated an association between paroxetine exposure and specific cardiovascular malformations, including right ventricular outflow obstruction defects (OR 3.3; 95% CI 1.3, 8.8;[54] OR 2.5; 95% CI 1.0, 6.0[55]) and atrial septal defects (OR 5.7; 95% CI 1.4, 23.7).[61]

A total of 20 studies investigating first trimester paroxetine exposure and congenital malformations were analysed together in a recent meta-analysis.[63] This meta-analysis found an increased risk of congenital malformations overall (OR 1.2; 95% CI 1.1, 1.4), likely due to an observed increase in cardiovascular malformations (OR 1.5; 95% CI 1.2, 1.8). Absent from this meta-analysis, however, are a number of recently published studies that have shown no association between prenatal paroxetine exposure and congenital malformations or cardiovascular malformations.[35,51,57] Consequently, the association between paroxetine and cardiovascular malformations is still the subject of much debate, as evidenced from two recent, but conflicting, commentaries from experts in the field.[64,65] Even if paroxetine were to be considered teratogenic, the question becomes whether this suspected teratogenicity is specific to paroxetine, or applies to other SSRIs as well.

4.5.2 Risks Associated with Other Selective Serotonin Reuptake Inhibitors (SSRIs)

A number of studies have demonstrated an association between prenatal SSRI use and an increased risk of congenital malformations (OR 1.3; 95%CI 1.1, 16;[57] relative risk [RR] 1.34; 95% CI 1.00, 1.79[48]). The risk was greatest for cardiovascular malformations (OR 1.7; 95% CI 1.1, 2.5;[57] RR 2.17; 95% CI 1.07, 4.39[56]), particularly septal heart defects (OR 1.99; 95% CI 1.13, 3.53).[51] Other studies have found no association between SSRI exposure and congenital malformations.[32,45-47,49-53,60] Individually, first trimester exposure to

sertraline (OR 3.0; 95% CI 1.4, 6.4),[57] citalopram (adjusted risk difference 2.28; 95% CI 0.19, 4.36)[52] and fluoxetine (OR 4.47; 95% CI 1.31, 15.27)[34] have all been associated with an increased risk of cardiovascular malformations. In particular, both sertraline (OR 3.25; 95% CI 1.21, 8.75;[51] OR 3.3; 95% CI 1.5, 7.5;[57] OR 2.0; 95% CI 1.2, 4.0[54]) and citalopram (OR 2.52; 95% CI 1.04, 6.10)[51] have been associated with an increased risk of septal heart defects.

One case-control study found that first trimester exposure to any SSRI was associated with an increased risk of omphalocele (OR 2.8; 95% CI 1.3, 5.7), craniosynostosis (OR 2.5; 95% CI 1.5, 4.0) and anencephaly (OR 2.4; 95% CI 1.1, 5.1).[55] Individually, paroxetine was associated with omphalocele (OR 8.1; 95% CI 3.1, 20.8), sertraline with anencephaly (OR 3.2; 95% CI 1.1, 9.3) and fluoxetine with craniosynostosis (OR 2.8; 95% CI 1.3, 6.1).[55] An additional case-control study found an association between sertraline and omphalocele (OR 5.7; 95% CI 1.6, 20.7).[54]

4.5.3 Ascertainment of Outcome

Because of differences in the definitions of congenital malformations, the observed prevalence of malformations reported in different studies is not always directly comparable. The majority of studies only include congenital malformations reported in live born infants,[30,31,34,44,45,48-54,56-59,61] while at least three studies include congenital malformations reported in infants who were stillborn.[46,55,60] Some authors have reported poor validity in using information on congenital malformations gathered from stillborn infants or elective abortions as justification for their exclusion.[51] However, there is evidence that women taking antidepressants have a higher rate of ultrasound examinations than women not taking antidepressants, potentially introducing detection bias and increasing the observed rate of malformations amongst fetuses exposed to SSRIs.[66] If these women go on to have elective terminations, relying purely on congenital malformations reported in liveborn infants could potentially underestimate the risk associated with SSRI exposure. In addition, the increased risk of neonatal hospital admission that has been reported following prenatal exposure to SSRIs could also introduce detection bias. This could result in the detection of malformations that would otherwise go unnoticed if the infant was not admitted to hospital following delivery.

Furthermore, there are differences between studies in relation to the age of infants assessed for congenital malformations. There is no standardized approach, with timing varying from 1 month to 3 years of age.[35] This has significant consequences, particularly for the detection of cardiovascular malformations such as septal defects that commonly resolve spontaneously in the first few months or years of life without treatment.[64] Some malformations may remain undetected in infants with short-term follow-up, while others may have resolved spontaneously by the time of later follow-up. Notably, some studies report cardiovascular malformations even if they resolved spontaneously,[50] while others exclude them from analysis.[35,57]

Numerous studies rely on discharge summaries following hospital admission to detect congenital malformations, meaning only congenital malformations that required admission to hospital would be identified.[48,49,52,57,59] This may result in a bias towards the detection of more severe (and therefore possibly more clinically relevant) congenital malformations, but could also introduce detection bias if children of mothers taking SSRIs are more likely to take their child to hospital for various health-related complaints, increasing the detection rate of congenital abnormalities that would otherwise go unnoticed. Other studies utilize population-based birth defects registries that rely on voluntary reporting of congenital malformations,[46,61] some of which require informed consent to be given by parents before their child can be included on the register.[61] In one birth defects registry, a reported 20% of parents do not consent to including their child on the register.[61] This is a particularly important source of potential bias if consent rates differ between women exposed and not exposed to SSRIs during pregnancy.

In a unique study, Merlob et al.[56] actively screened all infants born in their hospital for cardiac murmurs on the first day of life and found an increased risk of cardiovascular malformations following prenatal exposure to SSRIs (RR 2.17; 95% CI 1.07, 4.39). Those performing the screening were not always blinded to the exposure status of the infants. Notably, they detected a larger number of cardiovascular malformations than the reported background rate of cardiovascular malformations, owing to the increased detection of mild asymptomatic malformations that would otherwise have gone unnoticed.[56] Importantly, all cardiovascular malformations identified in the exposed group were mild and asymptomatic, often resolving spontaneously.

4.5.4 Timing and Duration of Exposure

Many studies focus on identifying exposures during the first trimester.[30-35,44,46,48-52,54-57,60,61] However, in one study, 45% of those in the exposed group were exposed only during the third trimester;[45] in two others, women were classified as exposed as long as they took an SSRI at some stage during their pregnancy, irrespective of timing.[47,58] Despite evidence from embryological studies highlighting critical periods in which exposures can alter fetal development (e.g. the greatest period of sensitivity towards structural cardiovascular malformations encompasses the second and third months of pregnancy),[67] few studies have investigated differences between use during these periods and the first trimester as a whole. In one study, a higher risk of congenital malformations was found among those women who were dispensed an SSRI in the second or third month of pregnancy (RR 1.84; 95% CI 1.25, 2.71) compared with those who were dispensed an SSRI at any other stage during the first trimester (RR 1.34; 95% CI 1.00, 1.79), although these risks were not compared with each other to determine if the difference was statistically significant.[48]

4.5.5 Maternal Dose

Most studies did not collect data on SSRI dose used during pregnancy[45-51,53-58,60,61] and, even from those that did, the majority did not use dose in the analysis of any outcomes.[30-35,52,58,59] Two studies have found no dose-response relationship between SSRI exposure and congenital malformations,[34,52] while another found an increased risk of congenital malformations and cardiovascular malformations following exposure to paroxetine at an average daily dosage >25 mg/day.[59] In this study, 25% of women had an average daily dose >25 mg/day.[59]

4.5.6 Confounding

No studies have compared the rate of congenital malformations amongst only depressed women who were exposed or not exposed to SSRIs during the first trimester of pregnancy, although four studies did include women taking other antidepressants in their control group.[30,33,44,59] Ramos et al.[60] restricted their analysis to women with a diagnosed psychiatric illness, excluding those with psychotic illness or mental retardation. Even by limiting inclusion to women with psychiatric illness, some may still have been taking antidepressants for

illnesses other than depression. The remainder of studies included in their control groups: women not exposed to an SSRI (but it is unclear if they excluded women exposed to other antidepressants),[47,48,56,58] women not taking an SSRI or other antidepressant,[31-35,46,49-54,57] or historic population controls.[37]

In an attempt to obtain similar maternal characteristics between control and treatment groups, some studies have matched each woman in the exposed group to a woman in the control group. This was accomplished by either matching according to maternal age (±2 years),[30,33] or advanced matching based on multiple variables such as year of delivery, maternal age, parity, social status and geographic area,[46,47] or even previous psychiatric diagnosis.[45,46] However, the majority of studies did not perform any matching when identifying a control group.[34,35,48-56,58-61]

Other studies have attempted to address potential confounding according to underlying maternal illness by comparing outcomes among women exposed to different antidepressants.[50] This may not be completely effective if there are underlying differences related to the disease state which influence the choice of a particular SSRI over another. For example, sertraline and escitalopram have been reported to be more efficacious than fluoxetine in relation to therapeutic response based on a meta-analysis of 117 randomized controlled trials conducted from 1991 to 2007.[68] Therefore, sertraline and escitalopram may be more likely to be prescribed to patients with more severe depression.

Furthermore, it is clear that women take SSRIs for many conditions; therefore, it is possible that differences in underlying maternal illness (not just in disease severity) could introduce bias. Based on calls made to a Teratogen Information Counselling Service based in Canada, Bar-Oz et al.[66] demonstrated that significantly more women reported using paroxetine for anxiety or panic disorders (49.3%) than women taking other SSRIs (19.9%) [OR 4.11; 95% CI 2.39, 7.08]. This difference has important clinical implications as the observed difference in risk currently observed with paroxetine over other SSRIs may be confounded by differences in maternal illness.

More recent studies that compare outcomes only in women with depression, or use propensity score matching to adjust for key differences between exposed and non-exposed women, have failed to detect any increased risk in congenital malformations following the use of paroxetine during pregnancy. While previous results obtained regarding paroxetine may highlight potential differences in

underlying behaviours or risk profiles of women with depression versus those with anxiety or panic disorders, no studies have compared outcomes among women exposed to SSRIs according to underlying maternal illness.

Given the well noted associations between maternal age, smoking, socioeconomic status, coexisting medical conditions and maternal BMI and poor maternal and neonatal outcomes, it is not surprising to see these amongst the most common statistical adjustments (table I). Factors associated with the severity of depression (i.e. depression diagnosis, number of psychiatric visits or hospitalizations prior to or during pregnancy) together with other significant factors often associated with depression, including antenatal care and substance use, have rarely been considered. Notably, a large number of studies made no statistical adjustment for potential confounders.[30-33,45,49,56,58]

Similarly, the exclusion criteria of studies differ substantially, with some excluding women with hypertension,[51] diabetes mellitus,[51,55,57,59] epilepsy,[52,57] women taking other psychotropic medications,[51] women exposed to known or suspected teratogens,[32-35,50,59] women with a chronic medical illness for which they take regular medication[46] and infants with chromosomal or genetic defects.[32,34,48,54-57]

Differences between studies in relation to inclusion and exclusion criteria and adjustments for confounders are essential to understand. In one study, more than 30% of women in the SSRI exposed group were also exposed to a benzodiazepine,[60] while in another, 3.5% were exposed to more than one antidepressant during the first trimester.[50] No statistical adjustments were made for potential confounding due to concomitant exposure to a benzodiazepine or additional antidepressant. This potential for confounding was recently demonstrated by Oberlander et al.[52] who observed an increased risk of congenital malformations only following exposure to both an SSRI and benzodiazepine during the first trimester, but not with either medication alone. This increased risk could be the result of important medication interactions or underlying physiological differences between women who took only one medication compared with both medications together.

Some studies included women with a multifetal pregnancy, including each liveborn infant in the analysis,[34,50,60] or just one of the infants in the analysis,[55] while the remainder of studies only analysed outcomes for singleton births.

Other studies have only included each woman's first pregnancy in the final analysis.[59,60]

4.5.7 Clinical Summary

While much focus has been on paroxetine use during pregnancy, there is no clear evidence that paroxetine confers a greater risk of congenital malformations, particularly cardiovascular malformations, over any other SSRI. The collective evidence suggests that there is a low risk of malformations following prenatal exposure to SSRIs. Any risk of cardiovascular malformations following exposure to SSRIs appear to be small, especially in absolute terms, with many reported to be mild, asymptomatic and commonly resolved spontaneously before 12 months of age. These malformations appear to be related to exposures occurring during the second and third months of pregnancy, in line with the critical periods of cardiac embryology. One study observed an increased risk of congenital malformations only following paroxetine doses of >25mg/day and, while this finding has yet to be corroborated in other studies, it may emphasize the importance of using the minimum effective dose for treating depression during pregnancy.

4.6 Spontaneous Abortions

A number of prospective cohort[30-32,75] and case-control[23] studies have investigated the relationship between antidepressant use during pregnancy and the incidence of spontaneous abortions. One prospective cohort study demonstrated a statistically significant increased risk of spontaneous abortions amongst 128 women taking fluoxetine during the first trimester of pregnancy compared with an age-matched control group of 128 women exposed to other medications considered to be non-teratogens (15% vs. 8%; p= 0.03).[30] Further analysis, however, of 74 women taking fluoxetine during pregnancy compared with a matched control group of 74 women taking tricyclic antidepressants, showed no significant difference in the risk of spontaneous abortions (14% vs. 12%; p= 0.31), suggesting that depression itself may be the cause of an increased rate of spontaneous abortions, or that both SSRIs and tricyclic antidepressants increase the risk of spontaneous abortions through a common mechanism.[30]

Other prospective cohort studies have failed to demonstrate any statistically significant difference in spontaneous abortions among women taking SSRIs during the first trimester.[31,32,75] Importantly, none of these studies identified were adequately designed

to be able to investigate any association between prenatal SSRI exposure and spontaneous abortions. Three of the studies presented no data on when women were enrolled in the study,[30,32,75] while in one study, there was a marked difference between the number of women exposed and not exposed to an SSRI during pregnancy who were enrolled in the first trimester (82% vs. 61%, respectively).[31] As the risk of spontaneous abortion decreases as the pregnancy progresses, enrolling women at different stages of pregnancy introduces significant bias.

The most recent evidence for a potential association between prenatal exposure to SSRIs and spontaneous abortions comes from a case-control study involving 5124 women with clinically detected spontaneous abortions who were each matched to ten controls (51 240 controls in total).[23] Utilizing linked Canadian administration databases, they demonstrated a statistically significant association between SSRI use during pregnancy and spontaneous abortion (OR 1.68; 95% CI 1.38, 2.06), with the association strongest for paroxetine (OR 1.75; 95% CI 1.31, 2.34).[23] Exposure was defined as dispensing an SSRI from the first day of gestation to the date of spontaneous abortion for cases, or equivalent gestational age for controls. Exposure to more than one antidepressant was associated with an even greater risk of spontaneous abortion (OR 3.51; 95% CI 2.20, 5.61).[23] This association was independent of the effect of physician-diagnosed depression itself, which was also associated with an increased risk of spontaneous abortion (OR 1.19; 95% CI 1.03, 1.38).[23]

4.6.1 Timing and Duration of Exposure

While most studies focused on SSRI exposure in the first trimester, in one study only 169 of 228 women in the exposed group had first trimester exposure to an SSRI.[31] Including all women in the initial analysis would have introduced significant bias, as those enrolled in the study later on in pregnancy would be expected to have a significantly reduced risk of having a spontaneous abortion compared with those enrolled at the start of their pregnancy. Notably, the rate of spontaneous abortion amongst those actually exposed during the first trimester was 13.6%, higher than originally described (10%).[31] No statistical tests were undertaken to compare outcomes in only those women exposed during the first trimester to the control group.

Nakhai-Pour et al.[23] recently demonstrated a relationship between the risk of spontaneous abortion during pregnancy and the duration of antidepressant exposure prior to pregnancy, with a longer duration of antidepressant exposure prior to pregnancy appearing to be protective against the risk of a spontaneous

abortion. Those who took antidepressants for more than 6 months prior to pregnancy had a decreased risk of spontaneous abortion (OR 0.72; 95% CI 0.54, 0.95) compared with those who had only taken them for <1 month prior to pregnancy (OR 1.18; 95%CI 0.95, 1.45).[23] This could possibly be explained by a downregulation of serotonin receptors in the uterus following prolonged exposure to antidepressants, which leads to a reduced risk of triggering contractile activity and a spontaneous abortion.

4.6.2 Maternal Dose

While all studies collected information on dose used during pregnancy, only one study that included prenatal exposure to paroxetine conducted a sub-analysis according to dose.[23] This study demonstrated a statistically significant dose-response relationship between the dose of paroxetine during pregnancy and the risk of spontaneous abortions.[23]

4.6.3 Confounding

It is important to consider elective abortions when assessing the impact of prenatal SSRI exposure on spontaneous abortions. An early elective termination of pregnancy would preclude a later spontaneous abortion. Similarly, an early spontaneous abortion would preclude a later elective termination of pregnancy. Therefore, it is important to include an accurate denominator when calculating the prevalence of spontaneous abortions. It may be more accurate to assess outcomes on a week-by-week basis or, as two studies have, to exclude women with elective abortions during pregnancy from analysis.[23,30] Notably, the two studies that excluded women with elective abortions from analysis are the only two studies to demonstrate an increased risk of spontaneous abortions following SSRI exposure.[23,30]

Only the recent case-control study by Nakhai-Pour et al.[23] made adjustment for multiple potential confounders. They adjusted for maternal age, socioeconomic status, gestational age at time of abortion, maternal co-morbidities (diabetes, cardiovascular disease, asthma, untreated thyroid disease, depression, anxiety and bipolar disorder), history of spontaneous abortion and elective abortion, visits to psychiatrists, number of prescribers, number of visits to physicians, duration of exposure to antidepressants and other medications in the year before pregnancy, and number of prenatal visits, visits to obstetricians and other medication use during pregnancy.[23]

4.6.4 Clinical Summary

Because of a paucity of methodologically sound studies, there is currently insufficient evidence to draw definitive conclusions about any relationship between prenatal SSRI use and spontaneous abortions.

4.7 Neonatal Outcomes

A mix of retrospective[17,45-47,53,69,70,76,77] and prospective[30-34,71,72,78-82] cohort studies and case-control studies[73,74,83] have been used to investigate neonatal outcomes following prenatal exposure to SSRIs.

There are conflicting data on the incidence of adverse outcomes for babies of women treated with SSRIs during pregnancy. Some studies have found an association between prenatal SSRI exposure and low birthweight (<2500 g),[17,31,34,47,69,84] while other studies have not.[32,45,46,53,71,72,78,85-87] There is additional evidence that prenatal exposure to SSRIs is associated with decreased mean birthweight,[31,34,45,46,84] but this has not been demonstrated in all studies.[17,30,32,33,71,78-82,87] Few studies have assessed birthweight after accounting for gestational age, with some identifying an increased risk of infants being born small for gestational age (SGA),[17,31] while others have not.[53,69] There are also conflicting data around SSRI exposure and the length of gestation (term 40 weeks), with some studies showing an increased incidence of premature birth (<37 weeks' gestation)[31,45,47,49,53,69,71,72,88,89] and decreased mean gestational age at birth,[34,45,46,71,84,87,90] while others have found no difference in the incidence of prematurity[17,30,33,34,70,78,83] or mean gestational age at birth.[32,33,46,78-82,85,86] Results from a 2005 meta-analysis of 20 studies found an increased risk of low birthweight (OR 3.64; 95% CI 1.01, 13.08), but not prematurity (OR 1.85; 95% CI 0.79, 4.29), associated with prenatal exposure to SSRIs.[91]

Furthermore, exposure to SSRIs in utero has also been associated with decreased Apgar scores at birth[31,45,46,53,69,71,72,78,80] and increased Neonatal Intensive Care Unit (NICU) or Special Care Nursery (SCN) admissions.[17,31,33,46,71,76,78,88,92] This observed increased risk of hospitalizations could be explained by the greater incidence of neonatal withdrawal syndrome and/or poor neonatal adaptation observed in infants exposed to SSRIs during gestation.[31,53,70,93] Neonatal withdrawal syndrome is characterized by irritability, abnormal crying, tremor and convulsions, while poor neonatal adaptation is characterized by respiratory distress, tachypnoea, jitteriness, lethargy, and poor tone or colour.[17,31,34,47,49,69,79,84,88,94-96] A recent meta-analysis demonstrated that prenatal exposure to SSRIs was associated with an increased risk of SCN/NICU admissions (OR

3.3; 95% CI 1.45, 7.54) and neonatal withdrawal syndrome (OR 4.08; 95% CI 1.20, 19.93).[91] Notably, symptoms associated with neonatal withdrawal syndrome following exposure to SSRIs are usually mild and self-limiting, commonly disappearing over 2–14 days.[70,95]

Lastly, Chambers et al.[31] were the first to provide evidence that maternal use of SSRIs in late pregnancy could be a risk factor for the rare, but serious and sometimes fatal, respiratory condition, persistent pulmonary hypertension of the newborn (PPHN).[31] Since then, only three further studies have been specifically undertaken to investigate this outcome.[53,73,74] Two large case-control studies[73,74] and one retrospective cohort study[53] have found an association between prenatal SSRI exposure and PPHN (adjusted OR [AOR] 6.1; 95% CI 2.2, 16.8;[73] AOR 3.6; 95% CI 1.2, 8.3;[74] AOR 3.44; 95% CI 1.49, 6.79[53]).

Notably, the absolute risk is noted to be only relatively small given the low prevalence of PPHN in the general population (increased from 0.1% to 0.5%).[97] The greatest risk of developing PPHN has been associated with late gestation exposure to SSRIs (i.e. after 20 weeks' gestation), with no increased risk observed when SSRI use was restricted to the first half of pregnancy.[31,73]

4.7.1 Timing and Duration of Exposure

Studies classified women as exposed to an SSRI if they were dispensed at least one SSRI during pregnancy,[17,34,45-47,69] or reported taking an SSRI at some stage during pregnancy,[30,32,53,71] while others required exposure to an SSRI in the 2 weeks prior to delivery for inclusion.[70]

Chambers et al.[31] found an increased risk of prematurity, admission to SCN and poor neonatal adaptation following 'late' exposure (exposed during the last trimester) to fluoxetine compared with 'early' exposure (exposed during the first trimester only). However, of those with 'late' exposure to fluoxetine, the majority (82.2%) were actually exposed to fluoxetine during all three trimesters. Therefore, it is unclear whether the results reflect risks associated with 'late' exposure to fluoxetine, or to fluoxetine throughout pregnancy, compared with exposure during the first trimester alone.

In contrast, Malm et al.[46] analysed pregnancy outcomes amongst 360 women with exposure to an SSRI during at least the second and third trimester (with some exposed during all three trimesters) compared with 1010 women with exposure only during the first trimester. Interestingly, they found no difference

in mean gestational age at birth, or birthweight between the two groups, but found a statistically significant increase in the number of infants born at <32 weeks' gestation in the group of women with only first trimester exposure.[46] No statistical adjustments were made for potential confounders. An increased risk of low Apgar score at birth (OR 1.6; 95% CI 1.0, 2.4) and admittance to SCN/NICU (OR 1.6; 95% CI 1.1, 2.2) was also observed in 597 women with third trimester exposure compared with 1000 women with only first trimester exposure.[46]

In comparison, Simon et al.[45] compared outcomes of 84 infants exposed in only the third trimester to SSRIs with 84 matched controls, finding a statistically significant reduction in mean gestational age and Apgar score at birth, but no difference in mean birthweight. In contrast, when they compared outcomes amongst 101 infants exposed in only the first or second trimester, with 101 matched controls, they found a statistically significant reduction in mean gestational age and mean birthweight, but not Apgar scores.[45] The increased risk observed with late gestation or exposure throughout pregnancy to SSRIs may reflect differences in the underlying severity of maternal illness, where those with more severe illness required medication for a longer period of time during pregnancy. In addition, Simon et al.[45] observed greater reductions in mean birthweight, mean gestational age and Apgar scores amongst infants whose mothers received two or more prescriptions for an SSRI during pregnancy, suggesting that duration of exposure is important.

There have been some suggestions that pregnant women should stop or taper their dose of antidepressant in the 2 weeks prior to delivery to minimize the risk of neonatal symptoms.[95] More recent evidence, however, suggests that reducing exposure to SSRIs towards the end of pregnancy has no significant clinical effect on improving neonatal health.[98] Warburton et al.[98] used linked healthcare and administrative databases to compare outcomes amongst 1605 infants exposed to an SSRI during the last 14 days of pregnancy with 2122 infants exposed to an SSRI, but not in the last 14 days of pregnancy. They found no difference in a range of neonatal outcomes, including length of stay in hospital, convulsions, feeding problems, jaundice or respiratory problems between the two groups.[98] Tapering or stopping an SSRI during late pregnancy may be viewed as a way of improving neonatal health, but this would require consideration of the importance of continuing maternal therapy to manage depressive symptoms.

4.7.2 Maternal Dose

Only Levinson-Castiel et al.[93] have observed a dose-response relationship between paroxetine use during pregnancy and poor neonatal adaptation. Other studies either did not have data on maternal SSRI dose[17,45-47,53,69,71,74,77] or did not perform any subgroup analysis.[30-34,70,73,76,78-82] Furthermore, there is no evidence of a correlation between cord blood or newborn plasma concentrations and neonatal symptoms.[90]

4.7.3 Confounding

Few studies have directly compared neonatal outcomes amongst women taking SSRIs during pregnancy to women with depression who were not taking any antidepressants during pregnancy.[17,71,82] Control groups in other studies comprised of women not taking an SSRI during pregnancy (but it is unclear if they were taking other antidepressants),[47] women not taking any other antidepressants,[30,31,33,34,45,53,69,70,79-81] or a specific group of women not taking antidepressants who did not suffer from a psychiatric illness[71] or depression.[72]

A number of studies matched exposed and non-exposed groups according to maternal age,[30,33,45] year of birth,[45-47,73] place of birth (i.e. hospital),[46,47,73] mother's postcode,[46,47,73] lifetime use of antidepressants[45] and/or lifetime history of psychiatric treatment.[45]

Two studies utilized more advanced propensity score matching (based on a large number of sociodemographic and illness variables) to identify, within the total cohort, individuals who were very similar to each other apart from the exposure of interest.[17,98]

Oberlander et al.[17] demonstrated an increase in prematurity, respiratory distress, jaundice and length of hospital stay, together with a reduction in mean birthweight, among infants prenatally exposed to SSRIs. Notably, following propensity score matching (including matching according to severity of depression), prenatal SSRI exposure was only associated with an increased risk of low birthweight and respiratory distress.[17]

While propensity score matching does not equate to true randomization, as it is based on proxies of comparability and not true comparability, it can be considered the best technique available in the absence of true randomized controlled trials. These results provide strong evidence that prenatal SSRI

exposure may be associated with some adverse pregnancy outcomes, but also that underlying maternal depression is a significant confounder.

Potential confounders most often identified and adjusted for in studies investigating neonatal outcomes include maternal age, smoking status, parity and race (table I). Less commonly adjusted for were socioeconomic status, alcohol use, substance use and other aspects related to maternal depression that are known to have negative impacts on pregnancy outcomes (table I).

A number of studies did not perform any statistical adjustments for potential confounders.[30,32-34,77,78,82,84] At least one study included multi-fetal pregnancies in their analysis,[34] despite well known differences in growth rates and pregnancy outcomes compared with singleton births. Additionally, only two studies specifically excluded women taking other antidepressants, benzodiazepines or antipsychotics.[17,70]

4.7.4 Effect of Prematurity

An important issue in the analysis of neonatal outcomes is consideration of potential confounding due to prematurity. One could argue that prematurity acts as an intermediary, rather than a confounder, between prenatal SSRI exposure and adverse neonatal outcomes. Therefore, adjusting for prematurity could adjust away any associations between exposure and outcome. In saying this, there appears to be little doubt that adverse neonatal outcomes seen following prenatal SSRI exposure are not solely due to an increased risk of premature delivery, as evidenced from studies that restricted analysis to term infants and still demonstrated an increased risk of adverse neonatal outcomes.[69]

There is evidence, however, of a greater incidence of adverse neonatal outcomes, such as poor neonatal adaptation among premature infants prenatally exposed to SSRIs, which may be related to pharmacokinetic differences, particularly as a result of reduced clearance due to immature drug metabolism pathways. Among infants exposed to SSRIs during the last 2 weeks of gestation, Ferreira et al.[70] demonstrated that 100% of those born prematurely had symptoms associated with poor neonatal adaptation, compared with only 69.1% of infants who were born at term ($p = 0.002$). In addition, 41% of infants in the premature control group also displayed symptoms associated with poor neonatal adaptation. While premature

neonates suffer from immature lung and CNS development, predisposing them to a range of complications, including respiratory distress syndrome, irritability and convulsions, prenatal SSRI exposure appears to increase the risk of these complications further.[70]

4.7.5 Clinical Summary

Evidence regarding maternal use of SSRIs and an increased risk of low birthweight and/or prematurity in infants is conflicting. It is likely that any elevated risk of low birthweight could be attributable to early births of babies that had appropriate weight for their gestational age, but further research is required.

There is more convincing evidence that exposure to SSRIs during late gestation is associated with an increased risk of admission to SCN/NICU, and neonatal withdrawal symptoms and/or poor neonatal adaptation that are usually mild and self-limiting. These outcomes are likely to be associated with dose, duration and timing of exposure during pregnancy. Therefore, it is important that healthcare providers are advised of a woman's use of SSRIs during pregnancy, especially during late pregnancy, so that neonates can be observed in the immediate postnatal period and appropriate care and support can be provided if necessary. There is currently no clear evidence that women should be told to stop or taper their SSRI dosage during late pregnancy.[99]

Other perinatal complications include the reported increased risk of PPHN following prenatal exposure to SSRIs, with the greatest risk attributed to those exposed later in pregnancy.[99] The absolute risk is relatively small given the low prevalence of the disease in the general population (increase from 0.5–2 per 1000 to 3–12 per 1000),[99] but it further signifies the need for neonates exposed to SSRIs during late pregnancy to be observed in the postnatal period for potential complications.

4.8 Child Neurodevelopment

Long-term outcomes have been assessed using prospective[78,85,86,100,101] and retrospective[42,45] cohort studies. The majority of these have focused on outcomes in children <4 years of age,[42,45,78,85,86] with only two studies including data from children aged 4–5 years.[100,101] Collectively, these studies have analysed neurodevelopment in

childhood amongst approximately 900 infants exposed to an SSRI during pregnancy, with almost 50% of those coming from one study.[42]

Oberlander et al.[102] demonstrated that infants exposed to SSRIs in utero have an attenuated response to acute pain during heelsticks compared with infants who were not exposed to SSRIs.[102] Follow-up evaluation of those same infants at 4 years of age revealed no difference in internalizing,[101] externalizing or attentional behaviours[100] between those who were exposed and not exposed to SSRIs. Internalizing behaviours examined include depression, anxiety and withdrawal; externalizing behaviours included aggression, defiance and tantrums.[101]

No studies have demonstrated any statistically significant differences in cognition, language development or behaviour between children exposed and not exposed prenatally to SSRIs.[78,85,86] While Simon et al.[45] found no difference in motor or speech delay between infants exposed and not exposed prenatally to SSRIs, two more recent studies have demonstrated an association between SSRI exposure and delayed psychomotor development.[42,78]

Casper et al.[78] compared neurodevelopment outcomes in children of depressed mothers exposed and not exposed to a range of SSRIs in utero.[78] Following a single-blinded assessment between the ages of 6 and 40 months, no significant differences were observed between the groups in relation to mental development and attention, orientation and emotional regulation. Children exposed to SSRIs, however, demonstrated statistically significant differences in motor development, with notable differences in fine motor movements and tremulousness.[78]

In the largest and most recent study undertaken to date, Pedersen et al.[42] investigated the effects of prenatal antidepressant exposure on normal milestone development at 6 and 19 months of age in children taking part in the Danish National Birth Cohort Study. From a total cohort of 81 946 children eligible for the study, 415 were exposed to an antidepressant (336 to an SSRI) at some stage during gestation, while 489 were born to mothers with depression who did not take an antidepressant during pregnancy.[42] At 19 months of age, there was an association between antidepressant exposure during the second or third trimesters and an inability for children to occupy themselves for >15 minutes (OR 2.1; 95% CI 1.09, 4.02). In addition, there were notable delays in the time taken for children exposed to antidepressants during the second or third trimester to reach developmental milestones such as sitting without support (15.9 days later; 95% CI 6.8, 25.0) and walking (28.9 days later; 95% CI 15.0, 42.7) compared with children of mothers with untreated depression. This association was also strongest for males.[42]

Despite these delays, achievement of developmental milestones was still within the expected normal range of child development. Therefore, while statistically significant, the clinical relevance of such findings is unknown.

4.8.1 Ascertainment of Outcome

A large number of diverse tests have been used to assess a broad range of developmental outcomes in children with prenatal SSRI exposure (table II). While a detailed description of the way in which these tests are performed and the exact differences between these tests is beyond the scope of this review, the key message is that because of the variety of outcome measures used and the small sample sizes in each study, it is very difficult to compare results.

4.8.2 Timing and Duration of Exposure

Nulman et al.[85] observed no difference in global IQ values, language development and behavioural development in children exposed to fluoxetine during the first trimester only and those exposed to fluoxetine throughout the entire pregnancy. However, Pedersen et al.[42] demonstrated a statistically significant difference in motor function between infants exposed to an SSRI during the second or third trimester compared with those exposed only during the first trimester.[42] These findings could reflect differences in the critical periods of CNS development in which SSRI exposure can influence neurodevelopment in later life.

4.8.3 Maternal Dose

No studies have investigated any associations between maternal dose during pregnancy and child neurodevelopment outcomes despite the fact that many studies have collected data on maternal dose.[78,85,86,101] Oberlander et al.[100] found no association between cord blood concentrations at birth and externalizing behaviours in infants exposed to SSRIs.

4.8.4 Confounding

Only two studies have compared outcomes of infants or children of depressed mothers who were exposed and not exposed prenatally to SSRIs,[42,78] or who were taking other antidepressants.[85] The remainder of studies have compared outcomes with a control group that was not exposed prenatally to SSRIs and whose mothers were not depressed during pregnancy.[45,85,86,100,101]

Given the potential adverse effects of prenatal exposure to more than one psychotropic medication, Pedersen et al.[42] excluded infants of women exposed to psychotropic medications other than antidepressants. This is in contrast to other studies that have identified statistically significant differences between exposed and non-exposed groups in relation to prenatal use of anxiolytics, but did not exclude or statistically adjust for these differences in the analysis.[86]

Studies have adjusted for a range of confounders including maternal age,[42] infant sex,[42] age at follow-up,[42,85] breastfeeding,[42] maternal IQ,[85,86] problems during pregnancy,[42] socioeconomic status,[85,86] depression severity during pregnancy,[42,85] mother-child connection,[42] postnatal symptoms of depression,[42,100,101] postnatal difficulties,[42] smoking during pregnancy,[42,86] alcohol exposure during pregnancy[42,86] and history of poor neonatal adaptation.[100]

4.8.5 Loss to Follow-Up

Loss to follow-up is a particularly important source of bias for studies investigating outcomes that may not become apparent until many years later. This is particularly important for the two studies by Misri et al.[101] and Oberlander et al.[100] for example, which utilized the same cohort of children prenatally exposed to SSRIs. They originally identified 82 women to participate in the study, of which 52 agreed to participate. One woman had a spontaneous abortion and another five left the study prior to delivery. Over 4–5 years a further 24 women and their children were lost to follow-up, leaving a total of only 22 children exposed prenatally to SSRIs in the study.[100,101]

Pedersen et al.[42] also suffered from a large loss to follow-up in their study, although the rate of loss to follow-up between the study groups was similar (58% vs. 54%).

4.8.6 Clinical Summary

The collective evidence of prenatal exposure to SSRIs suggests that SSRI exposure is not associated with impaired neurodevelopment; however, there have been major differences in study design, patterns of SSRI use, age at follow-up, outcome measures used and adjustment for confounding.[36,103] Therefore, it is difficult to draw any conclusions about the long-term effects of prenatal exposure to SSRIs on fetal brain development given the general heterogeneity of studies undertaken. In addition, as no study has followed

children beyond early childhood, neurobehavioural abnormalities that may become evident later in life have not been determined.[104]

Given the importance of serotonin as a neurotransmitter within the CNS, and its role in neurogenesis, migration and differentiation of the human brain, the potential long-term effects of in utero exposure to SSRIs remain an important area of concern.[91,105] Studies demonstrating the potential role that the serotonergic system plays in the etiology of disorders such as schizophrenia, autism and depression raise further questions regarding potential long-term effects of prenatal SSRI exposure.[106,107] Further large, population-based studies are required to investigate the potential adverse effects of in utero exposure to SSRIs on fetal brain development, with longer-term follow-up of children into adulthood needed.

4.9 Challenges in Assessing Outcomes with SSRIs in Pregnancy

No one particular research approach is able to completely delineate the effects of SSRI use during pregnancy, highlighting the importance of recognizing the limitations associated with different study designs when comparing results. The contradictory results obtained from prospective and retrospective cohort studies and case-control studies may be accounted for by heterogeneity between study populations, selection bias, detection bias, confounding and differences in underlying maternal illness (i.e. women taking an SSRI for depression vs. women taking it for anxiety or panic disorders), data sources used, exposure classification (i.e. dose, duration and timing), follow-up and statistical power/analysis.

While a detailed description of statistical limitations is beyond the scope of this review, there are a number of issues that are pertinent to studies on SSRI use during pregnancy. The first is that we must be cautious in the interpretation of statistically significant results, given the large number of comparisons and statistical tests that are often undertaken. Multiple testing, as occurs with subgroup analyses, increases the potential for 'chance' findings. At the frequently utilized 5% significance level (95% CI) there is a 5% chance of obtaining a statistically significant result that is false (i.e. due to chance alone). With studies performing 20–40 individual tests, there is a possibility that 1–2 will be statistically significant by chance alone.

The second issue is sample size, which will determine statistical power. While studies may report differences as not statistically significant, they may not have had sufficient power to detect a statistically significant finding in the first place. Some studies only

have statistical power to detect large increases in risk. For example, Andrade et al.[77] was powered to detect a 6-fold difference in the prevalence of PPHN among infants exposed prenatally to SSRIs, while other studies were powered to detect a 4-fold increase in risk of major malformations.[30] Studies with low power are still useful in ruling out large increases in risk, but studies with much larger sample sizes are required to more accurately define smaller, but still clinically relevant, differences.

Finally, there is the issue of differentiating clinically significant differences from statistically significant differences. This is particularly important for studies with large sample sizes, which often have no difficulty establishing statistically significant differences. For example, outcomes that are of little or no consequence, such as a statistically significant reduction in mean birthweight of 50 g, could hardly be considered clinically significant, whereas a small increase in the risk of a rare but serious adverse outcome, such as PPHN, can have significant clinical and public health importance given the prevalence of SSRI use.

4.10 Future Directions for Research on SSRI use during Pregnancy

Despite numerous studies suggesting that depression itself is associated with poor pregnancy outcomes, and the potential confounding of pregnancy outcomes due to differences in characteristics of women with and without depression, there is actually a dearth of quality studies comparing outcomes between those receiving pharmacotherapy or psychological interventions and those receiving no therapy for depression,[108] especially studies with sufficiently large sample sizes to generate statistically and clinically significant results.

Furthermore, while much emphasis is placed on considering the risks and benefits of medication use during pregnancy, there is a bias towards investigating the risks associated with SSRI use during pregnancy, with little focus on the potential benefits that treatment may provide. What is the optimum SSRI dose during pregnancy, given the significant physiological changes that occur over the three trimesters? Does treating depression during pregnancy with an SSRI reduce the prevalence of adverse pregnancy outcomes that would otherwise be expected if these women were not given an SSRI? Does treating depression during pregnancy with an SSRI reduce the incidence or severity of postpartum depression, and therefore reduce the negative impact postpartum depression has on mother-infant bonding and subsequent child health and development?

Further complexities are introduced when we question which SSRI is the safest, or riskiest, to use during pregnancy. While all SSRIs inhibit serotonin reuptake, across the class there are differences in regard to molecular structure, selectivity, receptor binding and pharmacokinetics.[109] Differences in drug metabolism, for example, could play an important role in explaining how outcomes may differ depending on the SSRI used. SSRIs including paroxetine, fluoxetine and fluvoxamine are metabolized by the cytochrome P450 (CYP) isoenzyme 2D6, while citalopram, escitalopram and sertraline are metabolized by CYP2C19, among others.[110-112] During pregnancy, CYP2D6 is induced, increasing metabolism of its substrates and therefore decreasing their plasma concentrations, possibly necessitating the need to increase the dose during pregnancy.[113] In contrast, CYP2C19 activity is decreased during pregnancy.[113]

In addition to changes in metabolism that occur during pregnancy, the presence of genetic polymorphisms in CYP enzymes can dramatically alter SSRI plasma concentrations. For example, if 5–10% of Caucasians have an inactive CYP2D6 allele, as evidenced in some studies,[114] and are therefore poor metabolisers, one would expect 5–10% of women to have higher blood concentrations of paroxetine, fluoxetine and fluvoxamine than those with normal CYP2D6 function, and therefore a potentially higher incidence of adverse events. The importance of genetic polymorphisms is highlighted in a case report of a neonate who demonstrated severe neonatal withdrawal symptoms following exposure to paroxetine during late gestation and was found, through genotyping, to have reduced CYP2D6 function.[115]

Despite differences between SSRIs in relation to pharmacology, pharmacokinetics and pharmacodynamics, their relationship with pregnancy outcomes has not been well investigated. These differences may hold the key to understanding conflicting results obtained from studies to date and could help to further elucidate which women, if any, are at an increased risk of an adverse pregnancy outcome if they were to take an SSRI during pregnancy.

4.11 Conclusions

Numerous observational studies have been undertaken to investigate a wide range of outcomes associated with the use of SSRIs during pregnancy. Many of these studies, however, suffer from a number of important methodological limitations that must be taken into account when interpreting their results both individually and collectively (when compared with other studies).

There is an urgent need for further research evaluating how the particular SSRI used, the dose, timing and duration of use, genetics, concomitant medication use, maternal characteristics and underlying maternal illness all interact to confer an increased or decreased risk of adverse pregnancy outcomes following exposure during pregnancy.

4.12 References

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Table 4.1 Statistical adjustments in studies investigating congenital malformations and neonatal outcomes (e.g. birthweight, gestational age) following prenatal selective serotonin reuptake inhibitor exposure

	No. of Studies	
Statistical Adjustments	Congenital Malformations	Neonatal Outcomes
Maternal Age	13 [46-48,50-55,57,59-61]	9 [31,46,47,53,69-73]
Smoking Status	9 [34,46,48,50,51,53-55,57]	9 [31,45,46,53,69-71,73,74]
Birth Year	8 [48,50,53,54,57,59-61]	3 [53,69,73]
Socioeconomic Status	6 [46,47,51,55,59,60]	3 [31,46,47]
Parity	6 [46,47,50,53-55]	8 [31,45-47,53,69,71,73]
Diabetes	5 [48,54,59-61]	NA
Hypertension	4 [54,55,59,60]	2 [31,70]
Geographic Area	3 [48,59,60]	NA
Alcohol Use	3 [54,55,61]	3 [31,71,73]
Epilepsy	3 [48,54,61]	NA
Maternal BMI	3 [53,54,61]	3 [53,71,73]
Living Alone	2 [59,60]	NA
Depression Diagnosis prior to pregnancy	2 [52,59]	NA
Physician visits prior to pregnancy	2 [52,59]	NA
Prenatal visits	2 [52,59]	NA
Race	2 [54,55]	4 [31,45,72,73]
Visits to psychiatrist before or during pregnancy	2 [52,59]	NA
Substance Use	1 [47,52]	3 [45,47,70]
Emergency department visits or hospitilisations in the year before or during pregnancy	1 [59]	NA
History of Birth defects in family	1 [54]	NA
Caffeine consumption	NA	1 [71]
Use of other psychotropic drugs prior to delivery	NA	1 [31]

NA = not assessed

Table 4.2 Neurobehavioural tests used in studies to assess developmental outcomes in children with prenatal exposure to selective serotonin reuptake inhibitors

Neurobehavioural test and developmental outcome assessed	Age at test in study
Cognition	
Wechsler Preschool and Primary Scale of Intelligence – Revised [100]	1.5 – 5 y
Cognition, motor and language development	
Bayley Scales of Infant Development – II [78,85,86,100]	15 - 30 mo
McCarthy Scales of Children's Abilities [85,86]	30 - 71 mo
Temperament and behaviour [a]	
Achenbach Behaviour Checklist [85,86]	24 – 86 mo
Carey Temperament Scale [85,86]	< 24 mo
Child Behaviour Checklist [100,101]	1.5 – 5 y
Child Teacher Report Form [100,101]	1.5 – 5 y
Language Development	
Reynell Developmental Language Scales [85,86]	15 – 71 mo

[a] Including internalizing and externalizing behaviours

CHAPTER 5

Effects of Prenatal SSRI Exposure on Child Growth and Body Weight

Manuscript

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Long term impact of prenatal exposure to SSRIs on growth and body weight in childhood: Evidence from Animal and Human Studies

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5.1 Abstract

Prenatal exposure to SSRIs has the potential to alter fetal 5-HT signalling during critical periods of development: the long-term consequences of which have not been well studied. Of particular interest are the potential long-term effects of prenatal SSRI exposure on growth and body weight in later life, given the role of the serotonergic system in regulating food intake and body weight. Animal studies demonstrate that changes in 5-HT homeostasis during critical periods of fetal development can lead to sex-specific molecular and functional alterations in the serotonergic and HPA systems, leading to an increased risk of overweight in male, but not female, offspring in later life. This review highlights the evidence and the need for studies in humans to determine whether prenatal SSRI exposure is associated with alterations in child growth and body weight and the importance of delineating these effects from those of the underlying maternal illness.

5.2 Introduction

The use of selective serotonin reuptake inhibitors (SSRIs) has increased dramatically over the past two decades. In the United States, SSRI use has increased from 1.5% of all pregnancies in 1996 to 6.4% in 2005, making them the most used antidepressant during pregnancy.[1] While most commonly used in the treatment of depression, SSRIs are also used in the management of a number of psychiatric disorders including social anxiety disorder, obsessive compulsive disorder and panic disorder.[2] SSRIs exert their pharmacological effects by selectively inhibiting the reuptake of serotonin (5-hydroxytryptamine or 5-HT) at the presynaptic junction, resulting in an increased concentration of 5-HT in the synaptic cleft and thus enhanced serotonergic neurotransmission.[3]

In humans, prenatal exposure to SSRIs *in utero* has been associated with a range of adverse neonatal outcomes including preterm delivery, low birth weight, intrauterine growth restriction and decreased Apgar Scores at birth.[4,5] These babies are also more likely to be admitted to Neonatal Intensive Care Unit (NICU) or Special Care Nursery (SCN).[5] This observed increased risk of hospitalisations could be explained by the greater incidence of neonatal withdrawal syndrome and/or poor neonatal adaptation observed in infants exposed to SSRIs during gestation.[6-9] Neonatal withdrawal syndrome is characterised by irritability, abnormal crying, tremor and convulsions while poor neonatal adaptation is characterised by respiratory distress, tachypnoea, jitteriness,

lethargy and poor tone or colour.[6,10-20] While it is not clear whether these symptoms are a result of drug withdrawal or drug toxicity, they provide evidence that infants can be exposed to neurobiologically relevant doses *in utero*.

As such, there are concerns that SSRI use during pregnancy could alter fetal 5-HT signalling during critical periods of fetal development, the immediate and long-term consequences of which have not been well studied. Animal studies demonstrate that prenatal SSRI exposure is associated with a range of neurobehavioural abnormalities in later life. These include anxiety and depression-like behaviour, sleep abnormalities, altered response to stress and decreased sexual behaviour.[21-26] In contrast, collective evidence in humans suggests that prenatal SSRI exposure is not associated with impaired neurodevelopment in the offspring, however, there have been major differences in study design, patterns of SSRI use, age at follow-up, outcome measures used and adjustments for confounding.[4,27,28] Therefore, it is difficult to draw any conclusions about the long-term effects of prenatal exposure to SSRIs on fetal brain development given the general heterogeneity of studies undertaken. In addition, as no study has followed children beyond early childhood, neurobiological abnormalities that may not become evident until later in life cannot be ruled out.[25]

Given the importance of 5-HT as a neurotransmitter within the central nervous system and its role in neurogenesis, migration and differentiation of neurons in the fetal brain, the potential long-term effects of prenatal SSRI exposure remains an important area of concern.[29,30] Of particular interest are the potential long-term effects of prenatal SSRI exposure on child growth, given the well established role of the serotonergic system in regulating food intake and body weight.[31-33] While a number of studies have investigated the effects of SSRI use while breastfeeding on infant weight gain,[34-37] to date only one study has directly investigated the effects of prenatal exposure to antidepressants (including SSRIs) on infant weight gain, but that was only in infant's up until 1 month of age.[11]

As such, the aim of this literature review was to outline the potential long-term effects of prenatal SSRI exposure on growth and body weight in the offspring in later life. The review begins with a discussion of 5-HT, its role in fetal brain development as well as its role in regulating food intake and body weight. The impact of prenatal SSRI exposure on the development of the serotonergic system is then explored using evidence generated from animal studies before examining the effects of prenatal exposure to maternal stress and the resultant development of the hypothalamic-pituitary-adrenal (HPA) axis and its effects on growth in later life. This is important in delineating any potential outcomes that are a result of prenatal SSRI exposure from those that are due to the

underlying maternal illness. The review then culminates in a summary of the effects of prenatal SSRI exposure on growth and body weight in the offspring in later life according to evidence generated from human studies.

5.3 Role of 5-HT in fetal brain development

Central to understanding any potential risks to the fetus following prenatal exposure to SSRIs is a consideration of the role of 5-HT itself in fetal neurodevelopment. As SSRIs have been shown to readily cross the placenta,[38] they have the potential to inhibit the reuptake of 5-HT in the fetus, resulting in an increased concentration of 5-HT at the synaptic cleft and thus enhanced serotonergic neurotransmission during fetal development.[3]

Serotonergic neurons are first evident by 3 weeks post conception in the human brain[39] and increase rapidly until 13 weeks post conception, at which point the typical organisation of 5-HT cell bodies into the raphe nuclei can be seen.[30] Prior to its role as a neurotransmitter, 5-HT plays a broad role in fetal brain development.[29,30] During the fetal period, 5-HT acts as a trophic factor, regulating cell migration, axon growth, and genesis of synaptic communication.[40-42] The 5-HT transporter (5-HTT) plays a major role in regulating the re-uptake of 5-HT from the synaptic cleft and also serves as the target for SSRIs.[43] The precise time course of developmental 5-HTT expression in humans is unknown. Evidence is available from animal studies, however, which demonstrates that 5-HTT mRNA expression is first evident around midgestation (embryonic day 11 in mice), [44] which matches the stage when 5-HT neurons first appear.[45]

Genetic alterations in the serotonergic system have been demonstrated to lead to alterations in 5-HT homeostasis, causing permanent changes in adult behaviour and modifications to fine wiring of brain connections.[46] It is possible that increased levels of 5-HT during gestation, secondary to SSRI exposure, could occur at critical sites where 5-HT plays an important role in the regulation of physiological systems, causing permanent disruptions to these developing physiological systems. This disruption could occur as a result of an initial acute increase in serotonergic tone which accompanies prenatal SSRI exposure, leading to an increase in negative feedback which inhibits the development of the serotonergic system, resulting in a chronic reduction in serotonergic tone later in life.[23] Furthermore, prenatal SSRI exposure could lead to neurobehavioural abnormalities in later life, such as anxiety and depression, which in turn could predispose an individual to a range of adverse health outcomes.[23]

5.4 Role of 5-HT in regulating food intake and body weight

Controlling energy homeostasis depends on balancing energy consumption with energy expenditure.[47] 5-HT plays an important role in the central regulation of food intake and body weight together with a number of molecular mediators linking the central nervous and endocrine systems, including neuropeptide Y (NPY), adipocytokines (e.g. leptin and adiponectin), pro-inflammatory cytokines and neurotrophins such as brain derived neurotrophic factor (BDNF).[48,49] These molecular mediators are closely regulated and linked with each other. The serotonergic system is involved in the regulation of NPY, with activation of the serotonergic system through 5-HT agonists decreasing NPY secretion, with a resultant reduction in food intake, while 5-HT antagonists increase NPY secretion.[49] In contrast to NPY, leptin acts to decrease food intake. Leptin receptors are located on serotonergic neurons,[50] with stimulation of leptin receptors resulting in a decrease in neuronal synthesis and release of 5-HT.[51] Lastly, 5-HT and the neurotrophin BDNF are both highly expressed in the hypothalamus and co-regulate each other.[52] 5-HT is involved in the expression and secretion of BDNF, while BDNF supports the maintenance of serotonergic neurons and the release of 5-HT.[48] BDNF has a profound effect on energy homeostasis and feeding behaviour,[52] with mice lacking BDNF displaying hyperphagia and a phenotype similar to the human metabolic syndrome.[48]

The role of 5-HT itself in regulating food intake and body weight was first recognised in the 1970s, with the observation that increased concentrations of 5-HT in the brain were associated with increased satiety.[53] Further studies have helped establish the role of 5-HT in regulating body weight,[54-58] with evidence that pharmacological stimulation of the serotonergic system reduces food intake and increases energy expenditure, while administration of 5-HT antagonists has the opposite effect.[59-63] Subsequent studies utilising 5-HT transporter knockout and transgenic mice provide additional evidence of the role of 5-HT in regulating body weight.[48,64,65]

The control of food intake and body weight is closely regulated within the hypothalamus,[49,66] which receives information generated from throughout the body via a complex network of cellular signals.[67] Table 5.1 presents a summary of the main 5-HT receptor subtypes involved in regulating food intake and body weight. The main inhibitory effects of 5-HT on food intake have been related to its interactions with 5-HT_{1B} and 5-HT_{2C} receptors in the hypothalamus.[31,32,68-73] This critical relationship between 5-HT_{1B} and 5-HT_{2C} receptors and regulation of food intake and body weight has been demonstrated in studies involving knockout mice who lack these receptors.[66,74-76] In these studies, the typical hypophagic effects of 5-HT are significantly attenuated, while only 5-HT_{2C} knockout mice were observed to have abnormal control of feeding behaviour

and an increased likelihood of becoming overweight compared to controls.[66,74,75] It is possible that in those mice lacking 5-HT_{1B} receptors, compensatory changes occur in other neurotransmitters and receptors involved in energy homeostasis, explaining the absence of a body weight phenotype.[75] Importantly, not all 5-HT receptors have the same effects, with activation of 5-HT_{1A}, and 5-HT_6 receptors demonstrated to increase food intake.[33,48,51,73,77] Furthermore, 5-HT_{1A} knockout mice demonstrate significantly reduced food intake and have lower fat pad mass,[51] while 5-HT_6 knockout mice are resistant to weight gain when exposed to a high-fat diet.[78] Therefore, when circulating 5-HT concentrations increase, as occurs with prenatal SSRI exposure, 5-HT may bind to several receptor subtypes that have opposing effects on feeding behaviour. This could result in an overall neutral net effect, with no observed difference in body weight.[48] This observation raises an important issue for human studies, where it is possible that alterations in the serotonergic system may predispose an individual to the development of an abnormal metabolic phenotype, but it also possible that compensatory adaptive responses could occur in alternative systems involved in energy homeostasis to maintain normal body weight.

The 5-HT transporter (5-HTT), which is responsible for the re-uptake of 5-HT from the synaptic cleft, is important in regulating 5-HT function and acts as the target for SSRIs.[43] There is evidence that alterations in 5-HTT expression which are present during early fetal life are associated with long-term metabolic outcomes. Over-expression of 5-HTT in the brain of mice has been demonstrated to result in lower body weight, but similar food intake, compared to controls.[79] In addition, other studies have shown that 5-HTT knockout mice develop an obese phenotype, despite normal food intake.[48,64,65] The increase in body weight in 5-HTT knockout mice may be due to either the observed decrease in physical activity,[48,65] or alteration in metabolic pathways, as these mice also demonstrate hyperleptinemia and hyperinsulinemia.[64]

Given the role of 5-HT in regulating food intake and body weight, targeting the serotonergic system for the treatment of obesity in humans has received much interest.[33] Administration of SSRIs has been demonstrated to reduce food intake and induce weight loss in both obese and lean individuals.[80-83] Furthermore, alterations in weight (i.e. weight loss/weight gain) have also been reported in individuals taking SSRIs for the treatment of psychiatric illness.[84] In addition, agents such as sibutramine, which act as 5-HT and NA re-uptake inhibitors, have been extensively studied and utilised clinically in the treatment of obesity.[85,86]

5.5 Impact of prenatal SSRI exposure on development of the serotonergic system – evidence from animal studies

Consequences of alterations in 5-HT homeostasis have been investigated using pharmacological and genetic approaches. It is essential to be aware of key differences in the timing of brain development between species. Animal studies investigating the effects of prenatal SSRI exposure on development of the serotonergic system are most often undertaken in rodents (mice and rats), where maturation of the brain occurs after delivery, from postnatal days 4 to 21, which corresponds to the third trimester of pregnancy and early postnatal life in humans.[23,24] Therefore, exposures occurring only to birth in rodent studies may not be sufficient in assessing outcomes that could occur as a result of prenatal exposure during the third trimester in humans. Furthermore, it would be more appropriate to investigate the developmental effects of prenatal SSRI exposure in species where the brain is relatively mature at birth, such as in the sheep and guinea pig.[87]

For the purposes of this review the outcomes of animal studies will be presented according to effects of prenatal exposure to SSRIs on 5-HT receptors and 5-HTT expression, as well as the effects of 5-HTT knockout status on the developing serotonergic system. A summary of the reported effects of prenatal SSRI exposure and 5-HTT knockout status on factors associated with growth outcomes in later life are presented in Table 5.2.

5.5.1 5-HT Receptors

Cabrera and Battaglia[88] demonstrated that prenatal exposure to fluoxetine results in a significant reduction in hypothalamic 5-$HT_{2A/2C}$ receptors observed in male rats at 70 days postnatal age. In addition to a significant reduction in hypothalamic 5-$HT_{2A/2C}$ receptors, 5- $HT_{2A/2C}$ receptor-mediated endocrine response to a 5-$HT_{2A/2C}$ agonist was markedly attenuated.[88] Interestingly these effects were not observed at postnatal day 28, suggesting a delayed decrease in receptor density and function.[88]

In 2000, Lauder et al.[89] demonstrated that both under-stimulation (by depletion of 5-HT) and over-stimulation (by 5-HT agonists) of 5-HT_{1A} receptors during prenatal development can produce a significant reduction in the expression of 5-HT_{1A} receptor transcripts. This alteration could significantly impact on levels of 5-HT_{1A} receptor expression in the postnatal brain, the implications of which are as yet unknown. The question of whether these

observed effects persist into adulthood also remains to be determined. Nevertheless, the fact that both under and over-stimulation of 5-HT_{1A} receptors can cause alterations, suggest that appropriate levels of serotonergic stimulation of 5-HT receptors may be required for normal developmental regulation.[89]

5.5.2 5-HT Transporter (SERT or 5-HTT)

In males, prenatal exposure to fluoxetine has been demonstrated to result in alterations in 5-HTT expression in various brain regions, including an overall increase in 5-HTT expression in the hippocampus and amygdala, together with both increases and decreases in 5-HTT expression within subregions of the hypothalamus.[90] These changes are important as these nuclei have important roles in regulating food intake and body weight. These alterations were observed in rats at postnatal day 28, but not in adult life.[90] While observed changes in 5-HTT density appeared to normalise by adulthood, functional deficits may still remain.[90] For example, Battaglia[91] demonstrated that lesions of serotonergic axons initially cause a 90% reduction in 5-HTT, with 5-HTT expression reaching normal levels 1 year after the lesion. Despite this normalisation in 5-HTT expression, a persistent functional alteration in presynaptic 5-HT neurons was observed.[91] This involved a marked attenuation of the effects of p-chloroamphetamine, a drug which inhibits 5-HTT and induces presynaptic release of 5-HT.[91] The same observation was made following prenatal exposure to fluoxetine, with no demonstrated difference in 5-HTT expression in adult mice, but a significantly attenuated effect of p-chloroamphetamine on 5-HT concentrations within the synapse.[92] Therefore, while 5-HTT expression may appear to normalise over time, functional deficits may remain.

In contrast, Noorlander et al.[22] recently demonstrated a persistent reduction in 5-HTT in the raphe nucleus which was evident from postnatal day 20 in mice exposed *in utero* to fluoxetine, but not fluvoxamine. In contrast to the previously reported study, male and female offspring were included in the analysis. In addition to these changes in 5-HTT expression, prenatal fluoxetine, but not fluvoxamine, exposure was also associated with depression and anxiety related behaviour in the offspring in adulthood. Given that placental transfer of fluvoxamine was less than half that of fluoxetine, it is possible that the differences observed between those exposed to fluoxetine and fluvoxamine are related to differences in the placental transfer rate of these medications and

therefore differences in the concentration of fetal exposure.[22] In addition, differences in metabolism and clearance may also be important. For example, fluoxetine, and its active metabolite norfluoxetine, both have a long half-life, compared to fluvoxamine which has a short half-life and no active metabolite.[93] Notably, prenatal exposure to fluoxetine and fluvoxamine was not associated with alterations in body weight in male or female offspring from birth to adulthood.[22] However, as 82% of fluoxetine exposed mice died by postnatal day 20, the ability to examine differences in body weight was restricted due to small sample sizes. Subsequent animal studies have also demonstrated alterations in 5-HTT expression,[90,92,94] as well as anxiety and depression related symptoms in later life,[24,95] following prenatal exposure to fluoxetine. The anxiety and depression related symptoms observed amongst these offspring are strikingly similar to those observed in 5-HTT knockout mice/rats.[44] As such, given the effects of developmental SSRI exposure are, to a large extent, mimicked by genetic 5-HTT down-regulation, 5-HTT knockout rodents are used as a model to help predict the effects of prenatal SSRI exposure on neurodevelopment and subsequent behaviours in later life.[44]

5.5.3 5-HTT Knockout Studies

5-HTT knockout rodents demonstrate clear alterations in 5-HT homeostasis, with an increased amount of 5-HT in the synaptic cleft that cannot be removed. This leads to overstimulation of 5-HT receptors, resulting in abnormal development of the thalamocortical and retinal axons.[46]

Most studies have been performed on male subjects, however, when females are included, sex differences in the effects of prenatal SSRI exposure on 5-HTT have been found. Females appear to be protected from late-onset obesity as occurs in 5-HTT knockout male mice.[48,96] Despite similar changes to males in relation to the expression of BDNF and leptin receptors, females did not demonstrate the same reduction in motor activity.[48] In contrast, female, but not male, 5-HTT knockout rats display a reduction in total body weight with an increased percentage of abdominal fat, suggestive of abdominal obesity.[97] Female 5-HTT knockout mice have been shown to be protected from the loss of 5-HT within the hypothalamus and other brain regions and display significantly attenuated behavioural abnormalities (i.e. anxiety-like behaviours) as compared to those which occurred in the male mice.[98] In addition, female 5-HTT knockout mice display a greater reduction in the density of 5-HT_{1A}

receptors in various brain regions, including the hypothalamus, compared to males.[99,100]

These sex-specific outcomes are not only limited to studies involving 5-HTT knockout rodents. Behavioural outcomes following prenatal exposure to SSRIs differ between males and females with prenatal exposure to paroxetine resulting in increased aggressive behaviour in adult male, but not female, rats.[95] In humans, greater delays in aspects of child development related to motor activity have been observed at 6 months of age in males, compared to females, following prenatal exposure to antidepressants (including SSRIs and other antidepressants).[101] Potential effects of prenatal SSRI exposure on motor activity in the offspring are important given the association between motor proficiency and physical activity in children.[102] Therefore, given the known sex differences in human brain development and function, these studies may suggest sex differences in the susceptibility of the developing fetal brain to prenatal SSRI exposure.[103,104]

5.6 Maternal stress, the hypothalamic-pituitary-adrenal (HPA) axis and 5-HT

Any efforts to understand the potential impact of prenatal SSRI exposure on fetal development must also take into account, and attempt to distinguish between, the impact of SSRI treatment itself and the maternal condition for which SSRI treatment is necessary. Animal studies provide an excellent opportunity to delineate any potential adverse effects of prenatal SSRI exposure from that of the underlying condition, however, the challenge exists in the ability to accurately mimic the physiological effects of that condition during pregnancy. Disorders such as depression and anxiety are often a consequence of exposure to stress or traumatic life events and have been associated with abnormalities in the function of the hypothalamic-pituitary-adrenal (HPA) axis, which is critical in regulating an individual's response to stress. Individuals with depression and anxiety are reported to have a deficiency in the underlying stress coping mechanism,[105] as indicated by hyperactivity of the HPA axis and resultant increased circulating concentration of maternal cortisol[106]. As such, to mimic these disorders during pregnancy the majority of animal models are based on exposure to various types of acute or chronic stressors.[105] These animals express symptoms similar to depression and anxiety, which can be reversed by the administration of antidepressants.[105]

Animal models of maternal stress during pregnancy have demonstrated a range of functional and behavioural abnormalities in the offspring in later life.[107] In particular, the 5-HT system has been shown to be altered by exposure to prenatal stress.[108] These

include increased concentrations of 5-HT in the hippocampus[107] and hypothalamus[109] as well as alterations in 5-HT receptor binding and modifications in the intensity of behavioural responses to 5-HT agonists in adult mice exposed to maternal stress during pregnancy.[108]

In addition to effects on the serotonergic system, exposure to maternal stress during gestation has also been demonstrated to adversely affect the development and regulation of the HPA axis.[110,111] This is likely the result of increased circulating concentrations of maternal and fetal stress hormones. Activation of the HPA axis is attenuated by a negative feedback circuit involving levels of circulating glucocorticoids.[112] Maternal stress during pregnancy results in increased circulating levels of glucocorticoids which can enter the fetal circulation and result in a persistent down regulation of central glucocorticoid receptors in the hippocampus.[112] This leads to reduced feedback inhibition and increased activity of the HPA axis in the offspring in later life, resulting in increased cortisol secretion in the basal state and under conditions of stress.[112,113] This has a number of important implications for metabolic function in later life as increased plasma cortisol concentrations promote triglyceride retention in visceral adipose tissue, increase levels of free fatty acids and glucose and inhibit the action of insulin on glucose uptake.[114] In addition, overactivity of the HPA axis has been associated with a range of cardio-metabolic outcomes including hypertension, impaired glucose tolerance, insulin resistance and obesity in later life.[115,116]

Sex-specific differences in the response to prenatal exposure to stress have also been observed. Numerous studies have demonstrated that female mice exposed to prenatal stress display significantly higher basal and stress-induced plasma corticosterone levels as well as reductions in the density of hippocampal glucocorticoid receptors than non-stressed controls.[117-119] In contrast, no consistent differences in HPA responses have been observed between males exposed to prenatal stress and controls.[117-119] These results suggest sex-specific effects of prenatal stress on HPA activity in later life, with a reduction in negative feedback mechanisms and overactivity of HPA axis function more likely among females, but the precise mechanisms underlying this sex mediated effect is not yet clear.

Notably, a recent human study demonstrated that exposure to prenatal stress (related to maternal bereavement immediately prior to pregnancy) is associated with an increased risk of overweight in childhood.[120] This was postulated to be the result of fetal programming of the HPA axis in response to excessive exposure to cortisol during pregnancy. The observed increased risk of overweight was only observed in the offspring from 10-years of age, indicating the need for long-term follow-up when considering

effects of fetal programming. Notably, no stratification was made according to sex and it was not clear how many women, if any, were taking antidepressants during pregnancy.

In contrast, Oberlander et al.[115] demonstrated altered HPA stress response patterns and reduced early evening basal saliva cortisol concentration among 3-month old infants exposed to SSRIs during gestation. However, whether these observed effects are the result of prenatal exposure to SSRIs or a result of underlying maternal illness is unknown, and reflects the inherent difficulty in separating one from the other. What we do know is that there is a strong functional link between the serotonergic and HPA regulatory systems with 5-HT modulating the development and function of the HPA system, while in turn HPA hormones regulate 5-HT function.[115] This suggests that alterations in the developing serotonergic system could lead to alterations in the HPA regulatory systems,[121] or that compensatory or adaptive processes occur between the serotonergic and HPA systems to maintain normal function.

Morrison et al.[122] demonstrated a rise in fetal plasma ACTH and cortisol concentrations in sheep treated with fluoxetine during late gestation due to either a premature increase in fetal ACTH at an earlier than expected gestational age, or a direct effect of fluoxetine on the fetal HPA axis to enhance either secretion of, or sensitivity to, hypothalamic secretagogues.[122] In addition, male 5-HTT knockout mice display increased HPA axis activity and a reduction in negative feedback regulation in later life, largely as a result of a significant reduction in the expression of the glucocorticoid receptor (GR) in several brain regions (hypothalamus, pituitary and adrenal cortex).[123] As these experiments were only undertaken in males, the potential for sex-specific differences were not examined.

Maternal postnatal psychiatric illness could also have an important impact on child growth. Maternal psychiatric illness during early phases of childhood development may result in suboptimal nutritional intake amongst these children. This may occur through negative effects on mother-child interactions, or differences in feeding practices.[124] Women with psychiatric illness may have more unhealthy behaviours (i.e. abnormal eating behaviours or physical activity levels), passing these on to their children. In addition, high levels of maternal postnatal stress have been associated with increased cortisol levels in newborns and adolescents.[125,126] This may be the result of adverse effects of postnatal illness on parenting behaviour and the social environment, producing a more stressful environment for the child, which in turn leads to elevated cortisol levels and cortisol reactivity in the offspring. However, despite concerns surrounding maternal psychiatric illness, the implications for long-term effects on growth and body weight are not quite clear. One study demonstrated that maternal postpartum depression was associated with greater overall adiposity in children at 3 years of age,[127]

while others have demonstrated that significant relapse of depressive illness during the post-partum period is associated with overall reductions in infant weight gain,[37] and that maternal postpartum distress is not associated with childhood overweight at 7-years of age.[128]

5.7 Impact of prenatal SSRI exposure on child growth – evidence from human studies

A number of studies have investigated the effects of SSRI use while breastfeeding on infant weight gain,[34-37] with the majority of studies finding no association.[35-37] This is an observation that could be expected, given the relatively minor concentrations of SSRIs observed in breast milk and infant serum.[34,35] While it is possible that there are individual and age-related differences in an infant's ability to metabolise an SSRI which may be present in breast milk, and that some may subsequently be exposed to higher concentrations than others, the overall effect from breastfeeding is believed to be low.[34] It appears more likely that exposure to much greater plasma concentrations during critical periods of brain development, *in utero,* could impact on child growth and body weight in later life. In support of this argument, the only study which observed effects on infant growth following exposure through breast milk, in that case to fluoxetine, was the only study where all infants were also exposed in utero.[34] Between 2 weeks and 6 months of age, infants who were breastfed by mothers taking fluoxetine during pregnancy and lactation demonstrated a growth curve significantly below that of infants who were breastfed by mothers who did not take fluoxetine, with a recorded average post natal weight deficit of 392g (95%CI -5, -750).[34] Notably, no stratification was made according to sex. While the authors conclude that breastfeeding while taking fluoxetine may be associated with reduced postnatal growth, it is not clear if this is due to pre- and/or post-natal exposure to fluoxetine as all women took fluoxetine during the 3rd trimester.

To our knowledge, only one study has directly investigated the effects of prenatal exposure to antidepressants in general on infant weight gain, and that was only up until 1 month of age.[11] They found a statistically significant difference in birth weight (-398 g; *P*=0.005) between those exposed to antidepressants during pregnancy and the controls, which persisted until 1 month of age (-551 g; *P*=0.010). Mean weight gain in the postnatal period was lower in those infants who were exposed to an antidepressant during pregnancy and controls (22.71 g/day vs. 31.81 g/day; *P*=0.002).[11] No adjustment was made for breastfeeding status or sex.

While not specifically designed to assess the impact of prenatal exposure to SSRIs on postnatal growth, a number of other studies have collected and presented data on

children's heights and/or weights from 6-86 months of age.[129-133] None of these studies demonstrated statistically significant differences in height or weight when analysed separately. However, as child growth was not the primary outcome investigated in any of these studies there were no statistical adjustments or considerations made for relevant maternal and/or infant characteristics that could act as confounders, making it difficult to draw any conclusions from the results obtained. In addition, assessment of appropriateness of childhood growth should consider the child's weight relative to their height. As such, while alterations in child growth following prenatal exposure to SSRIs is biologically plausible based on animal and human studies, the current literature does not allow a full assessment of these effects. There is a need for further research to follow-up infants exposed to SSRI's during pregnancy to examine whether there are long-term sustained effects on growth and body weight.

5.8 Summary and Conclusion

There are a number of potential neurobehavioural consequences following prenatal exposure to SSRIs. Animal studies provide clear evidence that changes in 5-HT homeostasis during critical periods of fetal development can lead to molecular and functional alterations in the serotonergic and HPA systems. There is evidence to suggest that auto-inhibitory feedback restrains the maturation of the 5-HT system.[23] It is therefore possible that in the situation where serotonergic tone is increased as a result of SSRI exposure, there is a resultant increase in negative feedback signalling, restraining the maturation of the serotonergic system, the effects of which may be sex-specific.

Animal studies suggest that prenatal SSRI exposure could increase the risk of overweight in male offspring in later life. This may occur as a result of decreased expression,[88] and/or function,[134,135] of hypothalamic 5-$HT_{2A/2C}$ receptors which are involved in maintaining satiety, or due to reductions in physical activity,[26,48] as observed in male 5-HTT knock-out mice that develop late-onset obesity[48,96].

Predicted growth outcomes for female offspring with prenatal SSRI exposure, however, appear less clear. Agonism of 5-HT_{1A} receptors has been demonstrated to result in hyperphagia,[77,136] suggesting a reduction in the density of 5-HT_{1A} receptors[99,100] may result in a reduction in the usual hyperphagic response to circulation levels of 5-HT, resulting in a net reduction in food intake and body weight. In addition, an increase in 5-HT_{2A} receptors in the hypothalamus[137] could result in increased feelings of satiety and therefore a reduction in food intake. Notably, while female 5-HTT knock-out rats display

a reduction in total body weight, they also display an increase in the percentage of abdominal fat highlighting potential alterations in metabolic function.[97]

In addition to the potential long-term effects of prenatal SSRI exposure, it is important to recognise the contribution of underlying maternal illness on influencing long-term growth outcomes in the offspring. Similarly to prenatal SSRI exposure, sex-specific differences in the response to prenatal exposure to stress have also been observed. Female mice exposed to prenatal stress display significantly higher basal and stress-induced plasma corticosterone concentrations as well as reductions in the density of hippocampal glucocorticoid receptors compare to non-stressed controls.[117-119] These results suggest sex-specific effects of prenatal stress on HPA activity in later life, with a reduction in negative feedback mechanisms and overactivity of HPA axis function more likely among females, which can lead to a range of negative growth outcomes in later life.

While there is clear evidence from animal studies that prenatal exposure to SSRIs could lead to alterations in growth outcomes in the offspring in later life, there is insufficient data from human studies to draw conclusions. As such, further research is required to investigate the potential long-term effects of prenatal SSRI exposure, as well as underlying maternal illness, on growth outcomes in the offspring in later life. In understanding the effects of prenatal SSRI exposure on growth and body weight in offspring across the lifespan, this review highlights that human studies may require investigation of not only body weight but also food intake, metabolism, behavioural mood state (i.e. presence of anxiety and/or depression-like symptoms) and physical activity.

5.9 References

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Table 5.1 5-HT receptor subtypes, knockout mouse phenotypes and effects on food intake

5HT Receptor sub-type	Knock-Out Phenotype	Effect of agonists on food intake
5-HT_{1A}	Reduced food intake and lower fat pad mass[51]	↑ [31,51,73,77]
5-HT_{1B}	Increased body weight and food intake without signs of obesity[76]	↓ [31,33,73,81]
5-HT_{2C}	Increased food intake and likelihood of obesity[66,74,75]	↓ [31,33,73,81]
5-HT_{6}	Resistant to weight gain when exposed to a high-fat diet[78]	↑ [33,73,81]

Table 5.2 Summary of reported effects from animal studies of prenatal selective serotonin reuptake inhibitor exposure and 5-HTT knockout status on factors potentially associated with growth and body weight in later life

Animal Studies	
Outcomes Following Prenatal SSRI Exposure	
Males	**Females**
Decreased 5-HTT expression in the raphe nucleus[22,138]	Decreased 5-HTT expression in the raphe nucleus[22]
Decreased concentration of hypothalamic 5-$HT_{2A/2C}$ receptors[88]	Not studied
Decreased concentration of mid-brain 5-HT[92]	Not studied
Decreased locomotor activity[26]	No change in locomotor activity[26]
Outcomes Among 5-HTT Knockout Rodents	
Males	**Females**
Decreased concentration of 5-HT_{1A} receptors in raphe nucleus[99,100]	Decreased concentration of 5-HT_{1A} receptors in hypothalamus and raphe nucleus (more extensive reduction in females than males)[99,100]
Increased synthesis rate of 5-HT in hypothalamus[139]	Increased synthesis rate of 5-HT in multiple brain regions which was significantly higher in females than in males (increased by 55%)[139]
Reduced tissue concentrations of 5-HT in multiple brain regions[140]	Reduced tissue concentrations of 5-HT in multiple brain regions[139]
Decreased response of $5HT_{2A}$[134] & 5-HT_{2C}[134,135] receptors to agonists	5-HT_{2A} receptors increased in hypothalamus and septum and 5-HT_{2C} receptors increased in amygdala[137]
Late-onset obesity[48,96]; decreased locomotor activity[48]	Reduction in total body weight with an increase in the percentage of abdominal fat[97]

Section II –

Validating the Use of Routinely Collected Health Data

	CHAPTER 1 Introduction	**Publication One** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(1): 46-9.
SECTION I **PART A** **Conceptual Framework**	**CHAPTER 2** Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology	
	CHAPTER 3 A Review of Methodological Challenges and Epidemiological Research Methods	**Publication Two** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 33(3): 280-9.
SECTION I **PART B** **Literature Review**	**CHAPTER 4** Safety of SSRIs in Pregnancy	**Publication Three** Grzeskowiak LE et al. *Drug Saf.* 2011; 34(11): 1027-48.
	CHAPTER 5 Effects of Prenatal SSRI Exposure on Child Growth and Body Weight	**Publication Four** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 34(1): 101-9.
SECTION II **Validating the Use of Routinely Collected Health Data**	**CHAPTER 6** Validating the Use of Hospital Pharmacy Dispensing Records to Identify Prenatal SSRI Exposure	**Publication Five** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(4): 265-8.
	CHAPTER 7 Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy	**Publication Six** Grzeskowiak LE et al. *Eur J Clin Pharmacol*. 2012 68(5): 459-67.
	CHAPTER 8 Prenatal SSRI Exposure & Neonatal Outcomes *Examined Using Routinely Collected Health Data*	**Publication Seven** Grzeskowiak LE et al. *J Clin Psychopharmacol*; In press.
SECTION III **Evaluating the Use of Routinely Collected Health Data**	**CHAPTER 9** Prenatal SSRI Exposure & Childhood Overweight *Examined Using Routinely Collected Health Data*	**Publication Eight** Grzeskowiak LE et al. *J Dev Orig Health Dis*. 2012; 3(4): 253-61.
	CHAPTER 10 Prenatal SSRI Exposure & Childhood Overweight *Examined Using Data from a Birth Cohort Study*	**Publication Nine** Grzeskowiak LE et al. *PLoS ONE*; Submitted.
	CHAPTER 11 Using Routinely Collected Health Data to Examine Long-Term Outcomes: Opportunities and Challenges	**Publication Ten** Grzeskowiak LE et al. *Ther Adv Drug Saf*; Submitted.
	CHAPTER 12 Discussion and Conclusion	

Preamble

The aim of this section is to validate and further explore the suitability of using routinely collected health data to examine long-term effects of medication use during pregnancy. This represents a crucial first step supporting the use of routinely collected health data.

One of the most important aspects of undertaking a study to assess outcomes following medication use during pregnancy is to have accurate data on medication use. Therefore, the first step involved the validation of hospital pharmacy dispensing data as a reliable indicator of late gestation exposure to SSRIs during pregnancy (Chapter 6).

This study, together with previous chapters describing methodological challenges, highlighted the importance of the way in which medication exposures are classified in studies using routinely collected health data. This formed the stimulus for a review (Chapter 7) on the way in which medication exposures are classified in various studies using routinely collected health data and the potential impact, in particular bias, that this can have on different outcome measures. The evidence from this review, together with that from Chapter 6, provided us with the confidence to pursue the use of available routinely collected health data in subsequent studies.

This section concludes with a study investigating neonatal outcomes following late gestation exposure to SSRIs. This serves two purposes;

- The first is that it provides further evidence of an association between prenatal SSRI exposure and adverse neonatal outcomes, an important contribution to clinical practice.
- The second is from a validation perspective in that the similarity of results obtained from this study, compared to others undertaken around the world, provides further support that available data and linkage methods used can be considered valid for investigating potential long-term outcomes.

CHAPTER 6

Validating the Use of Hospital Pharmacy Dispensing Records to Identify Prenatal SSRI Exposure.

Manuscript

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Hospital Pharmacy Dispensing Records for Pharmacoepidemiology Research into Late Gestation Exposure to Antidepressants

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6.1 Abstract

Aim: To determine the validity of electronic hospital pharmacy dispensing records as an indicator of late gestation exposure to antidepressants using medical records as the gold standard.

Method: Medical records (gold standard) were reviewed for a consecutive sample of 400 women who delivered at a large maternity hospital during 2005. Data on antidepressants used in pregnancy from the medical records were compared with the electronic hospital pharmacy dispensing records to ascertain sensitivity and specificity.

Results: According to the medical records, 12 (3%) women were identified as taking antidepressants during late gestation. The electronic hospital pharmacy dispensing records correctly identified 9 women as exposed to antidepressants (sensitivity score 75%; 95%CI 43–95). No women were classified as exposed according to hospital pharmacy dispensing records and classified as not exposed according to the medical records (specificity score 100%; 95%CI 99–100). 7 (1.8%) women were identified in the medical records as taking antidepressants but had either stopped prior to pregnancy or on finding out that they were pregnant. These patients were not identified in the hospital pharmacy dispensing records.

Conclusion: Electronic hospital pharmacy dispensing records may provide an efficient alternative to paper records for identifying late gestation exposure to antidepressants, but will underestimate the exposure by 25%.

6.2 Introduction

The availability of electronic healthcare and administrative datasets has led to a rise in the popularity of pharmacoepidemiology and outcomes research.[1] Access to electronic databases allows researchers to perform quick and efficient studies addressing questions about the effects of medication use in different populations. This is especially relevant for medication safety in pregnancy, as undertaking studies can be challenging, given the large sample sizes needed to obtain adequate power to detect mild or moderate increases in risk and the need to follow offspring over long periods of time. Electronic records allow large cohorts of women and children to be constructed to investigate medication exposures and resultant outcomes.

Linked electronic databases have many advantages over labour-intensive data collection methods that rely on paper records.[2] The traditional approach of constructing retrospective cohort studies using paper records or patient interviews is time

consuming, expensive, logistically challenging and raises issues of patient confidentiality. Conversely, electronic records are unobtrusive to patients and hospital staff and as the data are already collected it enables large cohorts to be constructed in a timely and efficient manner without the exorbitant costs associated with other research methods.[3] This approach also eliminates recall bias by using prospectively collected routine exposure data.[4] Despite these advantages, healthcare and administrative datasets are not designed to be used for research, therefore, it is essential to evaluate their validity.[3,5]

Accurate data on medication exposures is critical to the validity of study findings, as they are relied on to support evidence-based decision making. Concerns about the accuracy and reliability of electronic records have meant that some researchers are reluctant to use them, unless validation studies are undertaken to establish their usefulness in outcome studies. Other factors limiting the use of electronic records include privacy, security and confidentiality, as data are often used without an individual's knowledge or consent. However, these issues can be addressed and should not prevent valuable research opportunities using linked records. High-level security compliant with relevant privacy laws, regulations and codes, can be used to ensure data are protected during linkage and only provided in a de-identified format.[6]

In Western Australia, researchers have linked dispensing data from the Pharmaceutical Benefits Scheme with population-based health datasets, suggesting that it is a feasible and cost-effective means of investigating the effects of medication use in pregnancy.[7] Although this is an advancement towards improved data collection and analysis of medication use in pregnancy, there are limitations associated with its use. The key limitation of the Pharmaceutical Benefits Scheme data is the potential for under-ascertainment of medication exposures (medications dispensed below the patient co-payment, i.e. $33.30 for general patients and $5.40 for pensioners, are not included).[7] While the cost associated with newly marketed medications usually ensures that these remain above the patient co-payment for many years, postmarketing surveillance should not be restricted to newly marketed medications and must include all medications irrespective of cost.

For medicines where cheap generic alternatives exist, these are often dispensed below the patient co-payment, resulting in incomplete ascertainment of medication exposures that occurred at any stage during pregnancy. Incomplete ascertainment is prevalent among general patients and can introduce significant bias if there is a differential classification of medication exposures during pregnancy based on concession card status. This can result in the 'unexposed' group containing women who received a

medication dispensing or an overrepresentation of those with concession cards in the 'exposed' group. In addition, due to challenges involved in accessing Pharmaceutical Benefits Scheme data and linking it to population-based records, it is necessary to seek alternative methods of identifying medication exposures that occur during pregnancy.

The focus of this study was to investigate electronic capture of late gestation exposure to antidepressants. The high level of concern surrounding the safety of antidepressant use in pregnancy and the lack of evidence on the long-term effects of antidepressants on the offspring necessitates further research.[8-11] Although studies have reported that 11 to 50% of women stop taking antidepressants after discovering that they are pregnant, a large number continue taking antidepressants throughout pregnancy.[12,13] Studies have reported that 60 to 80% of women who were identified as taking antidepressants during pregnancy, took them in the first, second and third trimesters and the remainder took antidepressants during the second and/or third trimester.[13,14] An indication of late gestation exposure to antidepressants is useful when evaluating maternal and neonatal health outcomes. Given the need to evaluate the short- and long-term consequences of antidepressant use during pregnancy, and the difficulties in obtaining electronic data on medication use during pregnancy, hospital pharmacy dispensing records were considered a useful data source. No published studies have assessed the validity of using Australian hospital pharmacy dispensing records as an indicator of late gestation antidepressant use.

This study aimed to determine the validity of electronic hospital pharmacy dispensing records as an indicator of late gestation exposure to antidepressants using medical records as the gold standard.

6.3 Method

A retrospective review of medical records and comparison to hospital pharmacy dispensing records of antidepressant use during pregnancy was undertaken at the Women's and Children's Hospital, Adelaide, a major teaching hospital with around 4500 births each year (accounting for 25% of births in South Australia). The study was approved by the Human Research Ethics Committee of the University of South Australia and the Children, Youth and Women's Health Service.

Clinical Information Services at the hospital collect data on all pregnancies in accordance with national requirements. Clinical Information Services provided the researchers with the hospital unit record numbers of a consecutive sample of the first 400 women to deliver at the Women's and Children's Hospital in 2005. The unit record

numbers were used to source the patients' medical records and were the gold standard for data on medication use during pregnancy. Data were collated from the medical records by the same researcher for all women.

Information on depression and antidepressant use was obtained from two sections in the medical records – South Australian Pregnancy Record (current and past medications and medical conditions) and inpatient medication chart (medications prescribed and administered during the hospital stay). The South Australian Pregnancy Record is a comprehensive antenatal medical record that is given to women during the first antenatal visit after confirmation of their pregnancy. The record aims to better clinical outcomes by improving continuity of care, women's participation in their care and promotion of early and appropriate use of antenatal services. Following the birth, the South Australian Pregnancy Record (paper-based form) becomes part of the birthing hospital's medical record.

Women were classified as exposed to antidepressants during late gestation based on their South Australian Pregnancy Record or inpatient medication chart. Women were classified as not exposed if there was no evidence of antidepressant use during pregnancy or if it was recorded that they stopped taking the antidepressant on finding out that they were pregnant. Data collected from the medical records were linked to the hospital pharmacy dispensing records using the unit record number. Women were classified as exposed if they were dispensed antidepressants during any pregnancy-related hospitalisation in the third trimester. The dispensing may have occurred at any time during the third trimester or in the immediate postpartum period before discharge from hospital. Medications dispensed in the immediate postpartum period (1 to 2 days post delivery) were included as these were predicted to reflect ongoing mental health problems and use during late gestation.

6.3.1 Statistical Analysis

The number of women classified as either exposed or not exposed according to their medical records and hospital pharmacy dispensing records were tabulated and sensitivity and specificity scores as well as positive and negative predictive values were calculated. Statistical analyses were performed using Stata 11.

6.4 Results

6.4.1 Medical Records

According to the medical records, 12 (3%) women were identified as taking antidepressants in late gestation (Table 6.1). The 12 women were identified as taking antidepressants from their South Australian Pregnancy Records and inpatient medication charts. Eleven (92%) of these women reported that they took antidepressants throughout pregnancy (across the three trimesters), while one woman started taking an antidepressant during the second trimester.

Seven (1.8%) women were identified from their medical records as taking antidepressants, but had either stopped it prior to pregnancy or on discovering that they were pregnant. Nineteen (4.8%) women either used an antidepressant at some stage during pregnancy or had a history of antidepressant use prior to their pregnancy, with 37% stopping their antidepressant during the first trimester.

6.4.2 Hospital Pharmacy Dispensing Records

Nine (n = 400; 2.3%) women were correctly identified as using antidepressants from hospital pharmacy dispensing records (sensitivity score 75%; 95%CI 43–95) (Table 1). No women were classified as exposed to antidepressants according to hospital pharmacy dispensing records and classified as not exposed according to medical records (specificity score 100%; 95%CI 99–100). Positive predictive values (100%; 95%CI 66–100) and negative predictive values (99%; 95%CI 98–100) were high. Three women who were misclassified as not using antidepressants based on the hospital pharmacy dispensing records had antidepressants written up on their medication chart. Their medication charts were annotated to explain that they had brought their own medication into hospital.

6.5 Discussion

With electronically collected data increasingly being used for outcomes research, validation studies such as this become necessary. The prevalence of antidepressant use during late gestation identified in this study was 3% using paper-based medical records and 2.3% using electronic hospital pharmacy dispensing records. The prevalence of antidepressant use at any stage during pregnancy (including those who stopped taking

antidepressants on finding out that they were pregnant) identified in this study was 4.8% using medical records, which is consistent with two Australian studies (2.1 to 4.7%).[7,15] Of the 140 pregnant women interviewed by Henry et al.[15] at the Women's and Children's Hospital, Adelaide during antenatal visits, 4.3% took antidepressants before becoming pregnant and 2.1% took antidepressants throughout their pregnancy. Colvin et al.[7] linked Pharmaceutical Benefits Scheme data with population-based health datasets in Western Australia to investigate medication use in pregnancy. The final cohort consisted of pregnant women who delivered from 2002 to 2005, and while the data were only reported at the second level of the main therapeutic group (N06) using the WHO Anatomical Therapeutic Chemical classification, they reported that 4.7% of women were dispensed a psychoanaleptic at some stage during pregnancy.[7] Psychoanaleptics include psychostimulants, antidepressants and medications used for dementia, and given the age group, it would be expected that the majority of these dispensings would have been for antidepressants.

In this study, the number of women who stopped taking antidepressants either before or immediately after finding out that they were pregnant (37%) was consistent with studies investigating the prevalence of antidepressant use during pregnancy.[15-18] Furthermore, no women were identified in the hospital pharmacy dispensing records as using an antidepressant when their medical records did not identify them as using an antidepressant. The only way medications are dispensed from the pharmacy department is when they are written up on a hospital prescription pad or medication chart.

This study has several limitations. Firstly, medical records, the gold standard comparator, may be inaccurate or incomplete in certain circumstances.[19] Secondly, all participants were drawn from a single hospital, so the results may not be generalisable. Thirdly, with a sample of 400, only a small number of women were exposed to an antidepressant during pregnancy, resulting in a wide confidence interval for the sensitivity estimate. An additional limitation in the use of hospital pharmacy dispensing records is that it does not provide information on specific timing of exposures during pregnancy. Instead, it allows us to generate a cohort of women where exposure has occurred during late gestation.

Studies have reported that 60 to 80% of women who were identified as taking antidepressants in late pregnancy also took antidepressants during the first, second and third trimesters.[13,14] Late gestation exposure to antidepressants is associated with an increased risk of adverse pregnancy outcomes and identifying a cohort of women with late gestation exposure is important for investigating a range of outcomes.[14,20] This can be useful for studies investigating long-term effects of prenatal antidepressant exposure

on fetal neurodevelopment, as the period of susceptibility towards the harmful effects of various exposures is likely to be wide as brain development occurs throughout pregnancy and even continues into the postpartum period.

The *a priori* hypothesis of this study was that underestimation of antidepressant use during pregnancy could occur due to two factors. Firstly, data on antidepressant use may not have been included on some medical charts because the doctor did not realise that the patients were taking antidepressants or did not feel it was necessary due to the short-term nature of the postnatal hospital stay. Our results suggest that this is unlikely, as the 12 women identified as taking antidepressants according to their South Australian Pregnancy Records, were written up for antidepressants on their medication chart. Secondly, some women may bring their own medications into hospital instead of obtaining them from the pharmacy department. This was the sole reason for underestimation of medication exposures in this study, as all women classified as unexposed according to the hospital pharmacy dispensing records brought their own medications to hospital.

A critical result of this study was that the hospital pharmacy dispensing records underestimated the number of women exposed to antidepressants during late gestation by misclassifying some as unexposed. This underestimation can introduce bias into studies that rely on hospital pharmacy dispensing records as an indicator of late gestation antidepressant exposure, making it difficult to detect an association. Therefore, any associations between antidepressant use during pregnancy and adverse pregnancy outcomes may be underestimated.

In conclusion, electronic hospital pharmacy dispensing records may provide an efficient alternative to paper records for identifying late gestation exposure to antidepressants, but will underestimate the exposure by 25%.

6.6 References

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Table 6.1 Women exposed to antidepressants in late gestation according to medical records and hospital pharmacy dispensing records

	Medical Records		
Dispensing records	Exposed	Not exposed	Total
Exposed	9 (75%)	0	9 (2.3%)
Not exposed	3 (25%)	388 (100%)	391 (98%)
Total	12 (100%)	388 (100%)	400 (100%)

Sensitivity: 75% (95%CI 43-95). Specificity: 100% (95% CI 99-100). Positive predictive value: 100% (95%CI 66-100). Negative predictive value: 99% (95%CI 98-100).

CHAPTER 7

Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy

Manuscript

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Exposed or Not Exposed? Exploring Exposure Classification in Studies Using Administrative Data to Investigate Outcomes Following Medication Use During Pregnancy

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7.1 Abstract

Purpose: The aim of this systematic review was to examine and compare differences in the way medication exposures are classified in studies using linked administrative data to investigate outcomes following medication use during pregnancy. This was undertaken with a focus on studies investigating specific neonatal outcomes following prenatal exposure to selective serotonin reuptake inhibitors (SSRIs).

Methods: We searched Medline and Embase to identify studies that used linked administrative data to investigate specific neonatal outcomes (congenital malformations, birth weight, and gestational age) following prenatal exposure to SSRIs.

Results: Key factors such as dose, duration and timing of exposure were inconsistently addressed in the studies identified. In addition, there was a great deal of variability in the way medication exposures were classified and how women who stop taking their medication before or during early pregnancy are handled in analyses. Furthermore, there are issues in assuming how and when women who receive a dispensing for a medication actually take it during pregnancy. This creates a great deal of uncertainty around medication exposure during pregnancy in studies using linked administrative data, potentially resulting in biased risk estimates.

Conclusions: There is a need for greater focus on determining the most effective and accurate way of using linked administrative data to investigate outcomes following medication use during pregnancy in an effort to minimise potential biases.

7.2 Background

The common exclusion of pregnant women from clinical drug trials due to ethical concerns places a heavy reliance on observational studies to gather evidence on medication safety during pregnancy. It is well recognised, however, that there is no single approach for delineating the complete spectrum of risks or benefits associated with medication use during pregnancy. Methodological limitations associated with traditional study designs (i.e. case–control studies, prospective cohort studies and pregnancy registries), which have been previously well described,[1-4] have led researchers towards the development of novel approaches to gathering evidence on medication safety during pregnancy. Over the past decade, the use of linked administrative healthcare databases to undertake retrospective cohort studies has emerged as a new and novel approach towards investigating the effects of medication use during pregnancy. Its increase in popularity is not only due to improvements in availability of data sets and technological capabilities in handling large data sets, but

also due to a number of advantages that this method has over more labour-intensive data-collection efforts.[5] Linkage of existing administrative healthcare databases enables the establishment of very large cohorts of women and their children. This is a significant advantage, as very large samples are often required in order to obtain adequate power to detect low to moderate increased risks of an adverse outcome associated with medication use during pregnancy.[2] Further advantages are that data are collected prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and can be linked at the individual patient level.[6] Importantly, the routine and prospective manner in which data are collected and recorded in these data sets eliminates recall bias, which can be a significant issue in case–control studies relying on maternal recall of medication use.[5] In addition, as data have already been collected, it enables studies to be undertaken in a more timely and cost-efficient manner than is possible with other research methods, such as prospective cohort studies. Furthermore, the use of linked data can also aid in overcoming selection bias that can influence many studies that require individual patient consent and voluntary participation.

This approach, however, is not without its own limitations.[5] Of greatest concern is that administrative data were never designed to be used for research purposes, making it crucial that the quality and accuracy of these data be assessed together with an evaluation of their validity for use in record-linkage projects. This makes it important to carefully consider the way in which these data are used and how this can influence resultant outcomes. Whereas dose, duration and timing of exposure are all recognised as important factors in influencing outcomes following medication use during pregnancy,[7] how well these are characterised in studies relying on routinely collected administrative data has not been thoroughly investigated. Of particular concern in the use of routinely collected data is the issue surrounding uncertainty of medication exposure during pregnancy.

In light of this, the aim of this systematic review was to examine and compare differences in the way in which medication exposures are classified in studies relying on routinely collected data. The decision was made to focus on studies investigating outcomes following prenatal exposure to selective serotonin reuptake inhibitors (SSRIs), given the frequent use of these medications during pregnancy[8] and the great deal of uncertainty, and conflicting reports, as to their risks and benefits.[9] Outcomes included in the review are congenital malformations, birth weight and gestational age. Whereas issues around classifying medication exposures will be discussed in reference to SSRI use during pregnancy and in relation to specific outcomes, the results and subsequent

discussion is of relevance to all studies using routinely collected data to investigate outcomes following medication use during pregnancy.

7.3 Methods

Medline and Embase were searched from 1 January 1985 to 30 March 2011 using search terms SSRI, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline in association with pregnancy, prenatal exposure, malformation, birth defect, neonatal complications and newborn. Papers were limited to the English language and studies in humans. Reference lists of identified articles were examined for additional relevant publications.

7.4 Results

A total of 11 studies were identified that used linked administrative healthcare databases to investigate congenital malformations following prenatal exposure to SSRIs (Table 1.).[10-20] Three studies did not have data on gestational age, relying instead on an estimation of pregnancy duration to identify the beginning of the pregnancy.[15,19,20] The remaining studies used either gestational age or date of last menstrual period (LMP) to determine the beginning of the pregnancy. Five studies demonstrated an association between prenatal SSRI exposure and a range of malformations, but there appeared to be no clear pattern between the way in which medication exposures were classified and the outcome obtained. Timing of estimated exposure varied between studies, whereas two studies specifically looked at women who received a dispensing during the second or third month after conception.[13,17] Of the studies with known gestational age, seven of eight included medications dispensed in the month prior to the beginning of the pregnancy.[10-13,16-18] One study only included medications dispensed after the date of LMP.[14] In addition, one study examined and reported the effects of increasing maternal dose of paroxetine on the risk of malformation.[16]

Seven studies were identified that used linked administrative healthcare databases to investigate effects of prenatal SSRI exposure on birth weight and/or gestational age (Table 2.).[10,14,15,18,20-22] All identified studies demonstrated an association between prenatal SSRI exposure and negative effects on gestational age and/or birth weight. A number of studies investigated duration and timing of exposures, with one study specifically looking at the effects of late vs. early gestational exposure.[22] No studies looked at the effects of dose on neonatal outcomes.

7.5 Discussion

In the studies identified, there is a great deal of variability in the classification of medication exposures during pregnancy. These methodological differences are essential to understand as they have important implications for our ability to compare and combine results of these studies and assess their applicability to clinical practice. Before considering the way in which medication exposures are classified, it is important to first reflect on studies describing patterns of antidepressant use during pregnancy. According to the recent study by Colvin et al.[14] 2,827 women received a dispensing for an SSRI during the period from 76 days before to 14 days after LMP. Of those women, 1,003 (35%) did not receive another dispensing for an SSRI at any stage during pregnancy, reflecting a high discontinuation rate. Other studies demonstrated similar numbers of women (28–38%) who discontinued their SSRI before or very soon after the estimated date of conception.[8,23] This makes it highly likely that up to a third or more women who receive a dispensing for a SSRI at or around the time of conception do not actually take that SSRI during the pregnancy, the potential implications of this misclassification are demonstrated in Fig 1.

7.5.1 Overlap of medication use

Issues with overlapping of medication use are most significant for studies attempting to estimate first trimester exposure. Numerous studies investigating the association between SSRI use and malformations considered women as exposed when they received at least one dispensing for an SSRI during the first trimester or received a dispensing for an SSRI before gestation, but where the estimated number of treatment days supplied overlapped the first trimester.[11,16,19] For example, if a medication dispensed lasted 30 days on average, then women who received a dispensing for a medication 10 days prior to the first trimester may still be using the medication during pregnancy, even though they did not receive a new dispensing during that period. Importantly, this approach is no different to studies that include all medications dispensed 30 days prior to the first trimester.[10,12,13] This approach has the potential to misclassify women as being exposed if they received a dispensing for a medication in the 30 days prior to pregnancy but did not actually take the drug during pregnancy. The potential effect of this is demonstrated in Fig. 1, where misclassification of women as exposed when they were not actually taking the medication during pregnancy can result in a significant underestimation of an association with the outcome under investigation.

Other studies have classified women as exposed only if they received a dispensing for an SSRI during the first trimester or after the estimated date of conception.[14,15,17,18,20] Whereas this approach might reduce the potential for misclassification previously described, it too could misclassify women as not having been exposed during pregnancy when they actually were. Some women may have used an SSRI that was dispensed prior to the beginning of the pregnancy or that was dispensed for a relative or friend. Given that dispensing of up to 3 month's supply of medication is common in many countries (e.g. Sweden[24]), the SSRI used during pregnancy may have been obtained well before conception. The potential effect of this is demonstrated in Fig. 2, where misclassification of women as not exposed when they were actually exposed is shown not to have an appreciable effect on the risk estimate. Of interest, Simon et al.[20] excluded women who only received a dispensing for an SSRI in the 270–360 days prior to delivery. While not explicitly stated, it can be assumed that this was undertaken to reduce any potential misclassification bias as a result of women who have unknown or questionable exposure to SSRIs around the time of conception.

7.5.2 Issues with unknown gestational age

A number of studies did not have access to data on gestational age, relying instead on an estimation of pregnancy duration.[15,19,20] Two studies included women as exposed if they received a dispensing up to 270 days prior to delivery,[15,20] whereas the other included women as having been exposed if the amount supplied overlapped with the estimated date of conception, defined as 287 days prior to delivery for singleton births.[19] Subtracting 270 or 287 days from the date of delivery assumes that all pregnancies are of that many days in duration, which is obviously not the case. In the situation where the pregnancy lasts for <260 days (premature delivery<37 weeks), subtracting 270 or 287 days from the date of delivery classifies as exposed women who received a dispensing for an SSRI in the 10–27 days prior to pregnancy , regardless of whether they actually took it during pregnancy. The effects of this potential misclassification bias skews observed effects towards the null (Fig. 1). Of further concern is the potential for this misclassification to be differential, which occurs when exposure classification is associated with the outcome under investigation. Consider two women who stop taking their SSRI just prior to conception: one gives birth to a premature infant and the other to a term infant. Based on the 270-day gestation rule, the woman who gives birth to the

premature infant is more likely to be misclassified as having been exposed to the SSRI during pregnancy, even though she stopped it immediately prior to the pregnancy. As a further example, consider the fact that the proportion of infants with a cardiovascular malformation who are born premature (up to 23%) is much greater than the number of infants without malformations who are born premature (8%).[25] This could result in differential misclassification bias in situations where infants born with a congenital malformation are more likely to be born premature and are therefore more likely to be classified as exposed to an SSRI in utero than are infants born at term. This potential bias has the same effect as recall bias in retrospective studies relying on maternal recall of medication use during pregnancy, where mothers of infants with the outcome of interest may be more likely to recall exposure to the medication of interest during pregnancy. Differential misclassification bias can lead to an apparent association, even if one does not really exist, or to an overestimate of the real association.

Toh et al.[26] examined the sensitivity and specificity of using estimated dates of conception to define gestational periods in studies using administrative data. They found that whereas subtracting 270 days from the date of delivery may be an accurate way of determining first trimester medication use in women without pregnancy complications, the sensitivity of this approach is much lower among women with pregnancy complications (i.e. preterm delivery), suggesting this approach is only of limited validity for assessing drug safety for pregnancy outcomes associated with prematurity.[26] Whereas this issue has previously been acknowledged by Cole et al.,[27] no studies investigating the safety of SSRI use in pregnancy have assessed the potential impact of misclassification bias as a result of using estimated gestational age.

7.5.3 Assumptions around medication use

The underlying assumption associated with all studies relying on prescription databases is that a dispensing for a medication is actually associated with use of that medication. Nonadherence with medication use may result in misclassification bias, where some women classified as exposed were, in fact, not exposed during pregnancy. This has the same effect on the risk estimate generated as described in Fig. 1. The unknown is when and if women use a medication after getting it dispensed. Women who are dispensed a 30-day supply of a medication could decide not to use the medication at all or could use it for varying periods of time anywhere up to 30 days. The date of

dispensing may not also relate to the date the medication was taken; some women may hold off on commencing the medication until a later date.

7.5.4 Inaccurate medication reporting or issues with adherence

Concerns around accuracy of medication exposure are not unique to studies relying on linked administrative healthcare databases, as they affect other study designs as well. For example, some studies have questioned the accuracy of maternal self-reported exposure in various birth registries and birth cohort studies. Espnes et al.[28] compared recorded medication use in the Medical Birth Registry of Norway (MBRN) with prescribed medicines registered in the Norwegian Prescription Database (NorPD). They found that medication use in MBRN was poor compared with prescribed medicines in NorPD. For SSRIs in particular, sensitivity of the MBRN in identifying women who received a dispensing for an SSRI during pregnancy was 41% [95% confidence interval (CI) 39–43], suggesting that a large amount of SSRI use is underreported. There was great variability in sensitivity across medications, ranging from 0% to 71%. Similarly, Stephansson et al.[29] compared reported medication use in the Swedish Medical Birth Register (SMBR) with prescribed medicines registered in the Prescribed Drugs Register (PDR). They also found that reporting of medication use was highly variable, ranging from 0.8% to 85.3%, and that sensitivity depended on whether the medication was used for a chronic medical condition (i.e. diabetes) compared with occasional use (i.e. hayfever). For antidepressants, the reported sensitivity was 59.8% (95% CI 57.7–61.9). Olesen et al.[30] compared reporting of medication use during pregnancy among women enrolled in the Danish National Birth Cohort (DNBC) to the North Jutland Prescription Database (NJPD) for women living in the North Jutland area. Medications used by women for chronic medical conditions (i.e. diabetes, epilepsy, hypothyroidism) were always reported (100%), whereas sensitivity was poor for medications used for acute conditions (e.g. antibiotics). Overall, sensitivity for use of any medication was 43% (95% CI 40–46). For antidepressants as a group, the reported sensitivity was 80% (95% CI 56–100).

Kallen et al.[24] were the first to specifically investigate the effects of relying on different data sources on medication use during pregnancy and its resultant impact on influencing risk estimates. In a similar manner to Stephansson et al.[29], they examined data on antidepressant use during pregnancy according to reported use in the SMBR and recorded dispensing in the PDR. Overall, 22% of

women who received a dispensing for an antidepressant had no record of use in the SMBR.[24] That is, 22% of women dispensed an antidepressant did not state that they were taking an antidepressant during their antenatal visits. Furthermore, when looking at the time before LMP in which the antidepressant was dispensed, for those who received a dispensing in the month prior to LMP, it was estimated that 17% may not have used the antidepressant during pregnancy.[24] When including antidepressants dispensed up to 3 months prior to LMP, it was estimated that 43% of women may not have used the antidepressant during pregnancy.[24] Importantly, they observed significant differences in the odds ratio (OR) for pregnancy outcomes, such as preterm birth and neonatal complications, dependant on whether women were classified as exposed according to the SMBR alone, PDR alone or both the SMBR and PDR.

What we still do not know from these studies, however, is whether the discrepancy between interview data and dispensing data is due to women forgetting or not wanting to disclose medication use or if it is due to the fact that they got the medication dispensed but never took it during pregnancy. Which data are more correct? On one hand, there is the potential for underestimating medication use by relying on maternal self-report; on the other hand, there is the potential for overestimating medication use by relying on data from dispensing databases. The examples provided in Figs. 1 and 2 indicate that as long as data are collected without bias, then incomplete capture of medication use during pregnancy has little effect on the final risk estimate, suggesting it may be best to go with the approach that may underestimate medication use but gives the greatest assurance that those considered as exposed were actually exposed [3]. This suggestion is in accordance with that of Kallen et al.[24] who concluded that if both interview (i.e. SMBR) and dispensing data (i.e. PDR) are available, interview data is preferable, especially in relation to first trimester exposures. For late-gestation exposure, however, they found that dispensing data are likely to be more complete and so should be used in preference to interview data. In the absence of interview data, dispensing data are acceptable but come with the risk that they may overestimate exposure and therefore result in biased risk estimates.

7.5.5 Dose

The importance of dosage has only been investigated in one study to date. Bérard et al.[16] found an association between prenatal exposure to paroxetine and an increased risk of major malformations [adjusted OR (aOR) 2.23; 1.19–4.17] and major cardiovascular malformations (aOR 3.07; 1.00–9.42), but only with paroxetine average dose >25 mg/day during the first trimester.[16] The average daily dose was calculated based on the total cumulative dose of paroxetine dispensed (mg) divided by the estimated total duration of paroxetine use (days) during the first trimester. These results have not been replicated, likely due to difficulties involved in estimating total daily dose. However, given the expected importance of dose used during pregnancy, further studies should be undertaken to examine how dose can be most accurately estimated and used.

7.5.6 Duration

A less-often considered aspect of medication exposure is the effect of treatment duration. This can be examined by looking at the number of times a woman received a dispensing for an SSRI during pregnancy. If a woman was using an SSRI continuously during pregnancy, then during the first trimester, they should receive more than one dispensing (assuming each dispensing is a month's supply). Pedersen et al.[12] demonstrated the importance of treatment duration by examining outcomes among women with two or more dispensings during the first trimester. They observed an increased risk of septal heart defects (aOR 1.99; 1.13–3.53) associated with prenatal SSRI exposure. After including women with only one dispensing for an SSRI during the first trimester, the association with septal heart defects was still significant but became attenuated (aOR 1.83; 1.22-4.17). It is important to note that whereas receiving more than one dispensing potentially reflects an increased duration of exposure, multiple dispensing during the first trimester could also indicate a potentially increased likelihood that exposure occurred during the critical period of embryogenesis.

Duration of prenatal exposure to SSRIs is also important for studies investigating other outcomes, such as effects on gestational age and birth weight. Given up to 50% of pregnant women stop taking their SSRI during the first trimester,[21] classifying women as exposed if they received a dispensing only during the first trimester would result in outcomes being investigated

among a number of women with only a limited duration of exposure to SSRIs during pregnancy. To address this, Oberlander et al.[21] only classified women as exposed if they received a dispensing for an SSRI >49 days after conception. Similarly, Simon et al.[20] assessed the effects of exposure duration by including women as exposed if they received two or more dispensings for an SSRI during pregnancy. Two or more dispensings was associated with a reduction in mean birth weight (3,208 g vs. 3,423 g; P<0.05) compared with unexposed infants, whereas only one dispensing during pregnancy was not associated with a statistically significant reduction in mean birth weight (3,304 g vs. 3,366 g; P>0.05).[20]

7.5.7 Timing

Many studies are undertaken to investigate a wide range of outcomes (including different malformations) following prenatal SSRI exposure. Given the different windows of susceptibility towards negative outcomes, exposure windows are often wider than are necessary for specific outcomes/malformations. This has a number of potential consequences. In situations in which the exposure window is wider than the known or suspected susceptible period for outcomes (e.g. cardiovascular defects), women classified as exposed might not have actually been exposed during the critical period of susceptibility, resulting in misclassification bias and a likely underestimation of any true associations. For outcomes in which the exact period of susceptibility may be unknown, it may be useful to include a broader window of exposure but then consider narrowing this down to determine the critical period/s of exposure. Wogelius et al.[17] demonstrated an association between a dispensing for an SSRI during or in the 30 days prior to the first trimester, and an increased risk of malformations overall (aOR 1.34; 1.00–1.79). After restricting those classified as exposed to those who received a dispensing in the second or third month after conception, the authors demonstrated an increased risk of malformations overall (aOR 1.84; 1.25–2.71). These results, however, were not replicated in a subsequent study, which found no association between a dispensing for an SSRI during the second or third month of pregnancy and an increased risk of malformations overall (aOR 1.1; 0.8-1.6).[13]

The question is whether we can be confident in focusing on narrow intervals of medication exposure if there is a great deal of uncertainty as to the exact timing and duration of medication use? Whereas wider windows of exposure may be necessary to counter uncertainty of exposure, narrower windows are

necessary to guide clinicians in providing answers to women who are concerned about exposure during a particular period of pregnancy. There should also be a limit to how wide the exposure interval can be. For example, despite knowledge of the critical period of exposure for malformations being the first trimester, two studies included women as exposed if they received a dispensing for an SSRI at any stage during pregnancy.[18,20]

Timing is also an important issue for studies investigating effects on other neonatal outcomes. Oberlander et al.[22] compared the effects of late vs. early gestation exposure to SSRIs on birth weight and gestational age. Early exposure was defined as receiving a dispensing during the first and/or second trimester only, whereas late exposure was defined as receiving a dispensing during the first and/or second trimester and third trimester. They found a reduction in mean birth weight (3,392 vs. 3,478 g; $P<0.05$) and gestational age (38.7 vs. 39.0 weeks; $P<0.05$) associated with late exposure compared with early exposure. Differences have also been observed in other neonatal outcomes. For example, Malm et al.[10] found an increased risk of low Apgar scores at 1 min (aOR 1.6; 1.0–2.4) and admission to the intensive care unit (aOR 1.6; 1.1–2.2) following SSRI exposure in the third trimester compared to the first trimester only.

7.6 Conclusion

Significant differences exist in the way in which medication exposures during pregnancy are classified in studies using linked administrative data. Key factors such as dose, duration and timing of exposure have been inconsistently addressed, and there is a great deal of variability in the way medication exposures are classified and how women who stop taking their medication before or during early pregnancy are handled in analyses. Furthermore, there are issues related to not having data on gestational age to determine exact timing of exposure and in assuming how and when women who receive a dispensing for a medication actually take it during pregnancy. This creates a great deal of uncertainty around actual medication exposure during pregnancy, potentially resulting in biased risked estimates.

The misclassification of women as exposed during pregnancy when they were not exposed has a significant potential to underestimate any real associations between that exposure and the outcome under investigation. On one hand, the generation of more conservative risk estimates may be a positive in light of the many unknowns associated with studies using linked administrative healthcare databases (i.e. absence of data on

confounders or severity of maternal illness), and this conservative nature has the ability to reduce the generation of many spurious associations. On the other hand, in the context of medication safety during pregnancy, one could question whether it is such a good thing to be overly conservative in reporting on the risks associated with medication use. If a real association is there, the focus should be on generating the most accurate and informative risk estimates possible. However, how we do this in light of all of the uncertainty that exists is an important question. As such, there is a need for further research exploring differences in exposure classification and the effects this has on calculated risk estimates. In addition, there is a need for greater focus on identifying the most effective and accurate method of classifying medication exposure during pregnancy to minimise potential biases in studies using linked administrative data. Lastly, there is also a need for greater consistency across studies in the way in which medication exposures are classified.

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Table 7.1 Method of exposure classification used in studies investigating congenital malformations following prenatal exposure to selective serotonin reuptake inhibitors (SSRIs)

Study	Country	Exposure Classification	Outcome
Simon et al. 2002[16]	USA	At least one SSRI dispensing 270 days prior to delivery	No increased risk of malformations overall
Malm et al. 2005[6]	Finland	At least one SSRI dispensing in the 30 days prior to or during first 12 weeks pregnancy	No increased risk of major malformations among those exposed in the first trimester
Wen et al. 2006[14]	Canada	At least one SSRI dispensing in the year prior to the date of delivery	No increased risk of major or minor malformations
Wogelius et al. 2006[13]	Denmark	At least one SSRI dispensing 30 days prior to conception until the end of the first trimester	Increased risk of malformations overall (aRR 1.34; 95% CI 1.00-1.79)
Bérard et al. 2007[12]	Canada	At least one SSRI dispensing where the amount supplied overlapped with the period from the beginning of pregnancy to the end of the first trimester (98 days)	No increased risk in malformations associated with exposure to SSRIs as a group
Cole et al. 2007[15]	USA	At least one SSRI dispensing where the amount supplied overlapped with the period from the beginning of the estimated date of conception to end of the first trimester (91 days following the latest estimated conception date). For a singleton birth, the probable conception window was 287 days through 252 days before the delivery date. For multiple infants, the probable conception window as 273 days through 238 days before the delivery date	Increased risk of malformations overall with prenatal exposure to paroxetine compared to other antidepressants (aOR 1.89; 1.20-2.98). No increased risk of cardiovascular malformations
Davis et al. 2007[11]	USA	At least one SSRI dispensing 270 days prior to date of delivery until the end of the first trimester (180 days from date of delivery)	No increased risk in malformations
Oberlander et al. 2008[7]	Canada	At least one SSRI dispensing which overlapped with the period from the LMP to LMP plus 90 days (end of the first trimester)	No increased risk of malformations overall with prenatal exposure to SSRIs alone
Pedersen et al. 2009[8]	Denmark	At least two or more SSRI dispensings between 28 days prior to gestation and the end of the first trimester (112 days)	No increased risk of malformations overall, but, increased risk of septal heart defects (aOR 1.99; 1.13-3.53)
Kornum et al. 2010[9]	Denmark	At least one SSRI dispensing 30 days prior to conception until the end of the first trimester	Increased risk of any malformations (aOR 1.3; 1.1-1.6) and cardiac malformations (aOR 1.7; 1.1-2.5)
Colvin et al. 2011[10]	Australia	At least one SSRI dispensing during the period from 14 to 104 days after LMP	Increased risk of major cardiovascular malformations associated with any SSRIs (OR 1.6; 95% CI 1.1-2.3)

RR relative risk, CI confidence interval, OR odds ratio, LMP last menstrual period

Table 7.2 Method of exposure classification used in studies investigating gestational age and birth weight following prenatal exposure to selective serotonin reuptake inhibitors (SSRIs)

Study	Country	Exposure Classification	Outcome
Simon et al. 2002[16]	USA	At least one SSRI dispensing 270 days prior to delivery	Increased risk of premature delivery (aOR 4.38; 1.57-12.22) but not low birth weight (aOR 2.73; 0.92-8.09)
Malm et al. 2005[6]	Finland	At least one SSRI dispensing in the 30 days prior to or during first 12 weeks pregnancy	Reduced mean gestational age (39.1 vs. 39.4 weeks; P<0.001) and birth weight (3,476 vs. 3,574 grams; P<0.001)
Wen et al. 2006[14]	Canada	At least one SSRI dispensing in the year prior to the date of delivery	Increased risk of premature delivery (OR 1.57; 1.28-1.92) and low birth weight (OR 1.58; 1.19-2.11)
Oberlander et al.2006[17]	Canada	At least one SSRI dispensing more than 49 days after conception but before the data of delivery	Reduced mean gestational age (38.8 vs. 39.1 weeks; P<0.001) and birth weight (3,397 vs. 3,429; P<0.05) following prenatal exposure to SSRIs compared to a control group of infants born to mothers with depression but no SSRI use. Following propensity score adjustment there was no association with reduced mean gestational age or birth weight
Davis et al. 2007[11]	USA	At least one SSRI dispensing 270 days prior to date of delivery	Increased risk of premature delivery (OR 1.45; 1.25-1.68)
Oberlander et al. 2008[18]	Canada	At least one SSRI dispensing which overlapped the pregnancy	Late exposure to SSRIs compared to early exposure associated with reduced mean birth weight (3,361 vs. 3,443; P=0.04) but not mean gestational age (38.8 vs. 38.9 weeks; P=NS) after propensity score matching
Colvin et al. 2011[10]	Australia	At least one SSRI dispensing during the period from 14 days after LMP to the end of pregnancy	Increased risk of premature delivery (aOR 1.43; 1.24-1.65) and low birth weight (OR 1.40; 1.25-1.56) associated with a dispensing for a SSRI at any time during pregnancy

CI confidence interval, OR odds ratio, LMP last menstrual period, NS not significant

Figure 7.1 Hypothetical example of the effect of women being misclassified as exposed to a selective serotonin reuptake inhibitor (SSRI) during pregnancy when they were not actually exposed.

Each of the two-by-two tables cross-classifies columns of women who have birth to infants with (Y) and without (N) congenital malformations with those exposed (Y) and not exposed (N) to a SSRI during pregnancy. OR, Odds Ratio; Y, Yes; N, No; T, Total.

In part **A**, the exposed group includes women who received a dispensing for a SSRI up to the last menstrual period or estimated date of conception. However, given an estimated 40% of women stop taking their SSRI at or around the time of conception, a large number of women in the exposed group are not actually exposed (N=1,000).

In part **B**, the exposed group includes only women who were misclassified as exposed when they were not actually taking the SSRI during pregnancy. The unexposed group is the same as in part A – i.e., women who did not receive a dispensing for a SSRI in the period before or during pregnancy.

In part **C**, the exposed group includes only those women who were truly exposed to the SSRI during pregnancy. The unexposed group consists of the total number of women in part B – i.e., women not exposed to SSRI during pregnancy.

A

SSRI Exposure	Congenital Malformation: Y	Congenital Malformation: N	T
Y	100	2,400	2,500
N	800	40,000	40,800
T	900	42,400	43,300

OR = 1.63

B

SSRI Exposure	Congenital Malformation: Y	Congenital Malformation: N	T
Y	20	980	1,000
N	800	40,000	40,800
T	820	40,980	41,800

OR = 1.02

C

SSRI Exposure	Congenital Malformation: Y	Congenital Malformation: N	T
Y	80	1,420	1,500
N	820	40,980	41,800
T	900	42,400	43,300

OR = 2.02

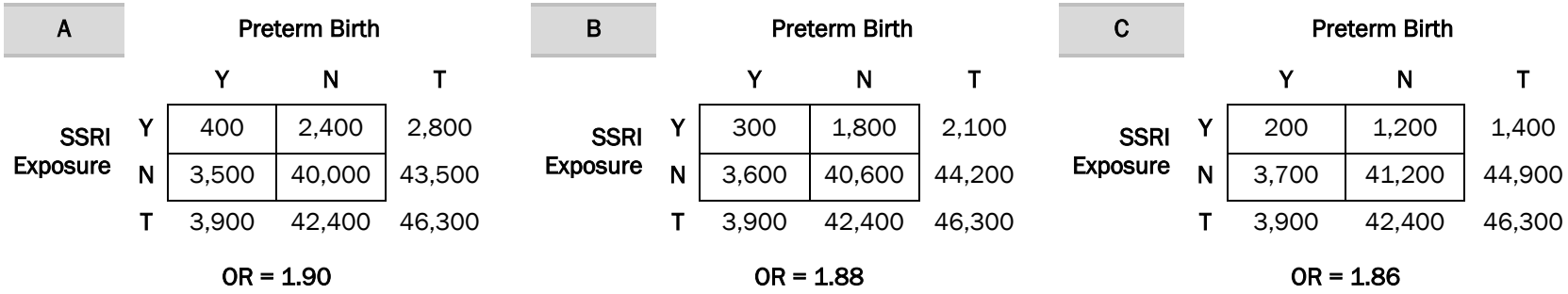
Figure 7.2 Hypothetical example of the effect of incomplete ascertainment of selective serotonin reuptake inhibitor (SSRI) use during pregnancy on the risk of preterm birth

Each of the two-by-two tables cross-classifies columns of women who have (Y) and have not (N) given birth to premature infants with those exposed (Y) and not exposed (N) to a SSRI during pregnancy. OR, Odds Ratio; Y, Yes; N, No; T, Total.

In part **A**, the exposed group includes all women who were taking a SSRI during pregnancy.

In part **B**, 25% of women who were taking a SSRI during pregnancy are misclassified as not exposed.

In part **C**, 50% of women who were taking a SSRI during pregnancy are misclassified as not exposed



CHAPTER 8

Prenatal SSRI Exposure and Neonatal Outcomes

Manuscript

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Neonatal Outcomes Following Late Gestation Exposure to Selective Serotonin Reuptake Inhibitors

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8.1 Abstract

Objective: To investigate neonatal outcomes following prenatal exposure to selective serotonin reuptake inhibitors (SSRIs) during late gestation.

Methods: A retrospective cohort study was conducted using linked records from the Women's and Children's Health Network (WCHN) in South Australia, Australia; including the Perinatal Statistics Collection and the Hospital Pharmacy Dispensing Records. Women were eligible to participate if they gave birth to singleton, live-born infants between September 2000 and December 2008 (n=33,965). Women were excluded if they received a dispensing for antidepressants other than SSRI's (n=93) or an antipsychotic (n=81). We estimated odds ratios (ORs) and 95% confidence intervals (CIs) for preterm delivery, low birth weight, small-for-gestational age (SGA), neonatal hospitalisation and length of hospital admission, adjusting for sociodemographic, lifestyle and medical factors.

Results: Two hundred and twenty-one women received a dispensing for a SSRI during pregnancy, 1,566 had a psychiatric illness but did not receive a dispensing for a SSRI, and 32,004 did not have a psychiatric illness and did not receive a dispensing for a SSRI. Compared to infants of women with a psychiatric illness but no SSRI use, infants of women exposed to SSRIs had an increased risk of preterm delivery (adjusted OR, 2.68; 95% CI, 1.83-3.93), low birth weight (adjusted OR, 2.26; 95% CI, 1.31-3.91), admission to hospital (adjusted OR, 1.92; 95% CI, 1.39-2.65) and length of hospital stay greater than 3 days (adjusted OR, 1.93; 95% CI, 1.11-3.36) but not SGA (adjusted OR, 1.13; 95% CI, 0.65-1.94). Psychiatric illness but no SSRI use during pregnancy was only associated with an increased likelihood of neonatal hospital admission (adjusted OR, 1.21; 95% CI, 1.07-1.38).

Conclusion: These results add to the growing body of evidence of an association between SSRI exposure during pregnancy and a range of adverse neonatal outcomes, but the potential for confounding according to severity of underlying maternal psychiatric illness requires further investigation.

8.2 Introduction

The use of Selective Serotonin Re-Uptake Inhibitors (SSRIs) during pregnancy remains controversial, largely due to the many conflicting reports surrounding their associated risks and benefits.[1,2] A major challenge in investigating outcomes following SSRI use

during pregnancy is that of differentiating the effects of exposure to the drug itself from that of the underlying maternal illness. The most common indication for SSRI use during pregnancy is depression, which itself has been associated with numerous adverse pregnancy outcomes including miscarriage,[3,4] preterm delivery,[5-9] low birth weight,[8,10-13] intrauterine growth restriction,[9,14,15] and increased admissions to neonatal care units.[15] Despite this, only a small number of studies have directly compared neonatal outcomes amongst infants of women taking SSRIs during pregnancy to women with depression (or other psychiatric illnesses), but who were not taking any antidepressants during pregnancy.[9,16-19] Adverse neonatal outcomes of interest include preterm delivery, low birth weight, small-for-gestational-age (SGA) and neonatal hospitalisations.

Preterm delivery is defined as delivery at < 37 weeks of pregnancy and is of clinical importance given its' association with short and long-term sequelae in terms of morbidity, mortality, disability and cost to society.[20] Studies to date have produced conflicting evidence following prenatal SSRI exposure, with some studies showing an increased risk of preterm delivery[16,18,21-28] while others have not.[9,29-34]

Low birth weight is defined as a weight at birth of less than 2,500g. Like preterm delivery (of which low birth weight is often a result), it is associated with a range of immediate and long-term health outcomes.[35] Some studies have found an association between prenatal SSRI exposure and low birth weight (birth weight less than 2500g),[9,23-25,29,36] while other studies have not[16,18,26,28,30,37-41]. Given the increased risk of preterm delivery observed in many studies, it is possible that the elevated risk of low birth weight observed in studies to date may be attributable to early births of infants that were appropriate weight for their gestational age. Despite this uncertainty, only a small number of studies have assessed birth weight after accounting for gestational age, with some identifying an increased risk of fetal growth restriction,[9,23,33,42] while others have not[25,28].

Furthermore, prenatal SSRI exposure has also been associated with increased Neonatal Intensive Care Unit (NICU) or Special Care Nursery (SCN) admissions.[9,16,22,23,30,34,41,43,44] This observed increased risk of hospitalisations could be explained by the greater incidence of neonatal withdrawal syndrome and/or poor neonatal adaptation observed in infants following prenatal SSRI exposure.[23,28,32,45] Neonatal withdrawal syndrome is characterised by irritability, abnormal crying, tremor and convulsions while poor neonatal adaptation is characterised by respiratory distress, tachypnoea, jitteriness, lethargy and poor tone or colour.[9,21-25,29,36,46-49]

The aims of this study were to compare the incidence of preterm delivery, low birth weight, impaired intrauterine growth and neonatal hospitalisations among infants of women exposed and not exposed to SSRIs and/or psychiatric illness during pregnancy.

8.3 Methods

This was a retrospective cohort study relating to all births in the Women's and Children's Health Network (WCHN) in South Australia between September 2000 and December 2008. The study utilised linkable health administrative data within the WCHN which included the Women's and Children's Hospital (WCH) Perinatal Statistics Collection and the WCH Hospital Pharmacy Dispensing Records. Maternal and neonatal records were matched using each individual's unique hospital identifier number. The WCH is a specialist metropolitan tertiary level teaching hospital and South Australia's largest maternity and obstetric service provider, caring for over 4,000 pregnancies each year.

During the study period there were a total of 36,355 pregnancies. Women who were eligible for the current analysis were those who gave birth to singleton, live born infants (n= 33,965). We excluded women who were taking antidepressants other than SSRI's during pregnancy (n=93) and those who were taking antipsychotics (n=81) leaving a final study cohort of 33,791 women.

Data on exposure to SSRIs during pregnancy were obtained from the WCH Pharmacy Dispensing Records, which is a record of all medications dispensed from January 2000. Women were classified as exposed if they received a dispensing for a SSRI during pregnancy. The hospital pharmacy dispensing records have previously been validated as an indicator of late gestation exposure to antidepressants during pregnancy.[50]

In an effort to obtain a suitable comparison group consisting of women with similar underlying disease as those exposed to SSRIs during pregnancy, we identified a cohort of women with a psychiatric illness during pregnancy, but who did not receive a dispensing for a SSRI or any other antidepressant during pregnancy. The remaining group consisted of women who did not have a psychiatric illness and did not receive a dispensing for a SSRI.

Clinical Information Services (CIS) at the WCH is responsible for maintaining the Perinatal Statistics Collection. Data is collected on the pregnancy and outcome of every live birth and late fetal death occurring at the WCH including on every baby admitted to the Neonatal Intensive Care Unit and Special Care Baby Unit. The data are collected according to the guidelines of the Pregnancy Outcome Unit of the South Australian Department of Health for the Supplementary Birth Records (SBRs) and in consultation

with the senior clinicians at the hospital. Data collection began in the late 1980s and complete, validated data are available from 1990. Data are collected from each woman's medical records following delivery by a specially trained research midwife. This is undertaken using a structured coding sheet. It is important to note that included in the medical record is the South Australian Pregnancy Record (SAPR), which is a hand-held antenatal record carried by each woman throughout her pregnancy and contains notes by all health providers consulted during the pregnancy.[51] From the medical records, information is collected on maternal illnesses (e.g. diabetes, gestational diabetes, epilepsy, asthma and psychiatric illness), lifestyle factors (e.g. smoking), obstetric history, course of delivery, pregnancy complications, and newborn characteristics (e.g. birth weight). The presence of a psychiatric illness during pregnancy is recorded by midwives if the woman is receiving medication for their psychiatric illness or if it was recorded in the notes that they received psychological/psychiatric support during the pregnancy. All SBRs are checked manually for completeness and data discrepancies and then go through a series of automated validation procedures during data entry. The information in the perinatal statistics collection has been previously validated and has been shown to be very reliable when compared with hospital case records.[52]

Appropriateness of intrauterine growth was assessed using percentage of optimal birth weight (POBW).[53] POBW is the ratio of the observed to the 'optimal' birth weight, with the later calculated from a regression equation which takes account of major non-pathological determinants of intrauterine growth including gestational age, infant sex, maternal height and parity.[53] POBW <1 indicates that actual birth weight is less than predicted optimal birth weight and is suggestive of impaired intrauterine growth. We used a POBW score less than the 10th percentile to define small-for-gestational-age (SGA) infants.

The estimated length of gestation at delivery is recorded in the Perinatal Statistics Collection and is based on the last menstrual period and ultrasound examination. Parity was defined as no previous deliveries (nulliparity) or 1 or more previous deliveries. Maternal race was classified as Caucasian, Asian or Other.

Socioeconomic status for each woman was determined using her residential postcode at the time of delivery. Women were then ranked according to their level of advantage, or relative disadvantage, based on data from the Socio-Economic Indexes for Areas (SEIFA), calculated from the Australian Bureau of Statistics' five-yearly Census of Population and Housing. These indexes are widely used measures of relative socio-economic status.[54]

The primary outcome measure was preterm delivery (< 37 weeks). Secondary outcome measures included low birth weight (<2,500g), SGA, neonate admission to hospital and neonatal length of hospital stay greater than 3 days. We compared dichotomized outcomes between groups using multivariate logistic regression to estimate prevalence odds ratios (ORs) and 95% confidence intervals (CIs). We used 1-way analysis of variance, the Wilcoxon rank-sum test, or Fisher's exact test to estimate group differences in baseline characteristics. Statistical significance was defined as a 2-sided *P* value of less than 0.05. Potential confounders were categorised as shown in Table 1. Adjustment for confounding factors was performed by multivariate logistic regression analyses. All potential confounding variables were coded as a number of dummy variables equal to the number of categories minus 1. Confounders considered a priori were maternal age, race, socioeconomic status, parity, smoking status, alcohol abuse, substance use, anxiolytic use and chronic medical conditions including asthma, pre-existing diabetes, thyroid disorder and epilepsy. In addition, preterm delivery was adjusted for previous history of preterm delivery and low birth weight was adjusted for maternal height. Interactions were investigated by stratified analyses and multivariate analyses with interaction terms.

All data analyses were undertaken on de-identified data using STATA 11 (Stata, College Station, TX). This project was approved by the Human Research Ethics Committees of The University of South Australia and the Children, Youth, Women's Health Service in South Australia.

8.4 Results

Of the women eligible to participate in this study (n=33,965), 221 received a dispensing for a SSRI, 1,566 had a psychiatric illness but did not receive a dispensing for a SSRI, and 32,004 did not have a psychiatric illness and did not receive a dispensing for a SSRI. All women who received a SSRI had a dispensing for only one type of SSRI (sertraline [n=96], citalopram [n=74], paroxetine [n=26], fluoxetine [n=15], fluvoxamine [n=8], escitalopram [n=2]).

Women exposed to SSRIs were more likely to be older, of higher parity and were more likely to have pre-existing diabetes and to receive a dispensing for an anxiolytic compared to women with a psychiatric illness but no SSRI use. Compared to women with no psychiatric illness, women exposed to SSRIs were more likely to be of higher parity, Caucasian, smokers, substance users, alcohol abusers, have pre-existing medical conditions such as epilepsy, thyroid disorders, diabetes and asthma and to receive a dispensing for an anxiolytic during pregnancy.

Neonatal outcomes according to exposure are shown in Table 2. Compared to infants of women with a psychiatric illness but no SSRI use during pregnancy, infants of women exposed to SSRIs had an increased risk of preterm delivery (adjusted OR, 2.68; 95% CI, 1.83-3.93), low birth weight (adjusted OR, 2.26; 95% CI, 1.31-3.91), admission to hospital (adjusted OR, 1.92; 95% CI, 1.39-2.65) and length of hospital stay greater than 3 days (adjusted OR, 1.93; 95% CI, 1.11-3.36) but not SGA (adjusted OR, 1.13; 95% CI, 0.65-1.94).

Compared to infants of women with no psychiatric illness, infants of women exposed to SSRIs had an increased risk of preterm delivery (adjusted OR, 2.46; 95% CI, 1.75–3.50), low birth weight (adjusted OR, 2.57; 95% CI, 1.57-4.21), admission to hospital (adjusted OR, 2.37; 95% CI, 1.76-3.19) and length of hospital stay greater than 3 days (adjusted OR, 2.20; 95% CI, 1.34-3.59). No increased risk of SGA was observed (adjusted OR, 1.17; 95% CI, 0.71-1.94)

The presence of a psychiatric illness but no SSRI use during pregnancy did not appear to have an appreciable effect on neonatal outcomes with only an increased likelihood of the neonate being admitted to hospital (adjusted OR, 1.21; 95% CI, 1.07-1.38).

8.5 Discussion

Our results suggest that infants exposed to SSRIs during pregnancy, particularly during late gestation, are at increased risk of preterm delivery, low birth weight, admission to hospital following delivery and increased length of hospital stay, but not SGA. The results were similar when compared to infants of women with a psychiatric illness but no SSRI use during pregnancy. The fact that we failed to observe an association between prenatal SSRI exposure and SGA suggests that the increased risk of infants born with a low birth weight may be due to the increased rate of preterm delivery of infants with otherwise appropriate for gestational age growth.

Based on a previous validation study, the use of the hospital pharmacy dispensing records largely identifies a cohort of women with likely exposure to SSRIs during late (i.e. second and third trimester) pregnancy. The validation study highlighted that women who were exposed to a SSRI during the first trimester, and subsequently stopped taking their SSRI during the second and third trimester, were not identified. Previous research has demonstrated that 11-50% of women stop taking their SSRI after finding out that they are pregnant, usually early during the first trimester.[25,42,55,56] In addition, it has been demonstrated that the majority of women (60-80%) who are taking a SSRI during late pregnancy also took it during the first, second and third trimesters. Therefore, as

discussed by Oberlander et al.[9] it was that late trimester exposure to SSRIs would identify those women with more substantial and prolonged exposure during pregnancy. These women, with late gestation exposure, have an increased risk of adverse neonatal outcomes compared to those with early gestation exposure.[17,23,41] This is well demonstrated by Toh et al.[33] who observed that women treated with SSRIs late in pregnancy had a higher frequency of delivering SGA infants. Compared with nonusers, the frequencies of SGA offspring (5.7%) were not increased among the 106 women who discontinued SSRIs before the end of the first trimester.[33] Among women who continued SSRIs beyond the first trimester, however, 17.4% had a SGA offspring (OR, 3.0; 95% CI, 1.7-5.5).[33] In addition, Malm et al.,[41] demonstrated an increased risk of admission to hospital in infants exposed to SSRIs during the third trimester, compared to infants exposed only in the first trimester (adjusted OR 1.6; 1.1-2.2). There still remains, however, the potential for confounding due to differences between women who continue taking their SSRI throughout pregnancy compared to those who stop taking it in the first trimester. It is possible that women with more severe psychiatric illness may be more likely to have required continued pharmacological management during pregnancy, resulting in an increased risk of negative neonatal outcomes in the group exposed to SSRIs.

Despite this, the risk of preterm delivery found in our study (adjusted OR 2.46; 95% CI 1.75-3.50) is within the range observed by Lund et al.[16] (adjusted OR 2.05; 95% CI 1.28-3.31) and Wisner et al.,[18] (adjusted OR 5.43; 95% CI 1.98-14.84). The higher risk estimate observed by Wisner et al.[18] could be due to the restricted inclusion of women who had continuous SSRI exposure during all three trimesters of pregnancy and the large confidence interval is reflective of the small sample studied. In addition, Lund et al.[16] demonstrated an increased rate of hospital admission in infants with *in utero* exposure to SSRIs during pregnancy compared to those who were not exposed to SSRIs or psychiatric illness during pregnancy (adjusted OR 2.39; 95% CI 1.69-3.39). The risk was somewhat attenuated when comparing hospital admission in infants exposed to SSRIs with infants of mothers with a history of psychiatric illness (adjusted OR 2.04; 1.42-2.94). We observed the same attenuation of risk when comparing outcomes between infants of women exposed to SSRIs to infants of women with no psychiatric illness (adjusted OR 2.37; 1.76-3.19) and infants of women with a psychiatric illness but no SSRI use during pregnancy (adjusted OR 1.92; 1.39-2.65). Psychiatric illness but no SSRI use during pregnancy was associated with a small increased risk of the neonate being hospitalised following delivery (adjusted OR 1.21; 1.07-1.38), but this appeared to be for temporary observation as there was no observed increased risk of hospital stay > 3 days.

Oberlander et al.,[9] demonstrated an increase in prematurity, respiratory distress, jaundice and length of hospital stay together with a reduction in mean birth weight among infants exposed to SSRIs prenatally. Following propensity score matching (including matching according to severity of depression), prenatal SSRI exposure was only associated with an increased risk of small for gestational age and respiratory distress syndrome in the neonate.[9] These results provide strong evidence that prenatal SSRI exposure may be associated with adverse neonatal outcomes, but also that there is confounding due to underlying depression. Notably, while the two comparison groups may be matched according to a range of measured characteristics, they may not be similarly matched based on those that are not measured. For example, maternal factors such as smoking, alcohol use, substance use, chronic medical conditions (e.g. diabetes), which are all associated with adverse neonatal outcomes, were not measured and adjusted for in that study.

A strength of this study is that we compared neonatal outcomes in women treated with SSRIs to those of women with a psychiatric illness but no SSRI use during pregnancy to investigate whether differences in outcomes could be attributable to confounding by indication. In this manner we were able to explore the association between prenatal SSRI exposure and adverse neonatal outcomes, taking into account unmeasured factors which are associated with having a psychiatric illness and which we were not able to adjust for in the multivariate analysis. In contrast to previous studies investigating the effect of depressive illness during pregnancy,[5-15] the infants of women with an untreated psychiatric illness in this study did not have higher rates of preterm delivery or low birth weight. An increased risk of SGA was observed (crude OR 1.37; 1.14-1.63), but this was not statistically significant after adjustment for confounding (adjusted OR 1.06; 0.88-1.28). The differing results may be related to the fact that we included women with a range of psychiatric illnesses, not just depression; however, we considered this to be a suitable comparison group as women are prescribed SSRIs for a range of psychiatric illnesses other than depression. A further strength of this study was the ability to adjust for a range of important maternal characteristics and important confounders such as maternal race, socioeconomic status, smoking status, substance abuse, alcohol abuse and maternal co-morbidities such as asthma, diabetes and epilepsy and concurrent use of anxiolytics.

As SSRI use occurs in the context of maternal psychiatric illness, our results suggest that combined exposure to SSRIs and psychiatric illness during pregnancy is associated with an outcome profile that appears to differ from that of exposure to psychiatric illness alone. The central question remains, however, of whether the observed increased risk of adverse neonatal outcomes justifies the benefits of treating a mother with a psychiatric

illness with a SSRI during pregnancy. It is important to recognise that the presence of a psychiatric illness itself may have adverse effects on the fetus and neonate, beyond those outcomes measured in this and other studies, and that the risk of no treatment may outweigh the risk of adverse consequences associated with prenatal SSRI exposure. Therefore it is vital to stress the importance of identifying and actively managing psychiatric illness during pregnancy, with the knowledge that treatment with SSRIs, together with the clinical need to initiate pharmacological treatment, may be associated with an increased risk of adverse neonatal outcomes. Knowledge of such risk is important in ensuring that these women and their infants can be effectively managed during and after the pregnancy.

There are a number of limitations associated with this study. The most significant limitation is that we had no information on the severity of the psychiatric illness, which would have added to our understanding of the independent effects of psychiatric illness on pregnancy outcomes. As such, there remains the potential for confounding due to underlying severity of psychiatric illness. It is possible that women with more severe psychiatric illness may be more likely to have required continued pharmacological management during pregnancy, resulting in an increased risk of negative neonatal outcomes in the group exposed to SSRIs. In addition, the identification of women with a psychiatric illness during pregnancy is based on data collected by midwives from the case notes. This could have resulted in an underestimation of the actual number of women with a psychiatric illness during pregnancy. On the other hand, women were classified as having a psychiatric illness if it was recorded that they were taking a medication for their psychiatric illness or received psychological/psychiatric support during the pregnancy. Therefore this group is likely to include women who actually suffered from a psychiatric illness during pregnancy, rather than women with just a previous history of psychiatric illness. Notably, the SSRI use and psychiatric illness but no SSRI use groups were similar in relation to a number of co morbidities and negative lifestyle risk factors (i.e. smoking status, substance use, alcohol abuse, asthma and epilepsy). However, they did differ substantially in relation to concurrent anxiolytic use, which could be reflective of a greater severity of psychiatric illness in the SSRI use group.

A second limitation is that given that the data obtained for this study is from a large metropolitan tertiary level teaching hospital, it is possible that the population studied is a higher risk sample compared to all of the pregnancies throughout the state. It is possible that there is a selective referral of women exposed to SSRIs who have a high risk pregnancy to deliver at this hospital rather than at other hospitals throughout the state. However, it is likely that women suffering from psychiatric illness during pregnancy

who are at high risk are also more likely to deliver at this hospital, making it difficult to assess the degree to which this may bias the observed outcomes. A third limitation is that while the hospital pharmacy dispensing records utilised in this study are an efficient alternative to paper-based medical records in determining late gestation exposure to SSRIs, they underestimate exposure by 25%.[50] As a result of this underestimation it is possible that some women in the control groups were actually exposed to a SSRI during pregnancy. This is likely to cause underestimation of any associations observed between prenatal SSRI exposure and the neonatal outcomes investigated. Finally, there is no way of confirming whether women who received a dispensing for a SSRI actually took it during pregnancy.

8.6 Conclusion

These results add to the growing body of evidence of an association between SSRI exposure during pregnancy and a range of adverse neonatal outcomes. While these increased risks were observed even after attempts to control for the presence of underlying maternal psychiatric illness, there remains a need to further investigate and adequately delineate any effects of underlying maternal illness from that of prenatal SSRI exposure.

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Table 8.1 Characteristics of pregnant women exposed to selective serotonin reuptake inhibitor (SSRI), with a psychiatric illness but no SSRI exposure and without a psychiatric illness

Characteristics†‡	SSRI Use (n=221)	Psychiatric Illness / No SSRI Use (n=1,566)	Unexposed (n=32,004)
Maternal age, mean (SD), y	29.5 (5.9)[a]	28.5 (6.2)[b]	29.2 (5.8)[a]
Maternal height, mean (SD), cm	164.5 (6.4)	164.1 (7.6)	163.6 (7.2)
Parity, No. (%)			
≥1	150 (68.5) [a]	867 (55.6) [b]	17 737 (55.7) [b]
Race, No. (%)			
Caucasian	199 (90.1)[a]	1412 (90.2)[a]	25 194 (78.7)[b]
Asian	16 (7.2)	112 (7.2)	3,083 (9.6)
Other	6 (2.7)	42 (2.7)	3,727 (11.7)
Socioeconomic Status, SEIFA, 5 groups, n (%)†			
5 (highest)	42 (19.0)[ab]	296 (18.9)[a]	6264 (19.6)[b]
4	37 (16.7)	290 (18.5)	6439 (20.2)
3	38 (17.2)	305 (19.5)	5868 (18.4)
2	48 (21.7)	260 (16.6)	6420 (20.1)
1 (lowest)	56 (25.3)	413 (26.4)	6925 (21.7)
Smoking habit, No. (%)			
Non Smoker	141 (65.9)[a]	983 (65.1)[a]	25,647 (83.6)[b]
Cigarettes/d			
1-9	25 (11.7)	183 (12.1)	2,321 (7.5)
10-19	26 (12.2)	230 (15.2)	2,021 (6.6)
≥20	22 (10.3)	113 (7.5)	686 (2.2)
Anxiolytic use, No. (%)	28 (12.7)[a]	41 (2.6)[b]	189 (0.6)[c]
Substance use, No. (%)	21 (9.5)[a]	152 (9.7)[a]	808 (2.5)[b]
Alcohol abuse, No. (%)	4 (1.8)[a]	28 (1.8)[a]	101 (0.3)[b]
Hypertension, No. (%)	4 (1.8)	26 (1.7)	427 (1.3)
Epilepsy, No. (%)	5 (2.3)[a]	23 (1.5)[a]	228 (0.7)[b]
Thyroid disorder, No. (%)	6 (2.7)	25 (1.6)	598 (1.9)
Pre-existing diabetes, No. (%)	7 (3.2)[a]	22 (1.4)[b]	271 (0.9)[c]
Asthma, No. (%)	40 (18.1)[a]	267 (17.1)[a]	2425 (7.6)[b]

SSRI, selective serotonin reuptake inhibitor; BMI, body mass index; SEIFA, socio-economic indexes for areas

† Percentages are calculated from non-missing data

‡ Different superscripts (e.g. a, b, c) denote a statistically significant difference between groups (P<0.05)

Table 8.2 Neonatal outcomes in women exposed to selective serotonin reuptake inhibitors (SSRIs), with a psychiatric illness but no SSRI exposure and without a psychiatric illness

Neonatal Outcome‡	No. (%) SSRI Use (n=221)	Psychiatric Illness / No SSRI Use (n=1,566)	Unexposed (n=32,004)
Preterm delivery (<37 weeks)	55 (24.9)	185 (11.8)	3,435 (10.7)
Low birth weight (<2500g)	42 (19.0)	150 (9.6)	2,734 (8.6)
SGA	19 (12.8)	146 (13.0)	2,205 (9.8)
Neonate admitted to hospital	87 (39.4)	414 (26.4)	6,114 (19.1)
Neonate length of hospital stay > 3 days	20 (9.1)	75 (4.8)	1,366 (4.3)

SSRI, selective serotonin reuptake inhibitor; SGA, small-for-gestational-age
‡ Percentages are calculated from non-missing data

Table 8.3 Association between late gestation selective serotonin reuptake inhibitor exposure and neonatal outcomes

Characteristics	SSRI Use vs. Psychiatric Illness/No SSRI Use	SSRI Use vs. No Psychiatric Illness	Psychiatric Illness/No SSRI Use Vs. No Psychiatric Illness
Preterm delivery (<37 weeks)			
Crude OR	2.47 (1.76-3.48)	2.76 (2.03-3.75)	1.11 (0.95-1.30)
Adjusted OR[a]	2.68 (1.83-3.93)	2.46 (1.75–3.50)	0.94 (0.79-1.12)
Low birth weight (<2500g)			
Crude OR	2.21 (1.52-3.23)	2.51 (1.79-3.52)	1.13 (0.95-1.35)
Adjusted OR[b]	2.26 (1.31-3.91)	2.57 (1.57-4.21)	1.05 (0.83-1.34)
SGA			
Crude OR	0.98 (0.59-1.64)	1.34 (0.83-2.17)	1.37 (1.14-1.63)
Adjusted OR[c]	1.13 (0.65-1.94)	1.17 (0.71-1.94)	1.06 (0.88-1.28)
Neonate admitted to hospital			
Crude OR	1.81 (1.35-2.42)	2.75 (2.10-3.61)	1.52 (1.36-1.71)
Adjusted OR[c]	1.92 (1.39-2.65)	2.37 (1.76-3.19)	1.21 (1.07-1.38)
Neonate length of hospital stay > 3 days			
Crude OR	1.98 (1.18-3.31)	2.23 (1.41-3.54)	1.13 (0.89-1.43)
Adjusted OR[c]	1.93 (1.11-3.36)	2.20 (1.34-3.59)	1.05 (0.82-1.36)

SSRI, selective serotonin reuptake inhibitor; SGA, small-for-gestational-age; OR, odds ratio; CI, confidence interval

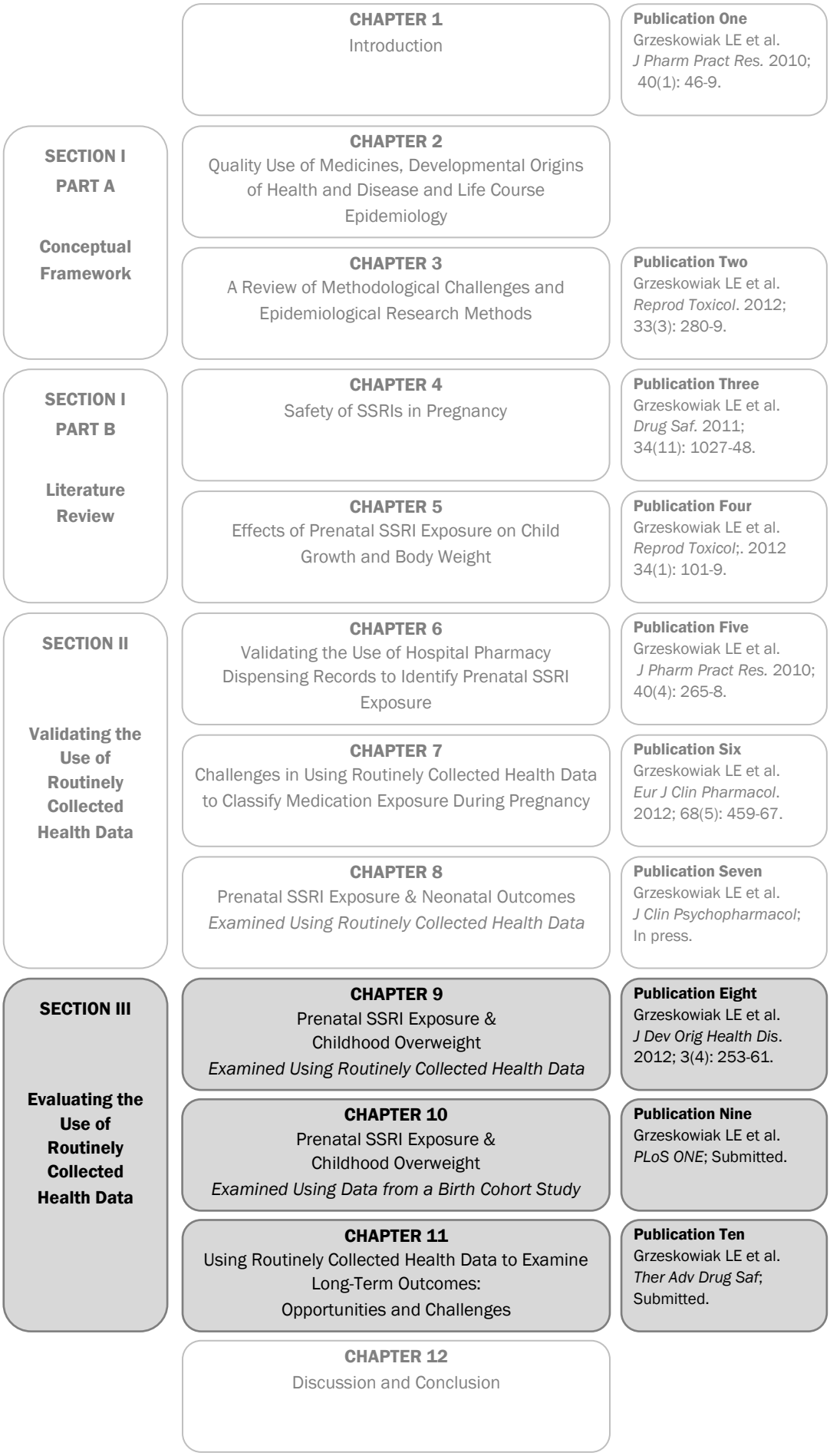
[a] OR adjusted for maternal age, socioeconomic status, smoking status, race, asthma, pre-existing diabetes, alcohol abuse, substance abuse, hypertension, parity, epilepsy, thyroid disorder, previous history of premature delivery and anxiolytic use

[b] OR adjusted for those above and maternal height

[c] OR adjusted for maternal age, socioeconomic status, smoking status, race, asthma, pre-existing diabetes, alcohol abuse, substance abuse, hypertension, parity, epilepsy, thyroid disorder and anxiolytic use

Section III –

Investigating the Use of Routinely Collected Health Data


CHAPTER 1
Introduction
Publication One
Grzeskowiak LE et al.
J Pharm Pract Res. 2010;
40(1): 46-9.
SECTION I
PART A
Conceptual Framework
CHAPTER 2
Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology
CHAPTER 3
A Review of Methodological Challenges and Epidemiological Research Methods
Publication Two
Grzeskowiak LE et al.
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33(3): 280-9.
SECTION I
PART B
Literature Review
CHAPTER 4
Safety of SSRIs in Pregnancy
Publication Three
Grzeskowiak LE et al.
Drug Saf. 2011;
34(11): 1027-48.
CHAPTER 5
Effects of Prenatal SSRI Exposure on Child Growth and Body Weight
Publication Four
Grzeskowiak LE et al.
Reprod Toxicol;. 2012
34(1): 101-9.
SECTION II
Validating the Use of Routinely Collected Health Data
CHAPTER 6
Validating the Use of Hospital Pharmacy Dispensing Records to Identify Prenatal SSRI Exposure
Publication Five
Grzeskowiak LE et al.
J Pharm Pract Res. 2010;
40(4): 265-8.
CHAPTER 7
Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy
Publication Six
Grzeskowiak LE et al.
Eur J Clin Pharmacol.
2012; 68(5): 459-67.
CHAPTER 8
Prenatal SSRI Exposure & Neonatal Outcomes
Examined Using Routinely Collected Health Data
Publication Seven
Grzeskowiak LE et al.
J Clin Psychopharmacol;
In press.
SECTION III
Evaluating the Use of Routinely Collected Health Data
CHAPTER 9
Prenatal SSRI Exposure &
Childhood Overweight
Examined Using Routinely Collected Health Data
Publication Eight
Grzeskowiak LE et al.
J Dev Orig Health Dis.
2012; 3(4): 253-61.
CHAPTER 10
Prenatal SSRI Exposure &
Childhood Overweight
Examined Using Data from a Birth Cohort Study
Publication Nine
Grzeskowiak LE et al.
PLoS ONE; Submitted.
CHAPTER 11
Using Routinely Collected Health Data to Examine Long-Term Outcomes:
Opportunities and Challenges
Publication Ten
Grzeskowiak LE et al.
Ther Adv Drug Saf;
Submitted.
CHAPTER 12
Discussion and Conclusion

Preamble

The final section brings together all of the information and evidence obtained from the previous chapters to culminate in a practical evaluation of the use of routinely collected health data to examine long-term effects of medication use during pregnancy.

Given the biological plausibility and previous evidence suggesting that prenatal SSRI exposure may have long-term effects on child growth and body weight, a study was undertaken using local routinely collected health data to investigate whether prenatal SSRI exposure was associated with childhood overweight (Chapter 9).

To further explore the strengths, limitations, challenges and recommended strategies in using routinely collected health data, we undertook a similar study using data obtained from an ongoing prospective birth cohort study in Denmark (Chapter 10). This enabled a comparison of two different research methodologies; the first being the relatively novel and emerging approach of using routinely collected health data and the second being the well established prospective birth cohort design which is often considered the gold standard.

The thesis culminates in a review of the opportunities and challenges associated with the use of routinely collected health data to examine long-term effects of medication use during pregnancy, with a particular focus on the Australian context (Chapter 11).

CHAPTER 9

Prenatal SSRI Exposure and Childhood Overweight:

Examined Using Routinely Collected Health Data

Manuscript

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Prenatal exposure to selective serotonin reuptake inhibitors and risk of childhood overweight

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9.1 Abstract

The objective was to investigate the association between prenatal selective serotonin reuptake inhibitor (SSRI) exposure and overweight in offspring at 4–5 years of age. We conducted a retrospective cohort study using linked records from the Women's and Children's Health Network in South Australia, Australia. Women were eligible to participate if they gave birth to singleton, live-born infants between September 2000 and December 2005. Women were excluded if they received a dispensing for an antidepressant other than SSRIs or an antipsychotic or an anti-epileptic or had a chronic medical condition. Of the 6560 eligible women, 71 received a dispensing for an SSRI (exposed), 204 had a reported psychiatric illness but did not receive a dispensing for any antidepressant (untreated psychiatric illness) and 6285 did not have a reported psychiatric illness and did not receive a dispensing for any antidepressant (unexposed). Childhood overweight was classified as a body mass index .85th percentile, based on age and sex. At 4–5 years of age, female offspring of exposed mothers were less likely to be overweight compared with female offspring of mothers with an untreated psychiatric illness [adjusted Prevalence Ratio (aPR) 0.23; 95% confidence interval (CI) 0.05–0.98] and female offspring of unexposed mothers (aPR 0.27; 0.07–0.99). No association with overweight was observed among male offspring of exposed mothers compared with male offspring of mothers with an untreated psychiatric illness (aPR 1.17; 0.54–2.51) and male offspring of unexposed mothers (aPR 0.93; 0.52–1.67). Further research is required to confirm these findings and examine the potential mechanisms behind the sex-specific differences.

9.2 Introduction

Since their introduction into clinical practice in the 1980s, selective serotonin reuptake inhibitors (SSRIs) quickly replaced tricyclic antidepressants as the treatment of choice for many psychiatric disorders due largely to their more favourable safety profile and less toxicity in overdose.[1–3] Consequently, there has been an increase in the number of women of childbearing age taking SSRIs, many of whom continue to take them throughout pregnancy, despite limited evidence of their effects in the offspring.[4]

While most commonly used in the treatment of depression, SSRIs are also used in the management of a number of psychiatric disorders including social anxiety disorder,

obsessive compulsive disorder and panic disorder.5 SSRIs exert their pharmacological effects by selectively inhibiting the reuptake of serotonin (5-hydroxytryptamine or 5-HT) at the presynaptic junction, resulting in an increased concentration of 5-HT in the

synaptic cleft and thus enhanced serotonergic neurotransmission.6 As such, SSRI use during pregnancy could alter foetal 5-HT signalling during critical periods of foetal development, the immediate and long-term consequences of which have not been well studied. To date, the collective evidence suggests that prenatal SSRI exposure is not associated with impaired neurodevelopment in the offspring; however, due to methodological differences and limitations associated with previous studies, it is difficult to draw any definitive conclusions.[7]

Given the importance of 5-HT as a neurotransmitter within the central nervous system and its role in neurogenesis, migration and differentiation of neurons in the foetal brain, the potential long-term effects of prenatal SSRI exposure remain an area of concern.[8,9] Of particular interest are the potential long-term effects of prenatal SSRI exposure on child growth, given the well-established role of the serotonergic system in regulating food intake and body weight.[10–12]

Animal studies provide clear evidence that changes in 5-HT homeostasis during critical periods of foetal development can lead to alterations in the serotonergic system and that these alterations are sex specific.[13–18] There is evidence to suggest that auto-inhibitory feedback restrains the maturation of the 5-HT system.[19] It is therefore possible that in the situation where serotonergic tone is increased as a result of SSRI exposure, there is a resultant increase in negative feedback signalling, restraining the maturation of the serotonergic system. As such, it is possible that altered development of the serotonergic system in early foetal life modifies serotonergic regulation of food intake and body weight in later life, influencing the risk of overweight. Supporting this hypothesis is evidence from animal studies demonstrating that exposure to high levels of 5-HT in utero leads to an increased risk of late-onset obesity in males, but not in females.[16–18]

A small number of human studies have investigated the short-term effects of SSRI use during pregnancy and/or breastfeeding on infant weight gain,[20–24] with the majority finding no association.[21–23] Chambers et al.[20] however, demonstrated that infants who were born to mothers who took fluoxetine during pregnancy and while breastfeeding displayed a pattern of growth that was significantly lower than that of infants who were breastfed by mothers who did not take fluoxetine.[20] Between 2 weeks and 6 months of age, infants of mothers taking fluoxetine while breastfeeding had an average weight deficit of 392 g (95% CI -5, -750).[20] It is unclear whether the observed effects were related to prenatal and/or postnatal exposure to fluoxetine. A recent study by Lewis et al.[24] specifically measured the effects of prenatal exposure to antidepressants on infant weight gain, up until 1 month of age.[24] They observed a reduction in mean weight gain

during the first month of life in infants exposed to an antidepressant during pregnancy compared with controls (22.71 v. 31.81 g/day; P=0.002).[24] It was not clear how many women exposed to antidepressants were using SSRIs, and no adjustments were made for breastfeeding status or sex. In addition, these studies did not control for underlying maternal illness, the effects of which are important to separate from those of prenatal SSRI exposure.

Based on available animal and human studies, there is evidence that prenatal SSRI exposure has the potential to affect growth and body weight in the offspring in later life, but no data are available from human studies that investigate this outcome beyond 6 months of age. While these infants may be smaller during early postnatal life, there is no evidence of what happens to these infants beyond this period and whether they have an increased risk of overweight as observed in animal studies. Therefore, we hypothesized that prenatal exposure to SSRIs influences growth and body weight in the offspring in a sex-specific manner, leading to an expected increased risk of overweight in males, but not in females. This study used routinely collected administrative and clinical data to examine the influence of prenatal SSRI exposure on the risk of overweight in the offspring at 4–5 years of age.

9.3 Method

This was a retrospective cohort study relating to all births in the Women's and Children's Health Network (WCHN) in South Australia between September 2000 and December 2005 that occurred at the Women's and Children's Hospital (WCH). The WCH is a specialist metropolitan tertiary-level teaching hospital and South Australia's largest maternity and obstetric service provider, caring for over 4000 pregnancies each year. The study utilized linkable health administrative data within the WCHN, which included the WCH Perinatal Statistics Collection, the WCH Hospital Pharmacy Dispensing Records and the WCHN Child Health Record, to obtain follow-up data on child weight and height. Electronic records were first matched using each individual's unique hospital identifier number, and where this was not possible, through an exact match on the following three variables: surname, sex and date of birth.

A total of 21,733 pregnancies occurred during the study period. Women who were eligible for the current analysis were those who gave birth to singleton, live-born infants (n=20,200). We excluded women who were dispensed an antidepressant other than SSRIs during pregnancy (n=75), antipsychotics (n=547) and anti-epileptics (n=123) as well as women with asthma (n=1836), hypertension (n=250), diabetes (n=140), gestational diabetes (n=705) and thyroid disorders (n=273), leaving a total eligible study

cohort of 16,751 mother–child dyads. These women were excluded due to the potential for these medications and medical conditions to negatively impact on foetal growth during pregnancy, which in turn could be an important factor in determining the risk of overweight in later life. We further obtained height and weight data at 4–5 years of age for 6573 children, of whom 13 were considered outside of biologically plausible values based on predefined criteria. This left a final study cohort of 6560 mother–child dyads (Fig. 1).

Data on exposure to SSRIs during pregnancy were obtained from the WCH Pharmacy Dispensing Records, which is a record of all medications dispensed from January 2000, and has been previously validated as an indicator of late gestation exposure to antidepressants during pregnancy.[25] In an effort to obtain a suitable control group consisting of women with similar underlying disease as those exposed to SSRIs during pregnancy, we identified a cohort of women with a reported psychiatric illness during pregnancy, but who did not receive a dispensing for any antidepressant during pregnancy (untreated psychiatric illness).

The primary outcome measure was childhood overweight at 4–5 years of age. Body mass index [BMI=weight(kg)/height(m)^2] was calculated based on measured height and weight at the health check. BMI-for-age percentiles were calculated using the Centres for Disease Control and Prevention SAS Program (CDC, Atlanta, GA, USA) designed for this purpose. International cut-off scores were utilized to define overweight as a BMI at or exceeding the age- and sex-specific 85th percentile.[26]

South Australia's WCHN (previously called Children, Youth and Women's Health Service and Child and Youth Health) provides a range of health and social services and programmes for parents, children and young people across the state. As part of these services, child and family health nurses have performed health checks on 4- to 5-year-old children at all kindergartens and preschool centres since 1995. During these visits, they have used a standard protocol to measure height with a fixed tape and weight of children dressed in underwear, and they have recorded data electronically. From 1997 through 2007, the period of child follow-up in this study, the average participation rate was ≈65% of South Australian children.

Information on maternal age, BMI, parity, race, socioeconomic status, smoking status and breastfeeding at discharge from hospital was obtained from the Perinatal Statistics Collection. Clinical Information Services at the WCH is responsible for maintaining the Perinatal Statistics Collection. Data are collected on the pregnancy and outcome of every live birth and late foetal death occurring at the WCH including on every baby

admitted to the Neonatal Intensive Care Unit and Special Care Baby Unit. The data are collected according to the guidelines of the Pregnancy Outcome Unit of the South Australian Department of Health for the Supplementary Birth Records (SBRs) and in consultation with the senior clinicians at the hospital. Data collection began in the late 1980s and complete and validated data are available from 1990. Data are collected from the woman's medical records following delivery by a specially trained research midwife using a structured coding sheet. It is important to note that included in the medical record is the South Australian Pregnancy Record, which is a hand-held antenatal record carried by each woman throughout her pregnancy and contains notes by all health providers consulted during the pregnancy.[27] From the medical records, information is collected on maternal illnesses (e.g. diabetes, gestational diabetes, epilepsy, asthma and psychiatric illness), lifestyle factors (e.g. smoking), obstetric history, course of delivery, pregnancy complications and newborn characteristics (e.g. birth weight). All SBRs are checked manually for completeness and data discrepancies by a senior research midwife and then subjected to a series of automated validation procedures during data entry. The information in the perinatal statistics collection has been previously validated and is reliable when compared with hospital case records.[28]

The estimated length of gestational age at delivery is recorded in the Perinatal Statistics Collection and is based on the last menstrual period and ultrasound examination. The appropriateness of intrauterine growth was assessed using percentage of optimal birth weight (POBW).[29] POBW is the ratio of the observed to the 'optimal' birth weight, with the latter calculated from a regression equation that takes account of the major non-pathological determinants of intrauterine growth including gestational age, infant sex, maternal height and parity.[29] We used a POBW score less than the 10th percentile to define small-for-gestational-age (SGA) infants and a score greater than the 90th percentile to define large-for-gestational-age (LGA) infants.

Parity was defined as no previous deliveries (nulliparity) or one or more previous deliveries. Maternal race or ethnic group was classified as Caucasian, Asian or other. Data on smoking are routinely collected during the first antenatal visit and therefore reflects smoking status during early pregnancy. The smoking variable was categorized into non-smokers and smokers and stratified according to the number of cigarettes smoked on average each day (1–9; 10–19; >20). Socioeconomic status for each woman was determined using her residential postcode at the time of delivery. Women were then ranked according to their level of advantage, or relative disadvantage, based on data from the Socio-Economic Indexes for Areas, calculated from the Australian Bureau of Statistics' 5-yearly Census of Population and Housing. These indexes are widely used measures of relative socioeconomic status.[30]

All data analysis was undertaken on de-identified data. We conducted univariate categorical analyses using the chi-squared test or Fisher's exact test where appropriate. Unpaired t-tests were used for two-group comparisons and one-way analysis of variance for three-group comparisons of normally distributed continuous variables. We compared the rates of overweight between groups using a generalized linear model (Poisson distribution) with robust variance estimates, with resulting prevalence ratios (prevalence of disease in exposed v. prevalence in unexposed) for the effect estimate and 95% confidence intervals (CIs). This model was chosen over a log binomial generalized linear model as the latter failed to converge. The commonly used logistic regression model for dichotomous outcomes was not used as the prevalence of overweight in the cohort was relatively common (i.e. >10–20%) and a measure approximating the relative risk was preferred to an odds ratio to enhance the interpretability of the results.[31] Potential confounding maternal and child covariates were categorized as shown in Table 1. All categorical variables were coded as a number of dummy variables equal to the number of categories minus 1. In the first adjusted model, we included confounders and covariates chosen a priori, which were maternal age, BMI, race, socioeconomic status, parity and smoking status. In the second adjusted model, we also included additional covariates including appropriateness of foetal growth (SGA and LGA) and breastfeeding at discharge from hospital. Interactions were investigated by stratified analyses and multivariate analyses with interaction terms. We further stratified analyses according to sex due to the possible presence of effect measure modification. Statistical analyses were performed using Stata IC 11.0 (Stata, College Station, TX, USA). Statistical significance was defined as a two-sided P-value of 0.05.

This project was approved by the Human Research Ethics Committees of the University of South Australia and the Women's and Children's Health Network in South Australia.

9.4 Results

Of the mother–child dyads who had follow-up data on weight and height (n=6560), 71 received a dispensing for an SSRI (exposed), 204 had a reported psychiatric illness but did not receive a dispensing for any antidepressant (untreated psychiatric illness) and 6285 did not have a reported psychiatric illness and did not receive a dispensing for any antidepressant (unexposed).

Women exposed to SSRIs had very similar characteristics compared with women with an untreated psychiatric illness, but were less likely to have been breastfeeding their infant at the time of discharge from hospital (Table 1). Compared with unexposed women, women who were exposed to SSRIs and those with untreated psychiatric illness were

more likely to be Caucasian, of lower socioeconomic status, smokers and were less likely to have been breastfeeding their infant at the time of discharge from hospital.

Statistically significant associations were only identified among female offspring (Table 2). Female offspring of exposed mothers were less likely to be overweight then female offspring of mothers with an untreated psychiatric illness (adjusted Prevalence Ratio (aPR) 0.23; 0.05–0.98). When compared with female infants of unexposed mothers, the observed reduced risk of overweight was similar in female offspring of exposed mothers (aPR 0.27; 0.07–0.99). In contrast to females, no association with overweight was observed among male offspring of exposed mothers compared with male offspring of mothers with an untreated psychiatric illness (aPR 1.17; 0.54–2.51) and male offspring of unexposed mothers (aPR 0.93; 0.52–1.67).

The sample size did not allow stratification according to individual type of SSRI. The age of the children at follow-up did not differ significantly between groups. While loss to follow-up was not statistically significantly different across groups, we found a number of overall differences between those lost to follow-up and those not lost to follow-up (Table 3). The mothers of those lost to follow-up were more likely to have a lower BMI, be younger, multiparous, of a higher socioeconomic status, to smoke during pregnancy and were less likely to be of Caucasian race and to have been breastfeeding at discharge from hospital.

9.5 Discussion

Our results suggest that prenatal SSRI exposure could be associated with sex-specific long-term alterations in child growth and body weight, with a decreased risk of overweight observed among females, but not males, at 4–5 years of age. These results could reflect a persistent reduction in growth among female offspring that could be a possible continuation of that observed in the first 1–6 months of postnatal life following prenatal exposure to fluoxetine and other antidepressants in previous studies.[20,24] Notably, the results of this study appeared to be independent of the effects of untreated psychiatric illness during pregnancy, which itself was not associated with the risk of childhood overweight at 4–5 years of age.

A recent review of Australian studies that included children aged 2–18 years of age demonstrated that the prevalence of overweight among males and females has steadily increased from ≈10% in 1985 and has settled around 21–25% in recent years (up to 2008).[32] This is similar to the prevalence of overweight observed in this study. Some may view the reduced rate of overweight observed among female offspring with prenatal

SSRI exposure as a positive; however, it is also important to consider the potential explanation and mechanism underpinning this reduced risk of overweight. Given that the effects on foetal growth are postulated to occur as a direct result of alterations in the programming of appetite control and regulatory pathways, these results are important in highlighting the potential vulnerability of the developing foetal brain to prenatal SSRI exposure. In addition, given the reported sex differences observed, these results may indicate sex differences in the susceptibility of the developing foetal brain to prenatal SSRI exposure.

Sex-specific outcomes, as observed in this study, are consistent with the literature. There are sex variations in human brain development and function, including differences in the serotonergic system.[33,34] In addition, sex-specific differences have been observed in many animal studies, highlighting sex differences in the susceptibility of the foetal brain to SSRI exposure.[13–18]

An association between prenatal SSRI exposure and childhood overweight could be expected, given the well recognized role of 5-HT in regulating food intake and body weight.[10–12] The inhibitory effects of 5-HT on food intake have been related to its interactions with 5-HT_{1B} and 5-HT_{2C} receptors in the hypothalamus,[10,11] while stimulatory effects of 5-HT on food intake have been reported following agonism of 5-HT_{1A}, and 5-HT_6 receptors.[12,17,35,36]

Animal studies provide clear evidence that changes in 5-HT homeostasis during critical periods of foetal development can lead to a number of alterations in the serotonergic system. Those studies that include females demonstrate striking sex-specific differences. For example, prenatal exposure to SSRIs has been demonstrated to result in an increase in the expression of 5-HT_{2A} receptors in the hypothalamus in female, but not male, offspring.[13] Given the important role of 5-HT_{2A} in regulating food intake and body weight, an increase in expression could result in increased feelings of satiety and therefore a reduction in food intake and net reduction in body weight. This could explain the observed reduction in the risk of overweight observed in female offspring with prenatal SSRI exposure compared with those who were unexposed. Furthermore, prenatal exposure to SSRIs has been demonstrated to cause a reduction in the expression of 5-HT_{1A} receptors in a number of brain regions.[14,15] Given that agonism of 5-HT_{1A} receptors has been demonstrated to result in hyperphagia,[36,37] a reduction in the density of 5-HT_{1A} receptors may result in a reduction in the usual hyperphagic response to circulation levels of 5-HT, resulting in a net reduction in food intake and body weight in females. Notably, further analysis revealed no statistically significant differences in the risk of underweight (BMI-for-age <5th percentile) in females at 4–5 years of age,

suggesting that these females have lower BMI-for-age percentiles that remain in the normal range.

While male mice exposed to excessive levels of 5-HT in utero display a number of alterations in serotonergic function that could influence their susceptibility towards the development of overweight in later life, no differences in the rates of overweight were observed between the groups. In contrast to the effects observed in females, prenatal SSRI exposure has been demonstrated to cause a decrease in expression,[38] and/or function,[39,40] of hypothalamic 5-$HT_{2A/2C}$ receptors in male offspring. Therefore, a reduction in the expression and/or function of 5-$HT_{2A/2C}$ receptors could be expected to result in a reduction in feelings of satiety and therefore an increase in food intake and net increase in body weight. In addition, male 5-HTT knockout mice have been demonstrated to develop late-onset obesity with associated reductions in physical activity, while females have been shown to be protected from this obese phenotype.[16–18] The lack of a clear effect in this study of prenatal SSRI exposure on childhood overweight in male offspring could be due to the compensatory adaptive responses that could occur in alternative systems involved in energy homeostasis to maintain normal growth throughout life. Alternatively, it is also possible that functional alterations may only become apparent at later time points, necessitating the need for longer-term follow-up data.

While prenatal exposure to maternal stress has been associated with an increased risk of overweight in childhood,[41] we observed no increased risk of overweight in either male or female offspring of mothers with an untreated psychiatric illness. This may be due to the shorter follow-up period in this study (4–5 years of age), as the previously observed increased risk of overweight only became apparent in the offspring from 10 years of age.

Based on a previous validation study, the use of the hospital pharmacy dispensing records largely identifies a cohort of women with likely exposure to SSRIs during the entire or late (i.e. second and third trimester) pregnancy. The validation study highlighted that women who were exposed to an SSRI during the first trimester, and subsequently stopped taking their SSRI during the second and third trimester, are not identified. Previous research has demonstrated that anywhere from 11% to 50% of women stop taking their SSRI after finding out that they are pregnant or early during the first trimester.[42–45] In addition, the majority of women (60–80%) who are taking an SSRI during late pregnancy have taken it during the first, second and third trimesters. Therefore, as discussed by Oberlander et al.[46] it was considered likely that late trimester exposure to SSRIs would identify those women with more substantial and prolonged exposure during pregnancy. Late gestation exposure increased the risk of adverse

neonatal outcomes compared with those neonates with early gestation exposure.[47–49] There still remains, however, the potential for confounding due to differences between women who continue taking their SSRI throughout pregnancy compared with those who stop taking it in the first trimester. It is possible that women with more severe psychiatric illness may be more likely to have required continued pharmacological management during pregnancy, resulting in an increased risk of negative neonatal outcomes in the group exposed to SSRIs.

A strength of this study is that it compared outcomes in offspring of exposed mothers with those of offspring of mothers with an untreated psychiatric illness to investigate whether differences in outcomes could be attributable to confounding by indication. The presence of a psychiatric illness during pregnancy is recorded by midwives if the woman is receiving medication for their psychiatric illness or if they received psychological/psychiatric support during the pregnancy. In this manner, we were able to explore the association between prenatal SSRI exposure and childhood overweight, taking into account unmeasured factors that are associated with having a psychiatric illness and that we were not able to adjust for in the multivariate analysis. Despite these adjustments, the possibility of confounding due to underlying maternal psychiatric illness remains possible. Continued SSRI use during pregnancy may be reflective of more severe psychiatric illness, which in turn could impact on child growth outcomes. Maternal psychiatric illness during early phases on childhood development may result in suboptimal nutritional intake among these children. This may occur through negative effects on mother–child interactions or differences in feeding practices.[50] Women with psychiatric illness may have more unhealthy behaviours (i.e. abnormal eating behaviours or physical activity levels), passing these on to their children. However, given that postnatal psychiatric illness is unlikely to be associated with the child's sex, it appears unlikely that the observed effects in females, and not males, are the result of confounding due to maternal postnatal psychiatric illness.

There are a number of limitations associated with this study. The major limitation is the relatively small sample size of infants exposed to SSRIs and untreated maternal illness during pregnancy, compared with the unexposed group. This makes it difficult to generate precise estimates for the risk of overweight, resulting in large CIs. In addition, the lack of data on postnatal factors such as the child's diet, energy intake and physical activity is a drawback. However, given the involvement of the serotonergic system in the regulation of appetite, which influences energy intake, as well as motor control, which influences physical activity in later life,[51] these factors could lie in any predicted pathway between prenatal SSRI exposure and childhood overweight and so should not be adjusted for. Other potentially important covariates that could not be adjusted for

include paternal BMI, pregnancy weight gain, alcohol consumption and duration of breastfeeding. There is also the potential for selection bias, with height and weight follow-up data only available for 40% of the original cohort eligible for this study.

A further limitation is that while the hospital pharmacy dispensing records utilized in this study have been validated as an efficient alternative to paper-based medical records in determining SSRI use during pregnancy, they underestimate exposure by 25%.[25] As a result of this underestimation, it is possible that some women in the control groups were actually exposed to an SSRI during pregnancy. This is likely to underestimate any associations observed between prenatal SSRI exposure and the neonatal outcomes investigated. Furthermore, a common assumption that is necessary in studies relying on electronic dispensing data is that women who receive a dispensing for an SSRI actually take that medication during pregnancy. However, based on the hospital pharmacy dispensing records used in this study, we are actually very confident that women identified as receiving a dispensing for an SSRI were actually taking that medication during pregnancy, as supported by previous validation results, indicating 100% specificity.[25]

Finally, while the prevalence of SSRI use reported in this study (1.1%) appears to be low in comparison with studies undertaken in other countries,[44] it is comparable to the prevalence of SSRI use reported in a recent Australian study based on data from a time period similar to this study (2002–2005).[42] In that study, ≈2% of women were taking an SSRI during late gestation. The lower prevalence reported in our study is likely related to the ≈25% underestimation of exposure due to the use of hospital pharmacy dispensing records (as previously described) and the exclusion of women with chronic medical conditions (e.g. asthma, diabetes) that are commonly associated with the use of SSRIs.[42,44]

In conclusion, our results suggest that prenatal SSRI exposure could be associated with sex-specific long-term alterations in child growth and body weight, with a decreased risk of overweight observed among females, but not males, at 4–5 years of age. This effect appeared to be independent of the effects of untreated psychiatric illness during pregnancy, which itself was not associated with the risk of childhood overweight at 4–5 years of age. Further research is required to confirm these findings and examine the potential mechanisms behind the sex-specific differences. There is also a need for continued research with longer follow-up of offspring to see whether these observed effects persist.

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Table 9.1 Maternal and child characteristics in each of the three comparison groups

	SSRI Use (n=71)	Untreated Psychiatric Illness (n=204)	Unexposed (n=6,285)
Maternal Characteristics‡			
Maternal Age, Mean (SD), y	28.8 (6.0)	29.0 (6.0)	29.3 (5.4)
Maternal BMI, Mean (SD), kg/m^2	26.5 (6.7)	25.2 (5.8)	25.2 (5.3)
Parity ≥1, n (%)†	43 (61.4)	118 (58.1)	3,337 (53.5)
Race Caucasian, n (%)†	67 (94.4)[ab]	189 (92.7)[a]	5,453 (86.8)[b]
Socioeconomic Status SEIFA, 5 groups, n (%)†			
5 (Highest)	10 (14.1)[ab]	35 (17.2)[a]	1,114 (17.8)[b]
4	15 (21.1)	31 (15.2)	1,343 (21.5)
3	10 (14.1)	47 (23.0)	1,203 (19.2)
2	19 (26.8)	31 (15.2)	1,314 (21.0)
1 (Lowest)	17 (23.9)	60 (29.4)	1,287 (20.6)
Smoking habit, n (%)†			
Non-smoker	50 (71.4)[a]	119 (60.4)[a]	5047 (84.6)[b]
Cigarettes, d			
1-9	6 (8.6)	23 (11.7)	399 (6.7)
10-19	8 (11.4)	40 (20.3)	397 (6.7)
≥20	6 (8.6)	15 (7.6)	122 (2.1)
Breastfed at Discharge from Hospital, n (%)†	55 (77.5)[a]	172 (84.3)[a]	5,638 (89.7)[b]
Child Characteristics‡			
Birthweight for gestational age, n (%)†			
< 10th Percentile (SGA)	7 (14.0)[ab]	24 (17.3)[a]	399 (9.4)[b]
> 90th Percentile (LGA)	5 (10.0)	10 (7.2)	435 (10.2)
Age of Child at Measurement Mean (SD), months	56.4 (4.3)	57.0 (4.1)	56.9 (4.0)
Sex, n (%)†			
Male	38 (53.5)	98 (48.0)	3,213 (51.0)
Female	33 (46.5)	106 (52.0)	3072 (49.0)
Overweight (BMI>85th Percentile), n (%)†			
Male	10 (26.3)	27 (27.6)	905 (28.2)
Female	5 (15.2)	28 (26.4)	877 (28.4)
Underweight (BMI<5th Percentile), n (%)†			
Male	2 (5.3)	4 (4.1)	103 (3.2)
Female	1(3.0)	3 (2.8)	93 (3.0)

SSRI, selective serotonin reuptake inhibitor; BMI, body mass index; SEIFA, socio-economic indexes for areas

† Percentages are calculated from non-missing data

‡ Different superscripts (e.g. a, b) denote a statistically significant difference between groups (P<0.05).

Table 9.2 Risk of childhood overweight at 4-5 years of age following prenatal exposure to selective serotonin reuptake inhibitors and untreated psychiatric illness

	PR (95% CI)		
Sex	SSRI Use vs. Untreated Psychiatric Illness	SSRI Use vs. Unexposed	Untreated Psychiatric Illness vs. Unexposed
Males			
Unadjusted	0.96 (0.51-1.78)	0.93 (0.55-1.60)	0.98 (0.71-1.36)
Model 1[a]	1.22 (0.57-2.62)	0.97 (0.55-1.71)	0.85 (0.56-1.29)
Model 2[b]	1.17 (0.54-2.51)	0.93 (0.52-1.67)	0.85 (0.56-1.28)
Females			
Unadjusted	0.57 (0.24-1.37)	0.53 (0.24-1.19)	0.93 (0.67-1.28)
Model 1[a]	0.25 (0.07-0.90)	0.26 (0.07-0.97)	1.05 (0.73-1.51)
Model 2[b]	0.23 (0.05-0.98)	0.27 (0.07-0.99)	1.09 (0.76-1.57)

SSRI, selective serotonin reuptake inhibitor; PR, prevalence ratio; CI, confidence interval

[a] Model 1: adjusted for maternal age, socioeconomic status, smoking status, race, parity and maternal BMI

[b] Model 2: adjusted for those in model 1 as well as fetal growth and breastfeeding status at discharge from hospital

Table 9.3 Differences in maternal characteristics between those lost and not lost to follow-up

Maternal Characteristics‡	Lost to Follow-up (n=10,191)	Not Lost to Follow-up (n=6,560)
Maternal Age, Mean (SD), y	28.8 (5.8)[a]	29.2 (5.5)[b]
Maternal BMI, Mean (SD), kg/m2	25.0 (5.3)[a]	25.2 (5.3)[b]
Parity ≥1, n (%)†	5,693 (56.3)[a]	3,498 (53.7)[b]
Race Caucasian, n (%)†	8,116 (79.6)[a]	5,709 (87.0)[b]
Socioeconomic Status, SEIFA, 5 groups, n (%)†		
5 (Highest)	2,234 (22.0)[a]	1,159 (17.7)[b]
4	1,990 (19.6)	1,389 (21.3)
3	2,009 (19.8)	1,260 (19.3)
2	1,904 (18.7)	1,364 (20.9)
1 (Lowest)	2,029 (20.0)	1,364 (20.9)
Smoking habit, n (%)†		
Non-smoker	7802 (80.8)[a]	5216 (83.7)[b]
Cigarettes smoked each day		
1-9	824 (8.5)	428 (6.9)
10-19	762 (7.9)	445 (7.1)
≥20	269 (2.8)	143 (2.3)
Breastfed at Discharge from Hospital, n (%)†	8993 (88.2)[a]	5865 (89.4)[b]

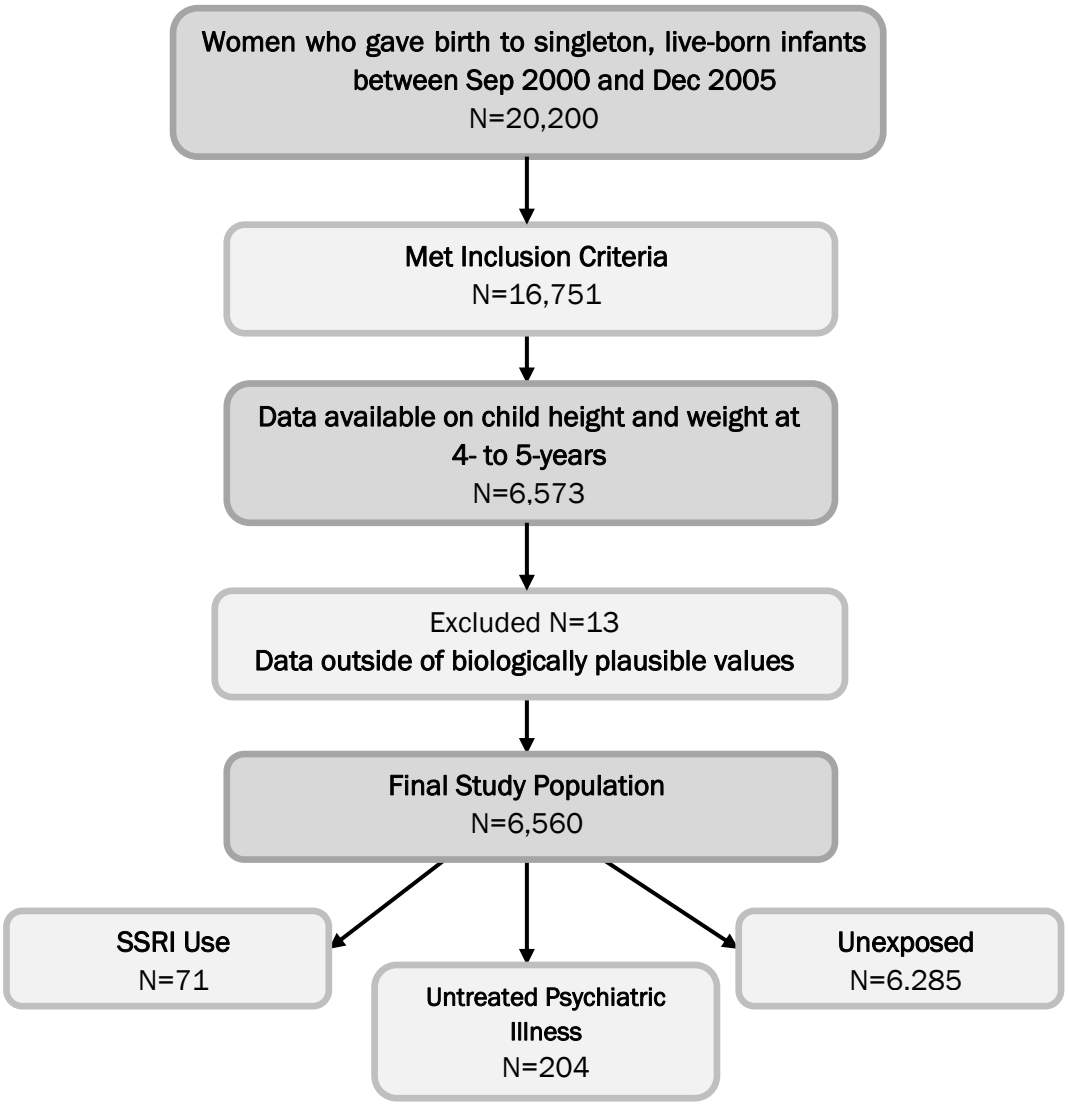
BMI, body mass index, SEIFA, socio-economic indexes for areas

† Percentages are calculated from non-missing data

‡ Different superscripts (e.g. a, b) denote a statistically significant difference between groups (P<0.05)

Figure 9.1 Selection of the study population.

SSRI, selective serotonin reuptake inhibitor



CHAPTER 10

Prenatal SSRI Exposure and Childhood Overweight:

Examined Using Data from a Birth Cohort Study

Manuscript

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Childhood Overweight Following Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Maternal Psychiatric Illness

PLoS ONE; Submitted

10.1 Abstract

Objective: To investigate a possible association between fetal exposure to SSRIs and childhood overweight at 7-years of age.

Methods: Information on pregnancy exposures and prevalence of childhood overweight at 7-years of age was obtained from the Danish National Birth Cohort. Childhood overweight was classified as a BMI>85th percentile, based on age and sex. Of eligible pregnant women, 123 used a SSRI, 467 reported psychiatric illness with no medical treatment, and 35,320 reported no psychiatric illness and no use of psychotropic medication.

Results: In comparison to offspring of women with an untreated psychiatric illness during pregnancy no statistically significant associations were observed between prenatal SSRI exposure and risk of childhood overweight in male (aPR 1.63; 95% CI 0.92-2.88) or female (aPR 0.30; 95%CI 0.08-1.12) offspring. However, for female offspring exposed to untreated maternal psychiatric illness during pregnancy we found a smaller, but statistically significant increased risk of overweight at 7-years of age (aPR 1.55; 1.12-2.15) compared with unexposed children. The association was not found for males (aPR 1.02; 0.71-1.46), which may suggest a sex-specific effect.

Conclusion: We did not find a statistically significant association between prenatal SSRI exposure and childhood overweight at 7-years of age. However, we did find evidence suggesting outcomes may be sex-specific with female, but not male, offspring exposed to untreated maternal psychiatric illness during pregnancy at increased risk of overweight at 7-years of age. Limitations of the present study, including the small number of children exposed to SSRIs, suggest further research in this area may be warranted.

10.2 Introduction

In the United States, use of selective serotonin reuptake inhibitors (SSRIs) during pregnancy has increased dramatically over the last 10-15 years, from 1.5% of all pregnancies in 1996 to 6.4% in 2005.[1] While commonly used to treat depression, SSRIs are also prescribed for other psychiatric disorders, including social anxiety disorder, obsessive compulsive disorder and panic disorder.[2]

Given the importance of serotonin (5-HT) as a neurotransmitter within the central nervous system and its role in neurogenesis, migration and differentiation of neurons in the fetal brain, the potential long-term effects of prenatal SSRI exposure remains an

area of concern.[3-5] Of particular interest are the potential long-term effects of prenatal SSRI exposure on child growth, given the established role of serotonin in brain development and the role of the serotonergic system in regulating food intake and body weight.[6-8]

Animal studies provide evidence that disruption of 5-HT homeostasis during critical periods of fetal development can cause sex-specific alterations in the serotonergic system.[9-14] When serotonergic tone is increased as a result of SSRI exposure, a resultant increase in negative feedback signalling is possible, which may blunt the maturation of the serotonergic system.[15] Thus, altered development of the serotonergic system in early fetal life could potentially modify serotonergic regulation of food intake and body weight in later life, influencing the risk of overweight. Supporting this hypothesis is evidence from animal studies demonstrating that disruption of 5-HT homeostasis *in utero* results in adult-onset obesity in males, but not females.[12,13]

A recent study investigated the effects of prenatal SSRI exposure on childhood overweight at 4- to 5-years of age,[16] finding that female offspring of exposed mothers were less likely to be overweight compared to female offspring of mothers with an untreated psychiatric illness (adjusted Prevalence Ratio [aPR] 0.23; 95% CI 0.05-0.98). No association was observed among male offspring of exposed mothers compared to male offspring of mothers with an untreated psychiatric illness (aPR 1.17; 95% CI 0.54-2.51). These results could reflect a persistent reduction in growth among female offspring as two previous studies, which assessed infant weight gain between 1-6 months of age, demonstrated that infants exposed to SSRIs demonstrate a reduction in mean weight gain compared to controls.[17,18]

Given existing evidence we sought to clarify whether prenatal exposure to SSRIs was associated with risk of overweight in male and female offspring at 7-years of age.

10.3 Methods

This study included mother-child dyads participating in the Danish National Birth Cohort, an ongoing nationwide, follow-up study of pregnant women and their offspring.[19] More than 100,000 pregnant women were recruited from 1996 to 2002, with 60% of invited pregnant women agreeing to participate.

Women were asked to report on medication use during early pregnancy in a self-administered questionnaire. After providing consent, women were interviewed by telephone twice during pregnancy, at 17 and 32 weeks gestation, and twice after pregnancy, when their children were 6 and 18 months old. The cohort has been

described elsewhere.[19] A self-administered questionnaire completed by parents was used to follow-up children at age 7.

Women who gave birth to live singletons were included in the current study if they met the following criteria: signed the original consent form, completed all 4 telephone interviews, and completed the follow-up questionnaire when their child was 7 years old (N=39,327).

We excluded dyads where child height and weight measurements were not recorded (N=2,395) or were outside of biologically plausible values (N=83), based on predefined criteria. In addition, we excluded dyads in which the child's age at follow-up was less than 5 years (N=57), the child was exposed to antidepressants other than SSRIs (N=34) or to other psychotropic medications (anxiolytics, anti-epileptics and antipsychotics) during gestation (N=394), or whose mothers had diabetes (N=107) or gestational diabetes (N=347), leaving a final study population of 35,910 mother-child dyads.

Use of SSRIs was defined as self-reported use of any drugs in World Health Organization-defined Anatomic Therapeutic Chemical Classification System[20] group N06AB during pregnancy. Information on drug use was coded either using predefined names or in a text string recorded by the interviewer and later coded for analysis by the investigators. SSRI exposure was classified for each of the 3 trimesters.

Presence of a psychiatric illness during pregnancy was identified based on questions asked at the 2 prenatal interviews. In the first interview women were asked: (1) Have you ever suffered from a mental disorder or neurosis? (2) Did you see a medical doctor or psychologist for the disorder? (3) What was the name of the disorder? and (4) Have you experienced symptoms of the disorder during pregnancy? In the second interview women were asked whether they had experienced a psychiatric illness during pregnancy; if they had, they were asked to disclose the diagnosis.

The primary outcome measure was childhood overweight at 7 years of age. The secondary outcome measure was Body Mass Index (BMI)-for-age z-scores. BMI (weight/(height(m)^2) was calculated based on parents' self-report of their child's height and weight. Child age at follow-up ranged from 5-8 years. BMI-for-age percentiles and BMI-for-age z-scores (BMI-z) were calculated using the Centres for Disease Control and Prevention SAS Program (CDC, Atlanta, GA) designed for this purpose. International cut-off scores were utilized to define overweight, *i.e.*, a BMI at or exceeding the age- and sex-specific 85th percentile.[21] BMI-z was expressed as a continuous variable. Information on maternal age, employment status, parity, prenatal exposure to alcohol and smoking, coffee intake and pre-pregnancy weight and height was obtained from the first prenatal

interview. Parity was categorised as either primiparous (0) or multiparous (1-8th previous births). Smoking was categorised according to number of cigarettes smoked on average each day (none, 1-10 cigarettes and >10 cigarettes per day). Maternal pre-pregnancy BMI was coded into three categories (<25; ≥25 to <30, and ≥30). Information on gestational weight gain and maternal postpartum distress was obtained from the first postnatal interview. Gestational weight gain was categorised as low, normal, or high based on the 2009 U.S. Institute of Medicine recommendations for gestational weight gain for singleton pregnancies.[22] Information on breastfeeding and paternal height and weight was obtained from the second postnatal interview. Breastfeeding was categorised as breastfed <1 month (including no breastfeeding), 1-4 months and ≥4 months. Paternal BMI was coded in the same manner as maternal BMI. Maternal pre- and postnatal distress was assessed using 9 questions, which asked mothers about feelings of anxiety, depression and stress. Possible responses included; "no", "a little" or "a lot" (forming a 3-point Likert scale) and were coded as follows "no" =1, "a little"=2, and "a lot"=3. The scores from the nine questions were summed together and treated as a continuous variable.

Statistical analyses were performed using Stata 9.2 (Stata, College Station, TX) and SAS version 9.2 (SAS Institute, Cary, NC). We used 1-way analysis of variance, the Wilcoxon rank-sum test, or Fisher's exact test to estimate group differences in baseline characteristics. We compared rates of overweight in the 3 exposure groups using a generalised linear model (Poisson distribution) with robust variance estimates, yielding prevalence ratios (PRs) for the effect estimate and 95% confidence intervals (CIs). In a secondary analysis we examined differences in BMI-z scores between the groups using multiple linear regression analysis. We also used multiple linear regression to assess differences in BMI-z scores after stratification according to timing of SSRI exposure. Statistical significance was defined as a 2-sided *P* value of 0.05.

We used causal diagrams (directed acyclic graphs) to guide selections of potential covariates for which to control.[23,24] In the first model we included the following covariates: smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress and paternal BMI. In the second adjusted model, we included additional covariates: weight gain during pregnancy, breastfeeding and maternal postnatal distress score. We further stratified analyses according to sex due to the possible presence of effect measure modification. Interactions between SSRI exposure and other covariates were investigated in relation to the outcome, but no interactions in the multiplicative model were found. The sample size did not allow for stratification according to individual SSRI type.

The Danish Data Protection Agency and the Institutional Board Committee of the DNBC approved this study, together with the Human Research Ethics Committee at the University of South Australia.

10.4 Results

Of the mother-child-dyads with follow-up data on weight and height (n=35,910), 123 (0.34%) mothers reported taking a SSRI during pregnancy (exposed), 467 (1.30%) mothers reported a psychiatric illness but no use of psychotropic medication (untreated psychiatric illness), and 35,320 (98.36%) mothers did not report taking psychotropic medications or having a psychiatric illness during pregnancy (unexposed) (Table 1).

Compared to women with untreated psychiatric illness, exposed women were more likely to have partners with a lower BMI and to have a lower prenatal distress score (Table 1). Compared to unexposed women, exposed women were more likely to have had partners with a lower BMI, to have gained more weight during pregnancy, to have had higher prenatal distress scores, and to have breastfed for a shorter time. Women with an untreated psychiatric illness were younger, had a higher BMI, and breastfed for a shorter time, compared with unexposed women. Exposed women or women who had an untreated psychiatric illness were more likely to be unemployed, smoke during pregnancy, and have a higher postnatal distress score, compared to unexposed women. Sex and age of the children at follow-up did not differ significantly between groups.

When examining the risk of childhood overweight among male and female infants exposed to SSRIs, we observed an increased risk among males compared to females (PR 2.58; 95% CI 0.99-6.75). While not statistically significant, this was suggestive of possible effect measure modification according to infant sex.

No statistically significant differences in overweight or BMI-z scores were observed among exposed female offspring (Table 2 and Table 3). However, female offspring of mothers with an untreated psychiatric illness were more likely to be overweight than female offspring of unexposed mothers (PR 1.54; 1.08-1.94), and were more likely to have an elevated BMI-z score (0.16; 95% CI 0.03 to 0.29). Both findings remained significant in adjusted analyses (aPR 1.55; 95% CI 1.12-2.15 and BMI-z score 0.21; 95% CI 0.06 to 0.36).

In contrast to females, male offspring of exposed mothers were more likely to be overweight than those of unexposed mothers (PR 1.75; 95% CI 1.10-2.78), but this finding did not remain statistically significant in adjusted analyses (aPR 1.45; 95% CI 0.93-2.28). There was no observed effect on the risk of overweight (PR 1.21; 95% CI

0.89-1.64) or on BMI-z score (0.04; 95% CI -0.09 to 0.17) in male offspring of mothers with an untreated psychiatric illness compared to male offspring of unexposed mothers.

When we stratified the data according to the timing of exposure to an SSRI during pregnancy (Table 3), the greatest reduction in BMI-z scores was observed following second/third trimester exposure in female offspring. No statistically significant associations were observed in male infants.

10.5 Discussion

We found no clear association between prenatal SSRI exposure and risk of childhood overweight and elevated BMI-z scores in offspring at 7-years of age. However, we found evidence of possible effect measure modification according to infant sex.

The sex-specific outcomes observed in this study are consistent with the literature. There are known sex variations in human brain development and function, including differences in the serotonergic system.[25,26] For example, male 5-HTT knock-out mice develop late-onset obesity,[12,13] while females are protected from this effect. While the mechanism underlying sex-specific differences is poorly understood, it has been hypothesised that observed differences could be related to sex hormones (i.e. oestrogen),[13] as there is evidence that oestrogen can influence serotonin system function.[11,27] Furthermore, female mice exposed to prenatal maternal stress display significantly higher basal and stress-induced plasma corticosterone levels as well as reductions in the density of hippocampal corticosterone receptors, compared to non-stressed controls.[28-30] These sex-specific differences may be associated with reductions in placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity, which has been associated with reduced fetal growth and higher cortisol concentrations in the umbilical vein of female, but not male, offspring of mothers with untreated asthma.[31]

It is important to note that the risks associated with adverse exposures during fetal life may be modulated by the postnatal environment. This has also been demonstrated to be sex-specific, with quality of maternal care in the early postnatal period shown to influence hippocampal volume in adulthood in females, but not males.[32] Therefore, differences in postnatal maternal care between those with treated and untreated psychiatric illness could play an important role in determining risk of disease in later life.

We observed an association between untreated psychiatric illness during pregnancy and increased risk of overweight in female offspring at 7-years of age. This finding is important, as it suggests that maternal psychiatric illness during pregnancy may be a risk factor for childhood overweight in female offspring, and that treatment with SSRIs

could counteract that increased risk. A further interesting finding was that when analysing BMI-z score according to timing of SSRI exposure, the greatest reductions were observed among females who were exposed throughout pregnancy or during the second and/or third trimester. This could suggest that adequate treatment during these time periods is important for reducing the negative impacts of untreated psychiatric illness on offspring health outcomes in later life. This hypothesis, however, requires further investigation in an independent and large data source.

This study has a number of strengths compared to our previous study,[16] which identified an association between prenatal SSRI exposure and a decreased risk of overweight among female, but not male, offspring at 4- to 5-years of age. The current study included more detailed data on the use of SSRIs and other psychotropic medications during pregnancy and more detailed assessment of potentially confounding maternal and infant covariates including prenatal stress score, weight gain during pregnancy, paternal BMI and duration of breastfeeding.

Taken together, current evidence suggests that prenatal SSRI exposure is associated with a reduction in weight gain in the first 6 months of postnatal life in males and females.[17,18] Among female offspring, this effect appears to persist until 4- to 5-years of age, where they are at reduced risk of being overweight[16], but is no longer apparent by 7-years of age. In contrast, male offspring are not at risk of overweight at 4- to 5-years of age,[16] but may be at increased risk of overweight at 7-years of age and beyond. Further research is required to clarify these findings and provide longer term follow-up of outcomes.

A major strength of this study is inclusion of women with untreated psychiatric illness during pregnancy. In addition to effects on the serotonergic system, exposure to maternal stress during gestation has been demonstrated to adversely affect development and regulation of the HPA axis.[33,34] Maternal stress during pregnancy increases circulating levels of glucocorticoids, which can enter the fetal circulation and down-regulate central glucocorticoid receptors in the hippocampus. This leads to reduced feedback inhibition and an overactive HPA axis, resulting in increased cortisol secretion in the basal state and in conditions of stress.[35,36] This has a number of important implications for metabolic function in later life, as overactivity of the HPA axis has been associated with a range of cardio-metabolic outcomes in later life, including hypertension, impaired glucose tolerance, insulin resistance and obesity.[37,38]

Notably, a recent human study demonstrated that exposure to prenatal stress (related to maternal bereavement immediately prior to pregnancy) is associated with increased

risk of overweight in offspring later in childhood.[39] Importantly, the increased risk of overweight was only observed in offspring after 10- years of age, indicating the need for long-term follow-up when examining effects of fetal programming. That study did not include stratification of data by sex, and it was not clear how many women, if any, were taking SSRIs during pregnancy.

A limitation of this study was the inability to generate precise risk estimates and to adjust for a number of potential confounders and/or covariates due to the small number of infants exposed to SSRIs during pregnancy. This is reflective of the low prevalence of SSRI use in Denmark, which has been reported in other studies.[40,41] Therefore, while this study did not find a significant association between prenatal SSRI exposure and childhood overweight, it is not possible to rule out an association. For example, this study had 80% power to detect a 2.2 fold increased risk of overweight among male offspring with prenatal SSRI exposure, meaning a smaller increased risk cannot be ruled out.

A further limitation was that not all women in the DNBC completed all 4 telephone interviews and the questionnaire when their child was 7-years of age, a possible source of selection bias. However, when we compared incomplete data from partial responders with estimates from the main analysis based on complete data, we found no evidence of selection bias. We had no data on non-responders. It is possible that some women did not accurately report taking a SSRI during pregnancy. However, since information on medication use was collected prospectively, any exposure misclassification was most likely non-differential, in most cases leading to a bias toward no association. Since participants and interviewers were not blinded, information bias could have occurred if exposure status was associated with systematic errors in reporting weights and heights. However, as the study data were extracted from the database of a large cohort study, neither the women nor the interviewers were aware of the specific aim of our study.

The lack of inclusion of data on postnatal factors such as the child's diet, energy intake and physical activity constitutes a study limitation. However, these factors lie in the predicted pathway between prenatal SSRI exposure and childhood overweight, given the involvement of the serotonergic system in the regulation of appetite (which influences energy intake[6-8]) as well as motor control (which influences physical activity in later life[42]). Adjustment for such factors may thus mask a causal association.

10.6 Conclusion

We did not find a statistically significant association between prenatal SSRI exposure and childhood overweight at 7-years of age. However, we did find evidence suggesting outcomes may be sex-specific with female, but not male, offspring exposed to untreated maternal psychiatric illness during pregnancy at increased risk of overweight at 7-years of age. Limitations of the present study, including the small number of children exposed to SSRIs, suggest further research in this area may be warranted. It is also important for future research to examine other potential long-term effects associated with prenatal SSRI exposure and the role of infant sex on those outcomes.

10.7 References

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Table 10.1 Characteristics of participants in each of the three comparison groups from the Danish National Birth Cohort, 1996-2002

Characteristic	SSRI Use (n=123)	Untreated Psychiatric Illness (n=467)	Unexposed Group (n=35,320)
Maternal Age, mean ± SD, years	30.4 (4.1)[ab]	29.8 (4.6)[a]	30.2 (4.2)[b]
Maternal BMI, n (%)†			
<25 kg/m²	88 (71.5)[ab]	314 (68.0)[a]	25,882 (73.7)[b]
≥25 & <30 kg/m²	22 (17.9)	108 (23.4)	6,658 (19.0)
≥30 kg/m²	13 (10.6)	40 (8.7)	2,587 (7.4)
Paternal BMI, n (%)†			
<25 kg/m²	65 (68.4)[a]	183 (52.1)[b]	15,510 (55.0)[b]
≥25 & <30 kg/m²	26 (27.8)	135 (38.5)	10,858 (38.5)
≥30 kg/m²	4 (4.2)	33 (9.4)	1,830 (6.5)
Weight Gain During Pregnancy, n (%)†			
Low	30 (24.6)[a]	85 (18.7)[ab]	5,767 (16.6)[b]
Normal	31 (29.4)	157 (34.6)	13,332 (38.3)
High	61 (50.0)	212 (46.7)	15,723 (45.2)
Parity			
≥1, n (%)†	68 (55.3)	268 (57.4)	18,924 (53.6)
Unemployed, n (%)†	34 (27.6)[a]	102 (21.8)[a]	3,413 (9.7)[b]
Smoking Status, n (%)†			
Non Smoker	76 (61.8)[a]	322 (69.0)[a]	28,494 (80.7)[b]
Smoker			
1-10 cigarettes per day	33 (26.8)	93 (19.9)	5,110 (14.5)
>10 cigarettes per day	14 (11.4)	52 (11.1)	1,714 (4.9)
Breastfeeding, n (%)†			
< 1 month	12 (9.8)[a]	46 (9.9)[a]	1,893 (5.4)[b]
1-4 months	27 (22.0)	87 (18.6)	4,209 (11.9)
≥4 months	84 (68.3)	334 (71.5)	29,189 (82.7)
Prenatal Distress Score, mean ± SD	14.2 (3.9)[a]	16.0 (4.0)[b]	11.6 (2.4)[c]
Postnatal Distress Score, mean ± SD	13.7 (4.1)[a]	14.1 (4.0)[a]	11.1 (2.6)[b]
Age of Child at Measurement, mean ± SD, months	84.1 (4.5)	84.6 (3.2)	84.5 (3.4)
Child Sex			
Male, n (%)†	64 (52.0)	237 (50.8)	18,129 (51.3)
Overweight (BMI>85th Percentile), n (%)†			
Male	14 (21.9)	36 (15.2)	2,272 (12.5)
Female	5 (8.5)	38 (16.5)	1,959 (11.4)
BMI-z Score, mean ± SD			
Male	0.09 (1.00)	-0.04 (1.16)	-0.08 (1.03)
Female	-0.16 (1.08)	0.06 (1.00)	-0.10 (1.00)

† Percentages are calculated from available (non-missing) data.

‡ Different superscripts (*e.g.* a, b) denote a statistically significant difference between groups ($p<0.05$).

Table 10.2 Risk of childhood overweight at 7-years of age following fetal exposure to selective serotonin reuptake inhibitors and maternal untreated psychiatric illness

	PR (95% CI)		
	Maternal SSRI Use vs. Untreated Psychiatric Illness	Maternal SSRI Use vs. Unexposed	Maternal Untreated Psychiatric Illness vs. Unexposed
All			
Unadjusted	0.97 (0.61-1.55)	1.29 (0.85-1.95)	1.32 (1.07-1.63)
Model 1[a]	0.93 (0.57-1.52)	1.17 (0.76-1.82)	1.22 (0.96-1.56)
Model 2[b]	0.91 (0.56-1.48)	1.18 (0.76-1.83)	1.25 (0.98-1.59)
Stratified According to Sex			
Males			
Unadjusted	1.44 (0.83-2.50)	1.75 (1.10-2.78)	1.21 (0.89-1.64)
Model 1[a]	1.62 (0.91-2.88)	1.44 (0.93-2.24)	0.99 (0.70-1.41)
Model 2[b]	1.63 (0.92-2.88)	1.45 (0.93-2.28)	1.02 (0.71-1.46)
Females			
Unadjusted	0.51 (0.21-1.25)	0.74 (0.32-1.72)	1.45 (1.08-1.94)
Model 1[a]	0.28 (0.07-1.08)	0.50 (0.13-1.95)	1.54 (1.11-2.13)
Model 2[b]	0.30 (0.08-1.12)	0.50 (0.13-1.93)	1.55 (1.12-2.15)

SSRI, selective serotonin reuptake inhibitor; PR, prevalence ratio; CI, confidence interval

Model 1: PR adjusted for smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress and paternal BMI

Model 2: PR adjusted as in Model 1 and also for weight gain during pregnancy, breastfeeding and postnatal distress

Table 10.3 Linear regression coefficients for BMI-z score at 7-years of age following fetal exposure to selective serotonin reuptake inhibitors and maternal untreated psychiatric illness

	Regression estimate (95% CI)		
	Maternal SSRI Use vs. Untreated Psychiatric Illness	Maternal SSRI Use vs. Unexposed	Maternal Untreated Psychiatric Illness Vs. Unexposed
All			
Unadjusted	-0.04 (-0.26 to 0.17)	0.06 (-0.12 to 0.24)	0.10 (0.08 to 0.19)
Model 1[a]	-0.04 (-0.28 to 0.21)	0.05 (-0.15 to 0.25)	0.06 (-0.05 to 0.17)
Model 2[b]	-0.05 (-0.29 to 0.20)	0.06 (-0.14 to 0.26)	0.06 (-0.04 to 0.17)
Stratified According to Sex			
Males			
Unadjusted	0.13 (-0.18 to 0.45)	0.17 (-0.08 to 0.43)	0.04 (-0.09 to 0.17)
Model 1[a]	0.20 (-0.17 to 0.57)	0.05 (-0.22 to 0.33)	-0.09 (-0.24 to 0.06)
Model 2[b]	0.21 (-0.17 to 0.59)	0.07 (-0.21 to 0.34)	-0.07 (-0.22 to 0.08)
Females			
Unadjusted	-0.23 (-0.53 to 0.06)	-0.07 (-0.32 to 0.19)	0.16 (0.03 to 0.29)
Model 1[a]	-0.26 (-0.57 to 0.06)	0.03 (-0.27 to 0.32)	0.22 (0.07 to 0.37)
Model 2[b]	-0.21 (-0.53 to 0.12)	0.04 (-0.26 to 0.33)	0.21 (0.06 to 0.36)

SSRI, selective serotonin reuptake inhibitor; BMI, body mass index; CI, confidence interval
Model 1: PR adjusted for smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress and paternal BMI
Model 2: PR adjusted as in Model 1 and also for weight gain during pregnancy, breastfeeding and postnatal distress

Table 10.4 Linear regression coefficients for BMI-z score at 7-years of age according to timing of fetal selective serotonin reuptake inhibitor exposure

	BMI z-score regression estimate (95% CI) Maternal SSRI Use vs. Untreated Psychiatric Illness		
	Unadjusted	Model 1[a]	Model 2[b]
Exposure at any point during pregnancy			
Males	0.13 (-0.18 to 0.45)	0.20 (-0.17 to 0.57)	0.21 (-0.17 to 0.59)
Females	-0.23 (-0.52 to 0.06)	-0.26 (-0.57 to 0.06)	-0.21 (-0.53 to 0.12)
First-trimester exposure only			
Males	0.34 (-0.10 to 0.77)	0.34 (-0.17 to 0.84)	0.37 (-0.15 to 0.90)
Females	0.03 (-0.29 to 0.36)	-0.01 (-0.38 to 0.36)	0.02 (-0.36 to 0.41)
Second/Third trimester exposure			
Males	-0.06 (-0.47 to 0.36)	0.02 (-0.46 to 0.51)	0.04 (-0.45 to 0.54)
Females	-0.88 (-1.38 to -0.37)	-0.71 (-1.21 to -0.21)	-0.62 (-1.13 to -0.11)

SSRI, selective serotonin reuptake inhibitor; BMI, body mass index; CI, confidence interval
Model 1: PR adjusted for smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress and paternal BMI
Model 2: PR adjusted as in Model 1 and also for weight gain during pregnancy, breastfeeding and postnatal distress

CHAPTER 11

Using Routinely Collected Health Data to Examine Long-Term Outcomes: Opportunities and Challenges

Manuscript

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Using Routinely Collected Health Data to Investigate Long-Term Effects of Medication Use During Pregnancy – Opportunities and Challenges

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11.1 Abstract

Objective: The objective of this review was to identify and explore opportunities and challenges associated with using routinely collected health data to examine long-term effects of medication use during pregnancy.

Approach: Firstly, a literature review was undertaken to examine local and international experience with using routinely collected health data and to identify key challenges associated with its use in examining long-term effects of medication use during pregnancy. Secondly, a review of all Australian data linkage centres was undertaken to identify available sources of routinely collected health data that could potentially be used to investigate the long-term effects of medication use during pregnancy.

Conclusion: While there are significant opportunities to utilise routinely collected health data in Australia to investigate long-term effects of medication use during pregnancy, there are also a number of key challenges. Identified challenges relate to aspects of study design and analysis and include obtaining access to data, the ability to match records across datasets and over long periods of time, how medication exposures are ascertained and classified, issues around loss to follow-up, how outcomes are ascertained and classified and the careful interpretation of results in light of study and data limitations.

Implications: Understanding key challenges associated with using routinely collected health data to investigate long-term effects of medication use during pregnancy is essential in supporting their appropriate use and interpretation, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained.

11.2 Introduction

The frequent exclusion of pregnant women from randomised controlled trials places a heavy reliance on observational studies to gather evidence on any associated risks and benefits of medication use during pregnancy. To date, the investigation of teratogenic effects of medications has largely focused on physical alterations (i.e. malformations) as opposed to functional alterations (i.e. neurodevelopment, metabolic function) that may not be apparent at birth but could influence an individual's health and risk of disease in later life.

A conceptual framework for understanding the contribution that maternal medication use during pregnancy could have on the health and development of the offspring in later life can be taken from the rapidly emerging and expanding field of the

Developmental Origins of Health and Disease (DOHaD).[1] Through the combination of experimental, clinical, epidemiological and public health research, there is an aim to understand how events in early life influence an individual's susceptibility towards health or disease in later life.[1] While much focus of this research is on early life exposures to factors other than medications (i.e. maternal diet), little is known about the potential long-term effects of medication use during pregnancy. The discovery of an association between the use of diethylstilbestrol during pregnancy and an increased rate of vaginal adenocarcinomas in young women exposed *in utero* is a pertinent reminder of the need for adequate follow-up of all medication exposures during pregnancy.[2] More recently, potential long-term effects following prenatal exposure to other medications have emerged. For example, there is evidence that *in utero* exposure to sodium valproate is associated with an increased risk of impaired cognitive function in the child at 3 years of age[3] and that prenatal antidepressant exposure is associated with an increased risk of autism spectrum disorders[4] and disturbed development of the enteric nervous system[5] in childhood.

While it is recognised that no single approach is sufficient for delineating the complete spectrum of risks or benefits of medication use in pregnancy,[6] the use of routinely collected health data represents one approach to better identifying, quantifying and understanding the long-term risks or benefits of medication use during pregnancy. The major advantage of approach is that data are already available, collected prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and can be linked at the individual patient level.[7] In addition, use of routinely collected health data enables the identification of very large cohorts of women and their offspring, which is particularly useful in assessing infrequent, but clinically important, outcomes.[7] Linkage of existing records is unobtrusive and the routine and prospective manner in which data are collected and recorded in these datasets eliminates recall bias.[7] In addition, as data have already been collected, studies can be undertaken in a more timely and cost efficient manner than is possible with other research design methods. While there are numerous potential benefits in using routinely collected health data, opportunities and challenges associated with its use in examining long-term effects of medication use during pregnancy have not been well described.

11.3 Objective

The objective of this review was to identify and explore opportunities and challenges associated with using routinely collected health data to examine long-term effects of medication use during pregnancy.

11.4 Approach

Firstly, a literature review was undertaken to examine local and international experience with using routinely collected health data. Medline and EMBASE were searched from 1 January 2000 to 15 January 2012 using search terms 'data linkage', 'administrative data', 'linked health data', 'medical record linkage' and 'pharmacoepidemiology'. The original search was not restricted to papers involving medication use during pregnancy, as many challenges were likely to be similar to those faced in other areas of research. This search identified editorials, reviews and original articles, which were critically analysed to identify key challenges associated with using routinely collected health data to examine long-term effects of medication use during pregnancy. Papers subsequently included in this review were those that provided clear examples of each of these defined challenges and those that demonstrate how these challenges can be recognised and addressed when examining the long-term effects of medication use during pregnancy. Secondly, a review of all Australian data linkage centre's was undertaken to identify available sources of routinely collected health data that could potentially be used to contribute towards the investigation of long-term effects of medication use during pregnancy. The data linkage centres were identified through the Australian Population Health Research Network.

11.5 Results

A number of key challenges to using routinely collected health data to examine long-term effects of medication use during pregnancy were identified. These challenges relate to aspects of study design and analysis and include obtaining access to data, the ability to match records across datasets and over long periods of time, how medication exposures are ascertained and classified, issues around loss to follow-up, how outcomes are ascertained and classified and the careful interpretation of results in light of study and data limitations.

11.6 Access to Data

Data security and confidentiality are two important issues associated with the use of routinely collected health data. Importantly, these issues can be addressed and appropriate protocols and procedures are in place in research centres, within Australia (Table 11.1) and internationally, to ensure this type of research can be undertaken in an ethical manner.[9] As such, while ethics approvals and/or data custodian approvals are required to obtain data, they do not prevent appropriately designed and managed projects from using routinely collected health data. Furthermore, a recent review of research outputs from the Western Australian Data Linkage System highlighted not only the enormous amount of research that has been undertaken using linked data, but was also able to demonstrate the public health benefits of this research through resultant improvements in policy and/or practice.[10] Subsequently, it can be argued that we have an ethical obligation to utilise data that has already been collected if it could be used to achieve a greater understanding of the long-term effects of medication use during pregnancy and lead to improved health outcomes for mothers and their offspring.

11.7 Data Linkage

A challenge in undertaking research using routinely collected health data is the ability to link data pertaining to the same individual, in this case mother-child pair, over long periods of time. The data linkage process can be undertaken using either deterministic or probabilistic matching. Deterministic matching is used when records can be linked using a single unique identifier. Unlike Scandinavian countries such as Denmark, unique healthcare/citizen identification numbers are not in use in Australia, meaning linkage must occur using probabilistic matching. Probabilistic matching involves linking records using a number of personal identifiers such as surname, first given name, date of birth, sex and address.[9] The difficulty encountered with longitudinal and cross-generational matching is accounting for changes in name (e.g. through marriage or divorce) or address and any spelling/typographical errors. Additionally, some people may be lost to follow-up as they change their state or country of residency. While growing project experience and advances in computer programming make the linkage of records less of a technical barrier, there is still the need to consider potential factors that may be associated with incomplete data linkage and whether these factors may introduce bias in reported clinical outcomes.[11, 12]

11.8 Exposure Ascertainment and Classification

A recent literature review outlined key methodological issues associated with studies using electronic dispensing data to classify medication exposure during pregnancy.[13] In this review, significant methodological differences were identified across studies. Key factors such as the dose, duration and timing of exposure were inconsistently addressed and there was a great deal of variability in the way medication exposures were classified and how women who stop taking their medication before, or during early pregnancy, are handled in analyses.[13] Further issues identified related to studies not having data on gestational age to determine exact timing of exposure and assumptions regarding how and when women who receive a dispensing for a medication actually take it during pregnancy.[13] This creates a great deal of uncertainty around actual medication exposure during pregnancy, potentially resulting in biased risk estimates.[13] These issues are discussed in more detail below.

11.8.1 Understanding Medication Use Patterns

Before using electronic dispensing data to classify medication exposures during pregnancy it is important to understand medication use patterns. Using SSRIs as an example, studies have demonstrated that up to 40% of women discontinue their SSRI before, or very soon after, finding out that they are pregnant.[14] This is important to understand as it means that up to a third or more of women who receive a dispensing for a SSRI at or around the time of conception may not actually take that SSRI during the pregnancy. Therefore, studies which classify women as exposed if they receive a dispensing in the month prior to conception are potentially subject to misclassification bias, as some women could be misclassified as exposed when they were not actually taking the medication during pregnancy.[13] This bias has the potential to result in an underestimation of the risk associated with medication use in pregnancy.[13]

11.8.2 Timing of Exposure

It is essential that studies investigating outcomes associated with medication use during pregnancy carefully consider and identify exposures occurring during relevant periods of fetal development that are likely to be associated with the outcome of interest. The majority of studies undertaken using routinely collected health data have focused on associations between prenatal medication exposure and congenital malformations. In these cases the critical

periods of exposure have been well studied and defined during the first trimester. In contrast, for studies looking at long-term outcomes (i.e. effects on child neurodevelopment or metabolic function), the critical period of exposure is often not so well defined and may be much wider. Therefore, it is important to have a sound understanding of expected biologically relevant periods of exposure. A significant strength of electronic data available in Australia is that it contains an estimated date of last menstrual period and/or gestational age of the infant at delivery, which is confirmed by antenatal ultrasound. This enables evaluation of outcomes according to timing of exposure.

11.8.3 Caution with dose

A limitation associated with many electronic dispensing datasets is that they only give an indication of the strength of the medication dispensed, but not the dose or frequency of use. This can make it difficult to investigate the effect of dose on various outcomes and the dose-response relationship. Previously, researchers have estimated dose by dividing the amount of medication supplied, by the number of days between each supply.[15] However, while evidence of a dose-response relationship strengthens arguments for establishing causality, relying on estimates of dose may not provide the complete picture. For example, key factors such as individual differences in pharmacokinetics (i.e. due to differences in body weight, concurrent medication use, placental transfer) and pharmacogenomics play important roles in influencing the concentration and effects of fetal exposure to particular medications. As such, the same dose administered to two different individuals may elicit different responses. In many cases these types of data are not available in electronic records and can only be examined further through additional data collection.

11.8.4 Assumptions Regarding Medication Use

The underlying assumption associated with all studies relying on prescription databases is that a dispensing for a medication is actually associated with use of that medication. Non-compliance with medication use may result in misclassification bias, where some of the women classified as “exposed” were in fact not exposed during pregnancy. For example, Olesen et al.,[16] compared reporting of medication use during pregnancy among women enrolled in the Danish National Birth Cohort (DNBC) to the North Jutland Prescription Database (NJPD), for those women living in the North Jutland area. Medications

used for chronic medical conditions (i.e. diabetes, epilepsy, hypothyroidism) were always reported to be used by women (100%), whereas sensitivity was poor for medications used for acute conditions (e.g. 40% for NSAIDs). Overall, sensitivity for use of any medication was 43% (95% CI; 40-46). The additional assumption made when using dispensing data is that the date of dispensing reflects the time at which the medication was taken. This may be an appropriate assumption for medications used for chronic medical conditions, but may not be valid for medications used on an intermittent basis for acute medical conditions.

It is important to note that as long as data on medication exposures during pregnancy are collected without bias, incomplete capture of medication exposure is unlikely to have a significant effect on the final risk estimate.[13, 17] A more significant issue is the need to ensure those who are considered exposed were actually taking the medication during pregnancy, as this can introduce significant bias and alter the final risk estimate.[13] There is a clear need for further research to determine the most effective and accurate way of using routinely collected health data to investigate outcomes following medication use during pregnancy in an effort to minimise potential biases.[13]

Following a sound understanding of the importance of the way in which medication exposures are classified during pregnancy, it is possible to move towards the consideration of various electronic datasets that could be used to identify medication exposures.

11.8.5 Hospital Pharmacy Dispensing Records

Hospital pharmacy dispensing records at the Women's and Children's Hospital in South Australia have previously been validated as an efficient alternative to paper-based medical records in determining late gestation exposure to antidepressants, but they do underestimate exposure by 25%.[18] As a result of this underestimation it is possible that some women who are classified as unexposed and therefore allocated to the control group, were actually exposed to an antidepressant during pregnancy. Incomplete capture of medication exposure was to be expected as women can obtain their medication from community pharmacies outside of the hospital. As previously discussed, however, incomplete capture of medication exposure is unlikely to have a major effect on the calculated risk estimates, as long as exposure is identified without bias.

A major limitation associated with using hospital pharmacy dispensing records is that it is only useful for identifying late gestation exposures, and does not adequately identify women who were exposed to a medication during the first trimester and subsequently stopped taking it during pregnancy. As such, these records are only suitable for generating a cohort of women where exposure has occurred during late gestation.[18] This, however, can still serve a useful research purpose in investigating outcomes associated with medication use during pregnancy. For example, in the case of antidepressants, as less than 15% of women commence an antidepressant during late gestation,[19] women identified as exposed during late gestation are likely to have been exposed for a significant portion of the pregnancy. Therefore, late gestation exposure is likely to reflect chronic medication use in pregnancy.

While the hospital pharmacy dispensing records were specifically validated as an indicator of late gestation exposure to antidepressants,[18] data were also collected on other medications. After comparing data on medication use according to each woman's medical case notes and the hospital pharmacy dispensing records, sensitivity (women correctly identified as exposed) was highest for medications used on a chronic basis such as anti-diabetics (88%), anti-epileptics (75%) and thyroid hormones (67%). In contrast, medications used on an acute basis (i.e. asthma relievers) had a much lower sensitivity (10%), indicating that hospital pharmacy dispensing records are of little use in identifying exposures to these types of medications.

Overall, electronic hospital pharmacy dispensing records appear to be a useful alternative to paper-based medical records for pharmacoepidemiological research, as long as researchers are clear about when it is appropriate to use them as an indicator of exposure during pregnancy. Notably, if one were only interested in exposures which occurred at a specific time during pregnancy, especially during the first trimester, alternative data sources would be required. The most obvious alternative source of Australian data on medication use during pregnancy comes from the pharmaceutical benefits scheme (PBS) claims database.

11.8.6 Pharmaceutical Benefits Scheme (PBS) Data

Researchers in Western Australia have recently linked electronic PBS claims data with other population-based health datasets, enabling them to investigate the effects of medication use in pregnancy.[20] While this is a significant

advancement towards improved data collection and analysis of medication use in pregnancy, there are current limitations associated with its' use in Australia. The key limitation of PBS data is the potential for under-ascertainment of medication exposures. Currently, medications dispensed through the PBS, where the Australian government subsidises prescription medications for residents to ensure affordable and reliable access, are only electronically recorded if the government is required to pay a subsidy. That means data are only recorded if the cost of the dispensed medication is greater than the maximum specified cost to the consumer, known as the co-payment level. Based on the PBS co-payment levels for 2012, individuals with a concession card are required to pay up to $5.80, while those without a concession card are required to pay up to $35.40. This results in under-ascertainment of medication exposures in situations where medications are dispensed below the co-payment level.[20] In recognition of this long-standing issue, the Australian government has recently introduced legislative changes which, from 1 April 2012, will require electronically recorded data be collected on all PBS medications dispensed, including those priced below the general co-payment level.

Importantly, the electronic capture of additional prescription data will only begin after the 1 April 2012, and will not include medications which have been dispensed prior to this date and have fallen below the patient co-payment. Therefore, in planning studies it is important to be aware of the times when medications under investigation were above and below the concession and general co-payment levels, as this will influence the ability to capture exposure data. Furthermore, selection bias may be an issue if incomplete ascertainment differs between those with and without a concession card.

11.9 Losses to Follow-Up

One significant issue affecting traditional prospective cohort studies is the difficulty in following individuals over long periods of time. High attrition rates during a study can lead to bias if there are systematic differences between those lost and not lost to follow-up. Studies undertaken using linked data have the potential to minimise the potential for follow-up bias by reducing the need to actively follow-up individuals over time, which is costly and time consuming. In true population based studies there are in essence no losses to follow-up, instead only failures in linking records. For example, if one were interested in investigating the association between prenatal medication use

and risk of cancer in the offspring in later life then it would be possible to utilise data collected in the South Australian Cancer Registry. In this case it is stipulated by South Australian law that all cancer events (i.e. diagnosis and/or death) are reported to the registry. Therefore, one would be confident that this dataset would contain relatively complete follow-up data for all South Australian residents. The underlying assumption made in this situation is that if an individual does not appear in the registry, they did not have a cancer related event (i.e. relies on completeness of that data source).

The challenge presents when utilising datasets that do not contain data for the entire population. For example, in a previous study we utilised electronic data from South Australia's Women's and Children's Health Network (WCHN) Child Health Records collected during preschool health checks.[21] From an initial cohort of 20,200 children, who were born between September 2000 and December 2005, follow-up data were only able to obtained for 7,878 (39%) children. From 1997 through 2007, the period of child follow-up in this study, the average participation rate was approximately 65% of South Australian children.[22] In this situation it is important to consider and explore potential explanations for loss to follow-up and whether it is possibly due to difficulties in linking records, or is subject to bias as a result of factors which are associated with individuals receiving and not receiving a preschool health check.

11.10 Outcome Ascertainment and Classification

The major limitation associated with routinely collected health data is that they were never collected with the intention of being used for research purposes. Therefore, one must be clear that the data available and the way in which outcome data are classified are relevant in answering the research question.

For example, in a previous study we were interested in the effects of prenatal SSRI exposure on growth and body weight of the offspring in later life.[21] In order to assess growth and body weight we used data collected from South Australia's WCHN (previously called Children, Youth and Women's Health Service and Child and Youth Health) Child Health Record. The WCHN provides a range of health and social services and programs for parents, children, and young people across the state. As part of these services, child and family health nurses have performed health checks on 4- to 5-year-old children at all kindergartens and preschool centres since 1995. During these visits they use a standard protocol to measure each child's height and weight which is recorded electronically. Given the routine and systematic manner in which these data are collected, confidence could be placed around their use for this study, with heights and weights used to calculate BMI-for-age percentiles to assess childhood

overweight. The obvious limitation in relying on this data as a measure of differences in child growth and body weight is that BMI is a relative indicator of weight, and does not differentiate between lean body mass and adiposity. Therefore, if one were more interested in the distribution of body mass and other measures of body weight, than they would require additional anthropometric data such as waist circumference, waist to hip ratio and tricep and subscapular skinfolds for example. These types of additional anthropometric data are only available from purpose built prospective cohort studies. In this case, the routinely collected data on height and weight can be used to identify potential signals for associations between prenatal medication exposure and effects on child growth and body weight which could then be investigated further in a prospective cohort study if necessary. Following the identification of a need for additional data there is also the potential to make policy recommendations that additional data, apart from just height and weight, be collected during these visits (i.e. use of scales that measure fat mass) to assist with future research endeavours.

When identifying outcomes of interest in inpatient or outpatient medical records, it is possible to utilise the World Health Organisation's (WHO) International Classification of Diseases (ICD), which is the international standard diagnostic classification system for all diseases and other health problems. Importantly, if coded outcomes are utilised, it is important to assess the correlation between coded outcomes and actual medical outcomes. For example, Davis et al.,[21] investigated the risk of congenital malformations among infants exposed prenatally to antidepressants. They utilised standard ICD codes to identify infants with a reported congenital malformation. Of 7 infants identified as having limb malformations, case notes were obtained and reviewed for 4. In 1 case the infant had no reported limb malformation, highlighting the potential limitations associated with relying on coded outcome data. In contrast, Croen et al.,[5] investigated the association between antidepressant use during pregnancy and childhood autism spectrum disorders (ASD). Prior to this study they undertook clinical evaluations for a sample of 50 children who had an ICD code indicative of an ASD. Using the Autism Diagnostic Interview-Revised and the Autism Diagnostic Observation Schedule-Generic, 94% of children met criteria for an ASD on both instruments, and 100% met criteria on at least one. Therefore, in order to improve the reliability of studies using routinely collected health data it is essential to consider the validity of the outcome date utilised, and this may necessitate the need for validation studies prior to the main study being undertaken.

When relying on previously coded data to ascertain outcomes it is important to be aware of how the coding of data may have changed over time. For example, the ICD codes are approaching their 11th revision, so it is important to identify any changes

that may have occurred over time and whether these could influence outcome ascertainment, especially for studies which are comparing or including subjects over long periods of time. Even local datasets, such as pregnancy outcomes statistics, can change over time making it essential to identify periods of time where pertinent data may not have been collected or where it may have been collected and recorded in a different manner to other years. Furthermore, when relying on routinely collected data it is important to remember that in these cases data are not being collected according to pre-defined criteria which would remain consistent across a prospective cohort study. In real-life the criteria can change over time to reflect the needs and requirements of the organisation collecting the data.

An overview of electronic datasets available in Australia (either state-based or national) and their potential uses and contribution towards investigating long-term outcomes associated with medication use during pregnancy is presented in Table 11.2. At present there is immense potential and opportunity to investigate long-term outcomes associated with medication use during pregnancy, much of which is just starting to be realised.

Each of these electronic datasets has enormous research potential, but they also have limitations to be aware of. Many of these limitations only become apparent after careful consideration and in-depth review of each dataset. For example, in South Australia, data from the National Assessment Program – Literacy and Numeracy (NAPLAN) can only be linked via the public school enrolments dataset produced by the Department of Education and Children's Services. This means data on individuals in private schools cannot be linked to other datasets at this point in time and the effects of this need to be considered when designing a cohort study using this dataset. Understanding such limitations is essential for researchers who want to utilise these data. In recognition of this, data linkage centres such as SA-NT DataLink, are developing Data Quality Statements for available datasets (see www.santdatalink.org.au/available_datasets for examples). The Data Quality Statement for each dataset will cover such information as the purpose of the data collection, population coverage (i.e. who is and who is not included in the data collection), reference period (i.e. how far back does data collection go), accuracy of data collected and reference to validation studies (if any available), and links to a data dictionary which describes all of the data available for linkage. These data quality statements will become an essential tool for researchers wanting to quickly evaluate the potential usefulness and limitations of various datasets in investigation long-term effects of medication use during pregnancy.

11.11 Interpretation of Results

The most important factor to consider when designing or interpreting a study which utilises routinely collected health data is that the original data were never collected with the intention of being used for research purposes. Therefore data on important confounders and/or risk factors are often missing and study findings must be interpreted in their absence. Even if important pieces of data have been collected, the quality and reliability of such could be questionable unless they have been previously validated.

11.11.1 Precision and Validity

Precision can be defined as the absence of random error.[24] The larger the sample size, the higher the statistical power, and the narrower the associated confidence interval (i.e. precision). This raises a number of issues. The first is the importance of not confusing precision with validity, as an estimate that has high precision is not necessarily one that is valid. The second is the need to be clear about separating statistically significant differences from clinically significant differences. High statistical power associated with large sample sizes makes it easier to establish even the smallest of statistically significant differences, but these differences may not be of any clinical relevance. There is also the need to be aware of the potential for finding unexpected or spurious associations, especially when working with very large datasets and looking at multiple outcomes. One must be cautious in interpreting unusual or unexpected results as they may be due to chance, but they may also represent the first evidence of harm or benefit associated with the exposure under investigation.[25]

In contrast to precision, validity can be defined as the absence of systematic error.[24] Validity is related to the confidence that can be placed on the inference drawn from a study after taking into account study methods, representativeness of the sample studied, and the nature of the population from which the sample was drawn. As such, study validity consists of two facets; internal and external validity. Internal validity relates to whether the groups being compared have been selected and measured in a manner that allows the results generated to be considered a good approximation of the truth. Threats to internal validity include the inability to identify and address potential sources of bias and/or confounding. External validity relates to whether the way in which the sample included in the study were selected and

described is sufficient such that the results generated can be applied and/or generalised outside of the study sample. Threats to external validity come from the selection and sampling of subjects for a study. There is often a trade off between internal and external validity, where restriction by use of strict inclusion/exclusion criteria may assist in improving internal validity, but at the same time reduce external validity.

It is important to point out that the use of health data can have benefits in relation to improving external validity. Through the presence of data across a population, it is possible to investigate outcomes amongst particularly vulnerable patient groups that would otherwise not be included in traditional prospective studies. For example, there may be many groups of women who choose not to participate in prospective studies (i.e. low socioeconomic status, mental health illness) or are commonly excluded, but these vulnerable groups could be included and studied in population-based datasets.

11.11.2 Confounding

As available data are limited to that which is routinely collected, studies using routinely collected health data are likely to face limitations associated with the absence of data on important confounders and/or risk factors of interest. For example, missing data on non-prescription medication use (i.e. complementary medicines and other medicines purchased without a prescription from the pharmacy or supermarket), maternal factors (i.e. alcohol use, substance use, diet during pregnancy), child factors (i.e. diet, exercise) and other confounders and/or covariates makes it difficult to clearly assess potential associations between prenatal medication use and long-term outcomes. In particular, the inability to control for the contribution of underlying maternal disease when investigating outcomes associated with medication use during pregnancy is a constant challenge. For many outcomes there may be the potential for significant confounding due to maternal illness (e.g. the effect of maternal depression on pregnancy outcomes when investigating the effects of antidepressant use during pregnancy[26]). Highlighting the importance of having access to these types of data could enable us to make strong recommendations on how to improve data collection in the future to assist in improving the quality of research projects undertaken. For example, the simple recommendation for the inclusion of electronically recorded data related to depression screening, which is

routinely undertaken during antenatal visits, would make a significant improvement for studies examining mental health during pregnancy.

11.12 Conclusion

There are significant opportunities to utilise routinely collected health data to investigate long-term effects of medication use during pregnancy on the health of the offspring in later life. Compared to other research methodologies, the timely and efficient manner in which routinely collected health data can be used to generate large cohort studies to examine long-term outcomes is a significant advantage. Australia is in an excellent position to undertake research using routinely collected health data due to its long-term, comprehensive and stable population datasets and as a direct result of the significant investment that is being made in population-based data linkage. With any opportunity, however, come challenges. These challenges relate to aspects of study design and analysis and include the ability to match records across datasets and over long periods of time, how medication exposures and outcomes are ascertained and classified, issues around loss to follow-up and the careful interpretation of results in light of data and study limitations. Knowledge of these challenges and recommended strategies in using routinely collected health data is essential in supporting the appropriate use and interpretation of routinely collected health data, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained. Furthermore, the improved collection and evaluation of data on medication use and long-term pregnancy outcomes using routinely collected health data could enable us to strengthen safety data, encourage medication use during pregnancy when necessary and support informed decision making based on identified benefits and risks associated with treatment.

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Table 11.1 Data linkage centres in Australia

Location	Name	Web Site
New South Wales & Australian Capital Territory	Centre for Health Record Linkage	www.cherel.org.au
Queensland	Health LinQ	www.healthlinq.org.au
South Australia & Northern Territory	SA-NT Datalink	www.santdatalink.org.au
Tasmania	Tasmanian Data Linkage Unit	Under Construction
Victoria	Victorian Data Linkages	www.health.vic.gov.au/vdl/
Western Australia	WA Data Linkage System	www.datalinkage-wa.org
National – Population Health Research Network	Centre for Data Linkage	www.phrn.org.au

Table 11.2 Overview of routinely collected health data available in Australia and their potential contribution to investigating long-term outcomes associated with medication use during pregnancy

Electronic Dataset	Potential Use
Maternal Medication Exposure During Pregnancy	
Pharmaceutical Benefits Scheme (PBS) Claims Data Hospital Pharmacy Dispensing Data	Maternal medication use during pregnancy (e.g. antidepressant medication use)
Maternal Health & Pregnancy Outcome	
Perinatal Statistics Collection (Midwives Notification Records - maternal)	Maternal medical conditions, obstetric history, course of delivery, pregnancy complications
Hospital Separations (i.e. inpatient, emergency department)	Admission to hospital prior to, during and/or after pregnancy for maternal illness
Mental Health Visits (i.e. inpatient, outpatient)	Use of mental health services prior to, during and/or after pregnancy
Childhood, Adolescent and Adult Health Outcomes	
Perinatal Statistics Collection	Infant characteristics (i.e. birth weight), complications (i.e. admission to neonatal intensive care)
Birth Defects Registry	Congenital malformations
Pharmaceutical Benefits Scheme (PBS) Claims Data	Medication use in the offspring (e.g. could be used as proxy for adverse health outcomes)
Hospital Separations (i.e. inpatient, emergency department)	Hospital admissions and/or emergency department presentations for the offspring (e.g. surgery for fracture)
National Assessment Program – Literacy and Numeracy (NAPLAN)	Assessment of literacy and numeracy skills in offspring in childhood
Australian Early Development Index (AEDI)	Measures five areas of early childhood development: • physical health and wellbeing • social competence • emotional maturity • language and cognitive skills • communication skills and general knowledge
Cancer Registry	Diagnosis of cancer

CHAPTER 12

Discussion and Conclusion

	CHAPTER 1 Introduction	**Publication One** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(1): 46-9.
SECTION I **PART A** **Conceptual Framework**	**CHAPTER 2** Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology	
	CHAPTER 3 A Review of Methodological Challenges and Epidemiological Research Methods	**Publication Two** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 33(3): 280-9.
SECTION I **PART B** **Literature Review**	**CHAPTER 4** Safety of SSRIs in Pregnancy	**Publication Three** Grzeskowiak LE et al. *Drug Saf.* 2011; 34(11): 1027-48.
	CHAPTER 5 Effects of Prenatal SSRI Exposure on Child Growth and Body Weight	**Publication Four** Grzeskowiak LE et al. *Reprod Toxicol*. 2012; 34(1): 101-9.
SECTION II **Validating the Use of Routinely Collected Health Data**	**CHAPTER 6** Validating the Use of Hospital Pharmacy Dispensing Records to Identify Prenatal SSRI Exposure	**Publication Five** Grzeskowiak LE et al. *J Pharm Pract Res.* 2010; 40(4): 265-8.
	CHAPTER 7 Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy	**Publication Six** Grzeskowiak LE et al. *Eur J Clin Pharmacol*. 2012; 68(5): 459-67.
	CHAPTER 8 Prenatal SSRI Exposure & Neonatal Outcomes *Examined Using Routinely Collected Health Data*	**Publication Seven** Grzeskowiak LE et al. *J Clin Psychopharmacol*; In press.
SECTION III **Evaluating the Use of Routinely Collected Health Data**	**CHAPTER 9** Prenatal SSRI Exposure & Childhood Overweight *Examined Using Routinely Collected Health Data*	**Publication Eight** Grzeskowiak LE et al. *J Dev Orig Health Dis*. 2012; 3(4): 253-61.
	CHAPTER 10 Prenatal SSRI Exposure & Childhood Overweight *Examined Using Data from a Birth Cohort Study*	**Publication Nine** Grzeskowiak LE et al. *PLoS ONE*; Submitted.
	CHAPTER 11 Using Routinely Collected Health Data to Examine Long-Term Outcomes: Opportunities and Challenges	**Publication Ten** Grzeskowiak LE et al. *Ther Adv Drug Saf*; Submitted.
	CHAPTER 12 Discussion and Conclusion	

12.1 Overview

The original research question posed at the beginning of this thesis was;

> *"Can we use routinely collected health data to examine long-term effects of medication use during pregnancy?"*

The evidence provided in this thesis demonstrates the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy on the health of the offspring in later life. In addition, it provides a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data. By outlining evidence-based strategies for using routinely collected health data this thesis provides a framework for guiding and supporting research in this area. Notably, evidence obtained throughout this thesis indicates that routinely collected health data cannot be used in all situations, as its suitability will be dependent on the exposure and outcomes under investigation, as well as the quality of data available. This highlights the importance of initial key validation studies as an integral first step in developing a greater understanding of the available data. By carefully outlining recommended strategies for using routinely collected health data this thesis provides a framework for guiding and supporting research in this area. This framework is essential in supporting the appropriate use and interpretation of routinely collected health data, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained.

Studies in this thesis have made a number of original contributions to the literature across several disciplinary areas. This cross-disciplinary approach, which takes into account the sciences of biology, physiology, pharmacology, statistics and epidemiology, reflects the breadth and complexity of the research. In addition, this thesis makes a number of original contributions to the existing literature, both on the broader level in relation to the use of routinely collected health data, but also specifically in relation to the use of SSRIs in pregnancy.

12.2 Using routinely collected health data to examine long-term effects of medication use during pregnancy

To date, the investigation of teratogenic effects of medications has largely focused on physical alterations (i.e. malformations) as opposed to functional alterations (i.e. neurodevelopment, metabolic function) that may not be apparent at birth but could influence an individual's health and risk of disease in later life. The impetus for

investigating the health of the offspring in later life is well supported within the theoretical constructs provided by the Developmental Origins of Health and Disease (DOHaD) hypothesis.[1] However, while the DOHaD hypothesis postulates that programming of the long-term structure and function of body systems can be influenced and altered by environmental exposures *in utero*,[2-4] most research has focused on the role of nutrition and fetal growth during pregnancy and subsequent development of chronic diseases in adulthood. At present, there has been little regard for the role that medication exposures during pregnancy could play in influencing susceptibility towards disease in later life. As such, a significant contribution of this thesis is highlighting the importance of investigating the potential for medication exposures during pregnancy to play an influential role in the health of the offspring in later life.

While routinely collected health data have been frequently used to examine short-term effects of medication use during pregnancy (i.e. malformations, pregnancy complications), their use for examining long-term outcomes represents a relatively new and novel approach. As such, there was a consequent need for research investigating the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy. In addition to directly demonstrating its feasibility, this thesis provides a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data. A key strength in achieving this understanding lies in the use of four key interdependent theoretical frameworks, as outlined in Figure 12.1. For example, the diagrammatical representation of the DOHaD hypothesis, previously referred to in Chapter 2, was utilised as a conceptual framework for understanding the potential effects of prenatal SSRI exposure on child growth and body weight, as demonstrated in Figure 12.2.

Initial validation studies presented in this thesis assessed the ability to identify medication exposures and to link data across datasets to produce meaningful results (Chapters 6 to 8). Importantly, these provided confidence that the data and methods utilised were suitable for investigating potential long-term effects of medication use during pregnancy. These data were then used to investigate the long-term effects of prenatal SSRI exposure on growth and body weight in childhood (Chapter 9). As a point of comparison of research methodologies, the effects on growth and body weight in childhood were investigated further using data obtained from the Danish National Birth Cohort (Chapter 10). This served as an illustrative example to achieve a greater understanding of the strengths, limitations, challenges and recommended strategies in using routinely collected health data to investigate long-term effects of medication use during pregnancy. A comparison of the methods and results of these two studies is provided in Table 12.1.

Despite differences in study methodology and age of the children at follow-up, both provided similar results in relation to the observation that prenatal SSRI exposure can influence child growth and body weight in later life and those outcomes may be sex-specific (Chapter 9 and 10). In addition, the direction of the observed associations were in concordance with available experimental evidence and well-established biologically plausibility mechanisms, as outlined through earlier literature reviews (Chapter 5). As such, this demonstrates the feasibility of using routinely collected health data to examine long-term effects of medication use during pregnancy.

Two notable limitations associated with both studies included small sample size and loss to follow-up. While the illustrative study using routinely collected health data had a small sample size, it is important to note that this does not reflect a limitation associated with the use of routinely collected health data in general. Sample size was only a limitation because the South Australian routinely collected health data utilised for this illustrative study was obtained from just the one maternity hospital. This hospital accounts for approximately 4,000 deliveries each year, representing 25% of births in South Australia and just 2% of births in Australia.[14,15] Had this study truly been population-based, utilising all available state or national data, then the number of children exposed to SSRIs would have been much greater. In contrast, the limitation associated with small sample size in the study using data from the Danish National Birth Cohort is a true reflection of the limitations often associated with prospective cohort studies. This is because data obtained from the Danish National Birth Cohort is restricted according to the total number of women initially enrolled in the study, the underlying prevalence of SSRI use among those women and the degree of loss to follow-up over time. Due to these restrictions, even if efforts are undertaken to minimise loss to follow-up, sample size remains a legitimate limitation.

In addition to small sample size, loss to follow-up was a limitation for both studies. Due to difficulties in following individuals over long periods of time, loss to follow-up is often a limitation associated with traditional prospective cohort studies, as was the case in this study. Loss to follow-up is often an issue affecting traditional prospective cohort studies due to difficulty with following individuals over long periods of time. While studies undertaken using routinely collected health data have the potential to minimise loss to follow-up by reducing the need to actively follow-up individuals over time, successful follow-up is still reliant on the availability of outcome data for all study subjects.

The challenge presents when utilising datasets that do not contain data for the entire population. For example, the study using routinely collected health data utilised electronic data from South Australia's Women's and Children's Health Network (WCHN)

Child Health Records, collected during preschool health checks. From 1997 through 2007, the period of child follow-up in this study, the average participation rate in the preschool health checks was approximately 65% of South Australian children.[16] This resulted in follow-up data not being available for all eligible study participants.

In addition to the two limitations previously discussed, the comparison of research methodologies resulted in the identification of a number of key challenges in using routinely collected health data to examine long-term effects of medication use during pregnancy. These were previously outlined in Chapter 11 and relate to aspects of study design and analysis and include the ability to link data across datasets and over long periods of time, how medication exposures and outcomes are ascertained and classified, issues around loss to follow-up and the careful interpretation of results in light of data and study limitations.

Following an understanding of these challenges, an important consideration is how the use of routinely collected health data compares to other approaches available to examine outcomes associated with medication use during pregnancy. It is clear that no single research method is sufficient for delineating the complete spectrum of risks and benefits associated with medication use during pregnancy,[17] with each method having its own strengths and limitations.[18,19] Importantly, routinely collected health data has a number of strengths over other research methods. These strengths are summarised in Table 12.2, in addition to the limitations associated with using routinely collected health data. A major strength is that data are already available, collected prospectively in a routine fashion (e.g. as prescription records or hospital discharge summaries), stored electronically and can be linked at the individual level.[20] In addition, use of routinely collected health data often enables the establishment of very large cohorts of women and their offspring, which is particularly useful in assessing rare, but clinically important, outcomes.[21] Linkage of routinely collected health data is unobtrusive and the routine and prospective manner in which data are collected and recorded in these datasets eliminates recall bias.[21] In addition, as data have already been collected, studies can be undertaken in a more timely and cost effective manner than is possible with other research methods.[22] This enables research questions generated from experimental evidence, clinical observations and/or sound biologically plausible arguments to be assessed quickly for their relevance and impact in humans.

While linkage of routinely collected health data is unobtrusive, there is a need to acknowledge legitimate issues and concerns surrounding consent and privacy. Importantly, these issues and concerns can be addressed and appropriate protocols and procedures are in place in research centres, within Australia and internationally, to

ensure this type of research can be undertaken in an ethical manner.[23] Furthermore, the use of well established linkage protocols, where health data are stored and managed separately to personal identifying information, can actually enhance privacy by reducing the need for the release of identifiable data to researchers.[23,24]

The use of routinely collected health data can serve a variety of purposes, from providing the first evidence of potential causal relationships to confirming and/or verifying the magnitude of previously reported associations.[25] In situations where associations are observed, any identified limitations could be addressed through the use of alternative research methods. However, the potential for more intensive and time-consuming efforts to provide a greater understanding of an observed association must be balanced against their associated costs. As such, it will not always be possible to utilise purpose built cohort studies to clarify all associations observed in studies using routinely collected health data. Therefore, in addition to alternative research methods, subsequent studies may utilise different sources of routinely collected health data, with verification of results using alternative research methods and/or data sources strengthening arguments for a causal relationship.[26]

It is important to note that there will always be significant differences between cohort studies undertaken prospectively, and those which use routinely collected health data. The most obvious difference being that routinely collected health data were never collected to be used for research purposes, whereas a prospectively designed cohort study has been undertaken to specifically address a research question or set of questions. As such, the depth and quality of data available in prospective cohort studies is often greater than what is available in routinely collected health data. Knowledge of these deficiencies, however, enables researchers to improve both the breadth and quality of data that are routinely collected, in turn improving research capabilities. For example, the simple recommendation for the inclusion of electronically recorded data related to depression screening, which is routinely undertaken during antenatal visits, would make a significant improvement for studies examining mental health during pregnancy. This can be compared to the similar change instituted by the South Australian Pregnancy Outcome Statistics Unit in 2007 to begin electronically recording data on maternal weight and height at the first antenatal appointment. This change was made in recognition of the importance of understanding maternal BMI and its effects on pregnancy outcomes.[27] Prior to this date, many individual hospitals had already been collecting these data as part of routine clinical practice, but were not required to submit these data electronically to the State based Pregnancy Outcome Statistics Unit. Notably, the Women's and Children's Health Network had been electronically recording data on

maternal weight and height at the first antenatal visit since 2000, enabling the use of these data in studies presented within this thesis (Chapter 8 and 9).

An additional example is the long-standing recommendation that electronically recorded data be available for all medications dispensed as part of the Pharmaceutical Benefits Scheme (PBS). Currently, medications dispensed through the PBS, where the Australian government subsidises prescription medications for residents to ensure affordable and reliable access, are only electronically recorded if the government is required to pay a subsidy. That means data are only recorded if the cost of the dispensed medication is greater than the maximum specified cost to the consumer, known as the co-payment level. Based on the PBS co-payment levels for 2012, individuals with a concession card are required to pay up to $5.80, while those without a concession card are required to pay up to $35.40. This results in under-ascertainment of medication exposures in situations where medications are dispensed below the co-payment level. In recognition of this long-standing issue, the Australian government has recently introduced legislative changes which, from 1 April 2012, will require electronically recorded data be collected on all PBS medications dispensed, including those priced below the general co-payment level.[28]

While these changes to the collection of data on maternal BMI and PBS medications are a positive step forward, they only improve future data collection and do not solve limitations associated with the fact these data were not collected prior to these changes being implemented. These examples do, however, demonstrate the adaptive ability of routinely collected health data and highlight the capability to initiate and implement changes that will significantly improve future research capabilities.

While the use of routinely collected health data does not replace the need for high quality, purpose-built prospective cohort studies, its ability to address many of the key limitations associated with prospective cohort studies makes it a useful alternative. For example, it may not be possible to enrol a sufficient number of individuals in a prospective birth cohort study, especially when examining rare exposures and outcomes. Furthermore, it takes many years to complete prospective cohort studies, due to the considerable time-lag between the development of the research question, design of the study and subsequent follow-up of participants for an adequate period of time to assess the outcome of interest. Notably, for newly marketed medications, no research methodology will be able to provide rapid results, as it will take a number of years for enough women to use the medication during pregnancy and then for their exposed offspring to reach the age at which long-term outcomes can be assessed. The time-lag associated with prospective studies, however, becomes a limitation when studying the

impact of medications that have already been on the market for a number of years and have been used by a large number of women during pregnancy. In these instances, while a prospective study could be constructed to follow-up subsequent pregnancy exposures for 5-10 years to obtain long-term outcome data, the alternative exists to utilise routinely collected health data to review the outcomes of individuals who were exposed to particular medications during pregnancy and have already reached 5-10 years of age. Accordingly, the use of routinely collected health data offers the potential to provide more timely answers to current clinical questions on potential long-term effects of medication use during pregnancy. This ability to provide timely evidence is of major importance in supporting clinical practice and achieving quality use of medicines.

Through its rigorous exploration of the strengths, limitations, challenges and recommended strategies in using routinely collected health data to examine long-term effects of medication use during pregnancy, this thesis provides a framework for guiding and supporting research in this area. This framework is essential in supporting the appropriate use and interpretation of routinely collected health data, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained. Emphasis is also placed on the importance of enhancing available data through improvements in access or through improved data collection. As such, researchers and clinicians need to have a greater voice in decisions around routine data collection, to ensure data can be utilised to their greatest potential.

Furthermore, this thesis makes a unique contribution towards the establishment of a strategic approach to using routinely collected health to examine long-term effects of medication use during pregnancy. This represents a key step forward in the development of evidence to assist in achieving quality use of medicines. In particular, novel surveillance techniques using routinely collected health data could enable more timely identification, quantification, and understanding of the long-term risks or benefits of medication use during pregnancy. We already have data available to assess the effects of medications used during pregnancy on the health and well-being of offspring from birth into later life. Outcomes, such as physical and mental health, cognitive development, risk of cancer and the development of chronic medical conditions (i.e. diabetes, asthma) can all be investigated. Now is the time to make the most of these data to support the quality use of medicines in pregnancy and improve health outcomes within the community.

12.3 Safety of Selective Serotonin Reuptake Inhibitors (SSRIs) in Pregnancy

The literature review on the safety of SSRIs in pregnancy (Chapter 4) provides a novel critical appraisal of the existing literature, with its focus on methodological issues. This review not only provides important clinical summaries on outcomes associated with SSRI use during pregnancy, but also highlights the significance of considering methodological issues when planning, undertaking, writing and evaluating studies.

The study assessing neonatal outcomes following late gestation exposure to SSRIs (Chapter 8) provides an important contribution to the growing body of evidence of an association between prenatal SSRI exposure and a range of adverse neonatal outcomes. This study had several strengths, including its large sample size and use of an age-adjusted birth weight to accurately assess the effects of prenatal SSRI exposure on intrauterine growth. Further strengths included the adjustment for a large number of important and relevant covariates (i.e. smoking, socioeconomic status, substance use, medical conditions and anxiolytic use), and inclusion of a control group of women with active psychiatric illness but who were not dispensed a SSRI during pregnancy. While it is imperative to emphasise the need to identify and actively manage psychiatric illness during pregnancy, this study demonstrated that combined exposure to SSRIs and psychiatric illness during pregnancy is associated with an outcome profile that appears to differ from that of exposure to psychiatric illness alone. Knowledge of such risk is important in ensuring that these women and their infants can be most effectively managed during and after the pregnancy, an essential step towards achieving quality use of medicines.

The literature review on the effects of prenatal SSRI exposure on child growth and body weight (Chapter 5) provided a biologically plausible argument for the need to investigate such an association in subsequent studies. This was further supported by the conceptual framework provided by of the Developmental Origins of Health and Disease and evidence that other prenatal exposures (i.e. maternal smoking, gestational diabetes) are associated with alterations in growth of the offspring in later life (outlined in Chapter 2). This association between prenatal SSRI exposure and child growth and body weight was then investigated in two studies, one using routinely collected health data (Chapter 9), the other using data from the Danish National Birth Cohort (Chapter 10). Prior to these studies, existing evidence suggested that prenatal SSRI exposure is associated with a reduction in infant weight gain in the first 6 months of postnatal life in males and females.[7,12] According to the results of the studies presented in this thesis, sex-specific differences in body weight begin to emerge beyond 6 months of age. Among female offspring, this initial reduction in infant weight gain appears to persist until 4- to

5-years of age, where they appear to be at reduced risk of being overweight (Chapter 9), but this reduction in weight is no longer apparent by 7-years of age (Chapter 10). In contrast, male offspring do not appear to be at increased risk of overweight at 4- to 5-years of age (Chapter 9), but may be at increased risk of overweight at 7-years of age and beyond (Chapter 10). Limitations associated with these studies, suggest further research in this area may be warranted to clarify these findings and provide longer term follow-up of outcomes.

Both studies investigating the association between prenatal SSRI exposure and child growth and body weight identified sex-specific differences. These results could indicate the potential for sex-specific differences in the vulnerability of the fetal brain towards prenatal SSRI exposure and/or maternal psychiatric illness during pregnancy. This raises important questions about the need to consider sex-specific differences in relation to other outcomes associated with prenatal SSRI exposure, as well as in relation to outcomes associated with the use of other medications during pregnancy. Notably, sex-specific differences are seldom investigated and/or adequately reported in published studies to date, reflecting the contribution of this research in highlighting this issue.

Additional findings of interest include the observed association between untreated psychiatric illness during pregnancy and increased risk of overweight in female offspring at 7-years of age. This finding is important, as it suggests that maternal psychiatric illness during pregnancy may be a risk factor for childhood overweight in female offspring, and that treatment with SSRIs could counteract that increased risk. Furthermore, when analysing BMI-z score according to timing of SSRI exposure, the greatest reductions were observed among females who were exposed throughout pregnancy or during the second and/or third trimester. This could suggest that adequate treatment during these time periods is important for reducing the negative impacts of untreated psychiatric illness on offspring health outcomes in later life. This hypothesis, however, requires further investigation in an independent and large data source.

12.4 Future Directions

This thesis demonstrates that the suitability of using routinely collected health data is dependent on the exposure and/or outcome under investigation and the ability for available data to address key methodological challenges. Therefore, the appropriate use of routinely collected health data requires a sound understanding of the data available and its potential uses. This highlights the importance of future studies utilising key validation studies to develop a greater understanding of available data, prior to their use in investigating unknown associations.

While concerns around security and confidentiality are paramount, from an ethical perspective, it is possible to argue that we have an ethical obligation to utilise routinely collected health data if it could achieve a greater understanding of the long-term effects of medication use during pregnancy. This, in turn, could support informed decision making on medication use during pregnancy and potentially lead to improved health outcomes. Futhermore, a greater understanding of the significance of this research can lead to improved quality of, and access to, various data collections, which would support and encourage more research to be undertaken.

Notably, with increasing studies utilising routinely collected health data comes the need for continual investigation and exploration of the methodological challenges associated with their use. Studies that contribute to a greater understanding of these methodological issues are essential in improving the reliability of results obtained using these methods. For example, future studies are required to identify the most appropriate way of using routinely collected health data to classify medication exposures during pregnancy. In addition, there is a need for future studies outlining how best to analyse available longitudinal data within a life-course approach. This requires a greater understanding of how various risk factors interact over time and how to model and incorporate that into analyses.

From a broader perspective, this thesis highlights the significance of investigating potential long-term effects of medication use during pregnancy. Importantly, this research should not only consider the risks associated with medication use, but also associated benefits. Evidence of long-term benefits is essential in encouraging and supporting the use of medications during pregnancy to manage conditions such as diabetes and hypertension, which themselves may be associated with negative long-term effects for the offspring if poorly managed.[29,30] Within the context of the DOHaD hypothesis, it is important to understand how medication use during pregnancy can promote optimal health of the offspring in later life, while also ensuring maternal well being.

The use of routinely collected health data also provides significant opportunities to assess utilisation of health services and medication use patterns prior to and during pregnancy and their resultant impact on pregnancy outcomes and the health of the offspring in later life. Through a greater understanding of the context in which medications are being used during pregnancy, a more thorough assessment of how to achieve quality use of medicines is possible. Subsequently, it would also be possible to examine the most effective way in which to manage maternal illness during pregnancy.

In specific relation to the use of SSRIs in pregnancy, there is a need for additional studies investigating long-term effects of prenatal SSRI exposure. Ideally these studies should take into account underlying maternal illness. A greater understanding of the severity and extent of maternal illness could be achieved through inclusion of data on health services utilisation (i.e. admission to hospital for psychiatric illness, duration of treatment prior to pregnancy). Many long-term outcomes could be assessed using routinely collected health data such as associations with child, adolescent and adult psychiatric illnesses (i.e. autism spectrum disorder, anxiety, depression) or the development of metabolic disorders (i.e. type 2 diabetes) as an indicator of effects of prenatal SSRI exposure on child growth and body weight. Furthermore, there is a need for greater understanding of the optimal way in which to manage maternal psychiatric illness during pregnancy.

Lastly, given the observed sex-specific differences in child growth and body weight following prenatal SSRI exposure, there is a need to assess potential sex-specific differences in relation to neonatal outcomes following exposure to SSRIs and maternal psychiatric illness during pregnancy. For example, sex may be associated with differences in the rates of preterm delivery, low birth weight and/or intrauterine growth restriction.

12.5 Conclusion

There are significant opportunities to utilise routinely collected health data to examine long-term effects of medication use during pregnancy. Australia is in an excellent position to undertake strong data linkage projects due to its long-term, comprehensive and stable population datasets and as a direct result of the significant investment that is being made in the area of population-based data linkage.

With any opportunity, however, come challenges. These challenges relate to aspects of study design and analysis and include the ability to match records across datasets and over long periods of time, how medication exposures and outcomes are ascertained and classified, issues around loss to follow-up and the careful interpretation of results in light of data and study limitations. By outlining evidence-based strategies for using routinely collected health data, this thesis provides a framework for guiding and supporting research in this area. This framework is essential in supporting the appropriate use and interpretation of routinely collected health data, which will contribute to improving the quality of research undertaken and ensure reliability of results obtained.

While this thesis provides the best clinical guidance available on the use of routinely collected health data for examining long-term effects of medication use during pregnancy, there remains a need for further research to identify and evaluate the most effective and efficient method of utilising existing data. In addition, with a greater understanding of the significance of using routinely collected health data to make improvements in evidence-based health care, there is a further opportunity for subsequent improvements in not only access to routinely collected health data, but also the ability to make recommendations in the range or types of data collected, such that these could be used in future research projects.

There is an urgent need to better understand the long-term effects of medication use during pregnancy on the health of the offspring in later life. Not only does this thesis demonstrate the feasibility of using routinely collected health data to achieve that understanding, but it also provides an evidence-based framework for guiding and supporting research in this area. The timely and efficient manner in which long-term outcomes can be examined using routinely collected health data represents a major step forward in improving our understanding of the consequences of medication use in pregnancy. The improved collection and evaluation of routinely collected health data on medication use and long-term pregnancy outcomes will strengthen safety data, guide medication use during pregnancy and support informed decision making based on identified benefits and risks associated with treatment.

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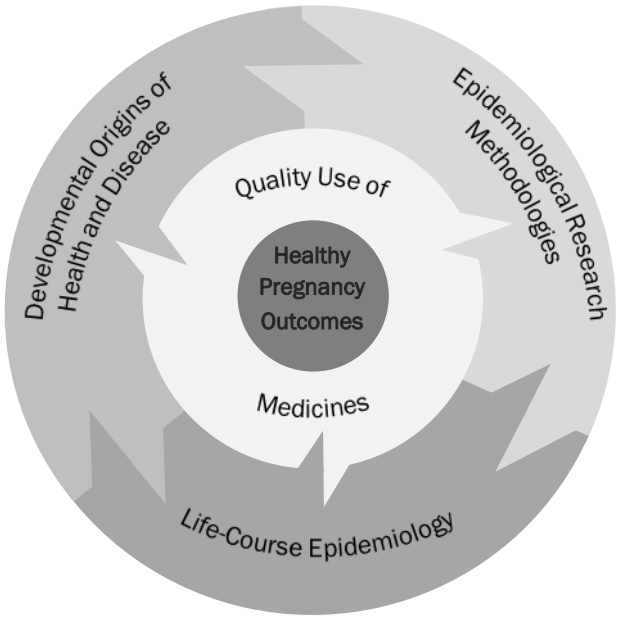
Figure 12.1 Interdependence of conceptual frameworks supporting this thesis

Adapted from [5(p 4)]



This figure illustrates the interdependence of the four conceptual frameworks drawn upon within this thesis to investigate the feasibility of using routinely collected health data to investigate long-term effects of medication use during pregnancy. Central to this aim is the optimisation of pregnancy outcomes for the mother and their offspring. Directly supporting this goal is the Quality Use of Medicines policy which requires evidence on the judicious, appropriate, safe and effective us of medicines in pregnancy. Essential in enabling and supporting quality use of medicines are the other three closely interlocked components.

• The first is the Developmental Origins of Health and Disease hypothesis which provides a theoretical framework for understanding and investigating the potential role that prenatal exposure to various medications could play in influencing the health of the offspring in later life. In addition, it provides the biological plausibility for examining relationships with long-term outcomes.

• The second is knowledge of epidemiological research methodologies. Various methodologies exist to examine long-term effects of medication use during pregnancy, each with their own strengths and limitations. Knowledge of these, together with a sound understanding of associated methodological challenges is essential in understanding the feasibility of using routinely collected health data to generate evidence on long-term effects of medication use during pregnancy.

• The third is life-course epidemiology. This serves to highlight the importance of conceptualising disease aetiology within a life course framework, as well as recognising that the aetiology of many later-life conditions may rest with prenatal and early-life biological and social factors, in addition to, or in synergism with, those of well-established adult exposures or risk factors.

Figure 12.2 **Diagrammatical representation of the Developmental Origins of Health and Disease hypothesis in the context of prenatal exposure to selective serotonin reuptake inhibitors during pregnancy and effects on child growth and body weight** (Adapted from[6 (p 2)])

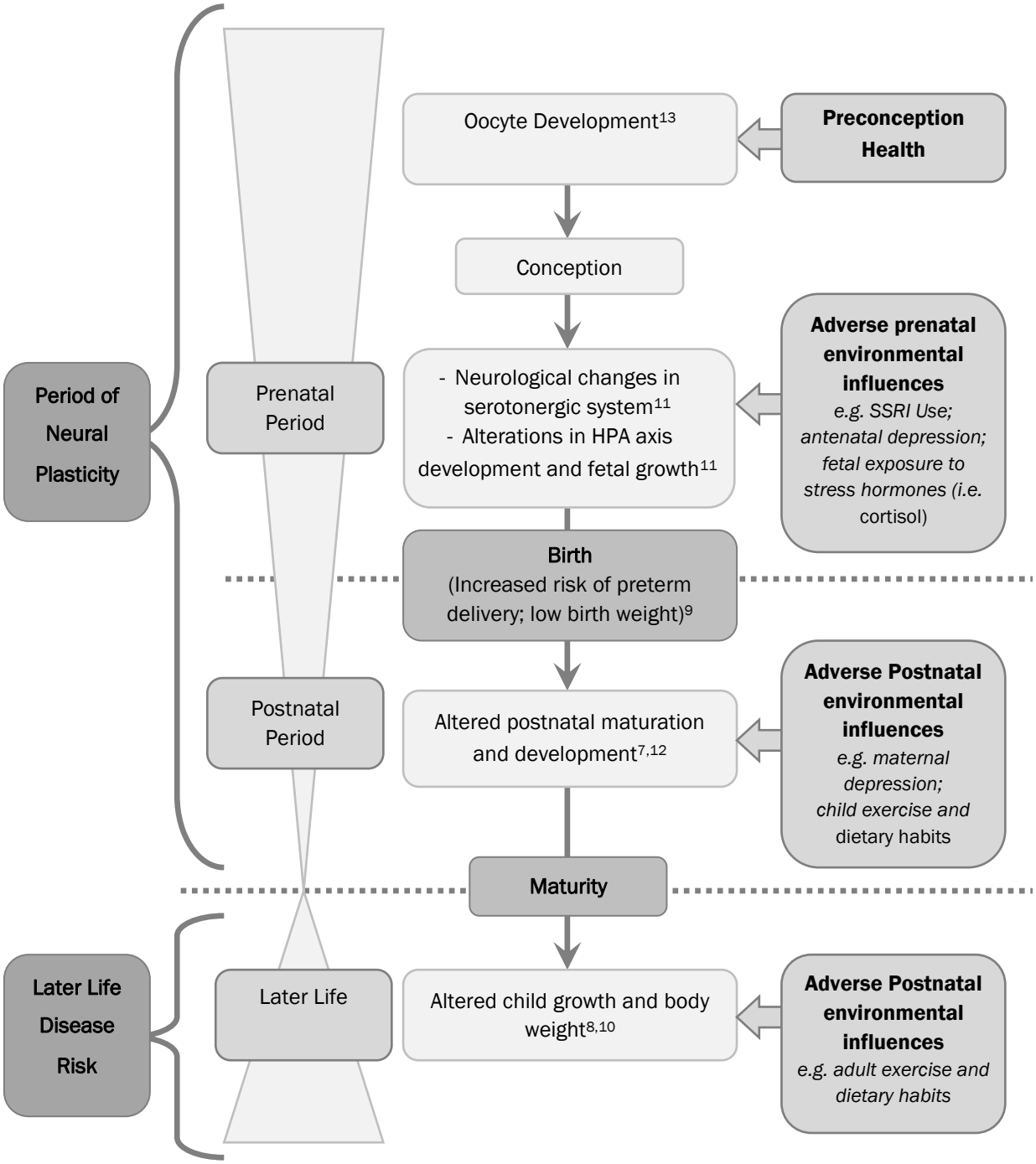


Table 12.1 Comparison of studies investigating the association between prenatal exposure to selective serotonin reuptake inhibitors and childhood overweight

Location of Study	South Australia	Denmark
Comparison of Methods	(Chapter 9)	(Chapter 10)
Data Source	Routinely Collected Health Data†	Danish National Birth Cohort
Year of Delivery	2000-2005	1996-2002
No. Eligible for Study‡	16,735	81,931
No. Children with Outcome Measures	6,560†	39,327
Loss to follow-up	60.8%	52.0%
Age of child at follow-up	4-5 Years	7 Years
Outcome Measure	Child weight and height used to calculate BMI-for-age percentiles Childhood overweight > 85th Percentile	
	Data measured by trained nurses as part of routine health checks	Data self-reported by parents
Data available in both studies	Measure of Socioeconomic status, smoking status, presence of psychiatric illness during pregnancy	
Data only available in Danish National Birth Cohort Study	N/A	Duration of breastfeeding, paternal BMI, prenatal and postnatal distress scores, weight gain during pregnancy
Maternal BMI	Based on weight and height recorded at first antenatal visit	Based on self-reported pre-pregnancy weight and height
SSRI Exposure During Pregnancy	Dispensing data validated as indicator of late gestation exposure (≈ 25% under-ascertainment)	Self-reported data available on timing of medication exposure (exposure not validated)
Comparison of Results	Risk of Childhood Overweight PR (95% CI)	
SSRI Use vs. Untreated Psychiatric Illness		
Males	1.17 (0.54-2.51) [a]	1.63 (0.92-2.88) [b]
Females	0.23 (0.05-0.98) [a]	0.30 (0.08-1.12) [b]
Untreated Psychiatric Illness vs. No Psychiatric Illness/No SSRI Use		
Males	0.85 (0.56-1.28) [a]	1.02 (0.71-1.46) [b]
Females	1.09 (0.76-1.57) [a]	1.55 (1.12-2.15) [b]
Sex-Specific Differences Observed	Yes	Yes

PR, prevalence ratio; CI, confidence interval; SSRI, selective serotonin reuptake inhibitor

† Data was obtained from the Women's and Children's Health Network in South Australia (which includes one maternity hospital accounting for approximately 4,000 births each year). Therefore, the sample size for this study is not reflective of the total potential sample size that could have been obtained if data were acquired from all maternity hospitals in the State.

‡ Totally number eligible for the study includes the total number who met the relevant inclusion/exclusion criteria

[a] RCHD: adjusted for maternal age, socioeconomic status, smoking status, race, parity, maternal BMI, fetal growth and breastfeeding status at discharge from hospital

[b] DNBC: adjusted for smoking status, pre-pregnancy maternal BMI, employment status, prenatal distress, paternal BMI weight gain during pregnancy, breastfeeding and postnatal distress

Table 12.2 Strengths and limitations of using routinely collected health data to examine long-term effects of medication use during pregnancy

Strengths	Limitations
Can answer a variety of research questions in a relatively timely and efficient manner	Restricted to investigating exposure and outcomes routinely recorded in the data
Commonly population-based, improving generalisability of findings and reducing potential for selection bias	Potential misclassification of medication exposures and outcomes
Datasets often contain data on many individuals and can therefore generate large sample sizes	Assumptions regarding dose, timing and duration of medication exposure based on dispensing data
Data routinely collected as part of clinical practice / administration requirements	Diagnostic data often not available (i.e. severity of underlying illness)
Unobtrusive data collection	Available data limited to that which is routinely collected. Relevant data of interest (i.e. potential confounders) not collected
Eliminates potential for recall bias	Data may differ across data sources (i.e. differences in the way data are collected in different settings or changes to data collection over time)
Enables long-term follow-up	Data quality and integrity may differ across data sources
Useful in assessing rare, long-term outcomes	Large sample size can lead to increased likelihood of chance findings

Appendix 1: Authorship and Contributorship

Chapter One: Introduction

Grzeskowiak LE, Gilbert AL, Morrison JL. Conception and Beyond – Using Population-Based Record Linkage to Monitor Long-Term Effects of Medications Used During Pregnancy. *J Pharm Pract Res.* 2010; 40(1): 46-49.

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Chapter Two: Quality Use of Medicines, Developmental Origins of Health and Disease and Life Course Epidemiology

No Publication

Chapter Three: A Review of Epidemiological Research Methods and Methodological Challenges

Grzeskowiak LE, Gilbert AL, Morrison JL. Investigating Outcomes Associated with Medication Use During Pregnancy: a review of methodological challenges and observational study designs, *Reprod Toxicol*. 2012; 33(3): 280-289.

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Chapter Four: Safety of SSRIs in Pregnacy

Grzeskowiak LE, Gilbert AL, Morrison JL. Investigating outcomes following the use of Selective Serotonin Re-Uptake Inhibitors for Treating Depression in Pregnancy - A Focus on Methodological Issues. *Drug Saf.* 2011; 34(11): 1027-1048.

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Chapter Five: Effects of Prenatal SSRI Exposure on Child Growth and Body Weight

Grzeskowiak LE, Gilbert AL, Morrison JL. Long term impact of prenatal exposure to SSRIs on growth and body weight in childhood: Evidence from Animal and Human Studies, *Reprod Toxicol*. 2012; 34(1): 101-109.

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Chapter Six: Validating the Use of Hospital Pharmacy Dispensing Records to Identifiy Prenatal SSRI Exposure

Chapter Grzeskowiak LE, Gilbert AL, Morrison JL. Hospital Pharmacy Dispensing Records for Pharmacoepidemiology Research into Late Gestation Exposure to Antidepressants. *J Pharm Pract Res.* 2010; 40(4): 265-268.

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Chapter Seven: Challenges in Using Routinely Collected Health Data to Classify Medication Exposure During Pregnancy

Grzeskowiak LE, Gilbert AL, Morrison JL. Exposed or Not Exposed? Exploring Exposure Classification in Studies Using Administrative Data to Investigate Outcomes Following Medication Use During Pregnancy, *Eur J Clin Pharmacol*. 2012; 68(5): 459-467.

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Chapter Eight: Prenatal SSRI Exposure and Neonatal Outcomes

Grzeskowiak LE, Gilbert AL, Morrison JL. Neonatal Outcomes Following Late Gestation Exposure to SSRIs, *J Clin Psychopharmacol*; In press.

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Chapter Nine: Prenatal SSRI Exposure and Childhood Overweight – Examined Using Routinely Collected Health Data

Grzeskowiak LE, Gilbert AL, Morrison JL. Prenatal Exposure to Selective Serotonin Reuptake Inhibitors and Risk of Childhood Overweight*, J Dev Orig Health Dis*. 2012; 3(4): 253-261.

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Chapter Ten: Prenatal SSRI Exposure and Childhood Overweight – Examined Using Data From a Birth Cohort Study

Grzeskowiak LE, Gilbert AL, Sørensen TIA, Olsen J, Sørensen HT, Pedersen LH, Morrison JL. Childhood Overweight Following Fetal Exposure to Selective Serotonin Reuptake Inhibitors and Maternal Psychiatric Illness. *PLoS ONE*; Submitted.

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Chapter Eleven: Using Routinely Collected Health Data to Examine Long-Term Outcomes: Opportunities and Challenges

Grzeskowiak LE, Gilbert AL, Morrison JL. Using Linked Healthcare and Administrative Data to Investigate Long-Term Effects of Medication Use During Pregnancy – Opportunities and Challenges, *Ther Adv Drug Saf*; Submitted.

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