Antidepressant use in pregnancy: knowledge transfer and translation of research findings

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ISBN: 978-90-393-6320-1

Antidepressant use in pregnancy: knowledge transfer and translation of research findings

Gebruik van antidepressiva tijdens de zwangerschap: kennisoverdracht en vertaling van onderzoekresultaten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 8 april 2015 des middags te 2.30 uur

door

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geboren op 1 oktober 1945 te Londen, Verenigd Koninkrijk

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CHAPTER 1

INTRODUCTION

INTRODUCTION

Since the thalidomide tragedy of the 1960's, there exists the general view that every drug has teratogenic potential, and that women should refrain from taking any medications during pregnancy if at all possible. As a result, health care professionals commonly advise pregnant women to avoid pharmacotherapy for fear of causing fetal malformations. However, recent epidemiologic studies have shown that many drugs are safe and viable options during pregnancy, including antidepressants. It is not always feasible that antidepressant drugs can be avoided during this period in a woman's life for several reasons. First, up to 25% of women of childbearing age suffer from depression. Secondly, up to half of all pregnancies are unplanned and because most women are taking an antidepressant prior to becoming pregnant, the fetus has already been exposed before the woman knows that she is pregnant. In addition, depending on the severity of the depression, some women do require pharmacological treatment and discontinuing the drug may put both themselves and their unborn child in jeopardy, in the most tragic case scenario, by committing suicide.

Studying the safety of drugs used in pregnancy, especially psychotropics, is a complex process with currently no ideal model for conducting studies. Because of the ethical issues surrounding pregnant women included in research, it is highly unlikely that Randomized Controlled Trials (RCT) will ever be conducted. Consequently, observational studies are used and all of the designs have their limitations, such as small sample size, bias, inability to know exactly if the women took the drug, dosing and during which period, other medication used in the pregnancy and missing data.

Teratogen information services were developed in response to the public and health care providers requirement for evidence-based information regarding the benefit/risk of exposures to drugs, chemicals, radiation and infectious diseases etcetera during pregnancy and lactation.[3] As it became clear that there was a paucity of this type of information, several of the teratogen information centers, often in collaboration with each other, began to conduct outcome studies on the safety/risk of various exposures.[4-10]

Over the years, the group also sought ways of improving how this research is carried out to ensure that it is as rigorous as possible.[11] Together with other groups around the world conducting research in this area who use data from national birth registries, pregnancy registries, prescription data bases and administrative data bases, a large body of research has accumulated, especially regarding the safety of antidepressants in pregnancy. The information from the results of these studies is subsequently passed on to women and their health care providers.

An important question then arises as to how this knowledge is effectively disseminated to the stakeholders who need this information to be able to use and apply in various situations. A relatively new field in science has been emerging, that addresses the issue of ensuring that information generated from research, reaches the right people in the right format. This has been coined knowledge transfer and exchange or knowledge translation (KT). Although KT is now accepted practice among many public health leaders internationally, its potential to advance the quality of health of women during the perinatal period has not been fully examined.

Overview of Knowledge Transfer

Traditional dissemination strategies have usually involved a fairly passive exercise of sharing knowledge, information and research findings, mostly through peer reviewed journals and conference presentations. Rarely have there been attempts made to extend knowledge to front-line users and decision-makers. Similarly, decision-makers typically do not turn to academics or academic research when making decisions.[12] However, for research to have an impact, it is critical that developers and consumers of knowledge take steps to bridge these gaps. Knowledge translation strategies address this conundrum by bridging the gap between information dissemination and uptake.

The Canadian Institutes of Health Research (CIHR) defines knowledge translation as "the exchange, synthesis, and ethically-sound application of knowledge - within a complex system of interactions among researchers and users - to accelerate the capture of the benefits of research for Canadians through improved health, more effective services and products, and a strengthened health care system." During CIHR consultation sessions, a number of challenges and opportunities related to the synthesis, exchange and transfer of the knowledge acquired through research initiatives were raised. The participants identified three priorities for action: 1) Research on the factors contributing to effective knowledge transfer by policy makers and practitioners, 2) Effective ways of communicating knowledge to key stakeholder groups and the public, including effective and innovative use of various media and accessible language for different audiences, 3) Greater investment in knowledge synthesis, diffusion and transfer initiatives such as the development of high quality syntheses and meta-analyses of public health interventions.[13]

The United States Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ), defines KT as communicating the results and significance of health services research and other AHRQ initiatives to the health care industry, health care providers, consumers and patients, policy makers, researchers, and the media with

particular emphasis on communications that are most likely to lead to behavior change, which is the desired primary outcome. In their model, knowledge translation is accomplished using multiple strategies.[14] In Europe, an EC Commission on the subject stated "The need for effective knowledge transfer among public and private research has never been greater than it is today. Companies, universities and research and technology organizations understand that leadership in their respective fields depends upon collaborating productively with each other, in ways that support and reinforce their distinct yet complementary missions". (http://ec.europa.eu/research/innovation-union/pdf/knowledge_transfer_2010-2012_report)

Good KT strategies should be developed from the outset when a research project is conceived, with research and stakeholder partners determining priorities, methods, interpretation of findings and dissemination strategies collectively. Following the conclusion of a study, KT strategies vary and might include formal presentations to non-academic stakeholders, brochures, pamphlets, summary reports, roundtable discussions, and face-to-face meetings.

Priority of KT in health care:

That KT is a "hot topic" is clearly evidenced by the priority placed on having a good KT plan in place as a consideration for funding among leading health research funders (e.g. CHSRF, CIHR); and by a growing body of literature and tools to support KT activities.[15-19] Despite these incentives and facilitators, advancing KT from the exception to the rule, requires careful thought and reduction of several barriers. For the decision-makers, these barriers include: lack of awareness of existing research; lack of capacity to access, critically evaluate and/or apply the available research evidence; poor or scarce evidence on which to base decisions; evidence that may not be relevant to user needs or not tested in practical settings; and few incentives to use the evidence and sometimes unclear benefits of research. For the researchers, barriers include lack of recognition for practicing knowledge transfer as compared to other scholarly activities; lack of awareness with whom to share research findings; lack of know-how concerning how to engage in knowledge transfer; and lack of access to appropriate funding/resources to practice knowledge transfer.[20] These barriers suggest that multi-factorial strategies are needed to promote knowledge translation strategies and that these should include, at a minimum, capacity building for both scientists and decision-makers, opportunities for scientists and decision-makers to liaise, changes to the current academic currency structure and proper resources and funding.

Currently, there are agencies in the US, Canada and Europe who have taken the initiative to address several of these barriers and so KT momentum is growing. Examples include initiatives to: train decision-makers on how to interpret research (AHRQ); grant funding to support KT activities (CHSRF); train scientists to more effectively communicate their findings to, and partner with, non-academic stakeholders (CAMH); and using Knowledge Brokers to facilitate several of these activities across Canada (CHSRF). Europe has also been making efforts to improve knowledge transfer and a commission was formed in 2008 with recommendations to facilitate these efforts.[21] This was followed by a survey from 2010-2012 which monitored implementation of these recommendation in 39 European countries; collecting information on the performance of almost 500 universities and other public research organizations (PRO's) in knowledge transfer, analysis of the implementation for a sample of 322 universities and other PRO's as well as 59 enterprises and 15 experts workshops were held to discuss current issues in knowledge transfer in 38 European countries. The results of this survey revealed that implementation in 2012 was found to be on average 53%. In general, KT policy is accepted as an important issue in Europe, with most of the countries (90%) reporting that national and regional governments promote policies and procedures for promoting KT. Almost all countries (92%) also reported that national and regional governments support the development of KT capacity and skills in universities and other PROs [22]

Superficially, it would appear that Teratogen Information services (TIS) have been practicing KT to a degree, as this is what is carried out on a daily basis, transfer of knowledge to pregnant women and their healthcare providers on the risk/benefit of drugs and other exposures during pregnancy, which has been translated from the scientific literature. However, this task may not be performed with optimum effectiveness and there may be key stakeholder groups who have not been included in the "loop" of knowledge sharing. The main stakeholder groups are policy makers, financial decision-makers, health care providers, the media and the patient. There have been a few examples in TIS that could be described as KT; however, much more could be accomplished with well-planned strategies. For example; armed with research findings regarding the safety of Bendectin®, Motherisk approached Health Canada, which resulted in this drug being the only one on the market to be indicated for use in pregnancy in Canada.[23] Using research findings to approach the US government to adopt changes in the labeling of a drug such as Accutane® resulted in an evaluation and revision of the risk management program by the Food and Drug Administration, Center for Drug Evaluation and Research (FDA).[24]

Current sources of information regarding use of drugs in pregnancy

Since the thalidomide tragedy, there have been efforts made to disseminate information about the safety/risk of drug use in pregnancy. The FDA implemented labeling requirements in 1979 with the aim of providing evidence-based information regarding use of medication in pregnancy. Each drug is classified into 1 of 5 categories based on the absence or presence of data on the safety of its use during pregnancy, the type of study subjects, and the study results. These categories are intended to guide drug choice prior to fetal exposure, rather than provide information on exposure during pregnancy. Critics of the FDA classification pointed out that, although the system is easy to use, it may oversimplify the complexity of weighing risks to the fetus against the need to adequately manage maternal medical conditions. In response to these concerns, the FDA made an announcement in May 2008, stating that they will replace the A, B, C, D, and X classification system with a narrative framework consisting of three sections. The new labeling information will contain a risk summary section that incorporates human and animal data and a clinical consideration section that addresses risk assessment and how to handle inadvertent fetal drug exposure. In addition, there will be therapeutic alternatives and a data section summarizing the evidence discussed in the other two sections.[26] However, to date, the pregnancy risk categories have not yet been revoked and continue to be used by health care providers around the world.

A commonly used resource, available in book form, is often used in community pharmacies; “Briggs; Drugs in Pregnancy and Lactation” which has been compiled by pharmacists. (http://www.accp.com/bookstore/product.aspx?pc=th_09dpl)

In addition, online resources that are commonly used are; Developmental and Reproductive Toxicology Database (www.reprotox.org), and The American Hospital Formulary Service (AHFS)Drug Information; (www.the free library.com / American +Hospital+Formulary +Service+Available+Online). Mothertobaby, (formerly OTIS), also offers information in the form of fact sheets for pregnant women, written at a grade 5 level; www.mothertobaby.org/otis-fact-sheets-s13037.

Outside of North America, commonly used resources are SmPC guidelines (EU) www.ema.europa.eu/docs/en_GB/document.../WC500137019 and TGA (Australia) https:// www. tg.org.au/etgdemo/ desktop /tgc/plg/5a57ea5, in which drug safety/risk in pregnancy is evaluated in a similar fashion to the FDA categories, while NICE guidelines (UK), www.nice.org.uk/guidance/cg107 offer a more narrative format.

Stakeholders

The practice of KT involves a wide variety of individuals, groups and organizations and the following describes the major stakeholders who use the knowledge created by researchers, regarding the use of drugs in pregnancy.

Health care providers: every day thousands of pregnant and breastfeeding women are counseled by their physicians, pharmacists, nurses and other health care professionals on the risk/benefit of an exposure of concern to them. Subsequently, women make important decisions based on the information they receive, including, keeping an otherwise wanted pregnancy that was scheduled for therapeutic abortion, or discontinuing a needed drug, such as an antidepressant, due to misinformation.[25]

Financial decision makers: these stakeholders are extremely important as Teratogen Information Services and other information services require financial support to continue their endeavors. Consequently, the message must be packaged in a way that is mutually satisfying to both partners, because institutions do not want to give away money with no return on their investment. For example, drug companies support teratogen information research when there is a positive result for them, i.e. showing that they are contributing to the welfare of women and their unborn children.[26]

Media: this group must never be underestimated, as they carry great weight in the decision-making of the public regarding their health-care, as this is where many individuals get much of their information about the risk/benefits of medical treatments. It is very rare that studies about drugs that are safe to use in pregnancy are published in the media. In contrast they are eager to write about studies that show an increase risk, which can be very frightening for a pregnant woman to read or to see on television. An example of this, involved a health care advisory from both Canada (Health Canada) and the USA (FDA), that prompted some pregnant women to abruptly discontinue a needed antidepressant due to the misinterpretation by the media of a health care advisory from both Canada (Health Canada) and the US (FDA). At Teratogen Information Services, following media coverage regarding an exposure in pregnant women which is “scary”, the number of calls to the service increases dramatically.[27] Subsequently, it is very difficult to reassure a pregnant women following exposure to negative media translation. Many women are afraid to take any medication at all during pregnancy fearing harm to her unborn child even if epidemiologic studies have proved the drug to be safe. For example, a study published by Motherisk, attempted to determine the factors that influence a woman's decision whether or not to treat nausea and vomiting of pregnancy (NVP) with pharmacologic measures. All the women who called the line with severe NVP that required treatment, were advised that there was a safe drug

(doxylamine/ vitamin B6) indicated for the treatment of NVP. At a follow-up telephone call, 34% were not using any pharmacologic treatment, and of those who were taking the drug, 26% were using less than the recommended dose. One of most important determinants that affected the decision-making of the women who decided not to take the drug, was where they heard the information first. They could recite all the reassuring evidence-based information they had received, but still did not feel comfortable using the medication, because they had previously heard that this drug was not safe to take in pregnancy.[28]

Need for Optimal Drug Therapy during Pregnancy

While women and their care providers are extremely concerned with avoiding possible teratogenic exposures, they often overlook the importance of optimally controlling and treating underlying maternal conditions. Maternal depression has been linked to several adverse outcomes including an association with irritability in the newborn and poor maternal-infant interactions. In addition, maternal depression is associated with spontaneous preterm births, low birth weight and small-for-gestational-age newborns.[29] Therefore, is important to know that anti-depressant medications based on many reported outcomes, have been found to be relatively safe for use in pregnancy. A study conducted at Motherisk followed 36 women who abruptly stopped taking anti-depressant medication. Twenty-eight of whom discontinued pharmacotherapy on the advice of their physician. Of these 36 women, 26 reported physical and psychological effects from the discontinuation of their anti-depressant, eleven women reported suicidal ideation and four were admitted to a hospital for depression.[30] Another study found a 26% relapse rate of depression in women who continued medication through pregnancy compared to 68% in those who discontinued their medications, leading to a hazard ratio of 5.0.[31] The real and potentially dangerous adverse events from under-treating underlying maternal disease must be fully understood and considered carefully, against fears of increased risk of congenital malformations.

Summary

It is apparent that KT processes associated with providing teratogen information to women and their health care providers require improved strategies to enable sound clinical decision-making. It is also evident, that women and their health care providers are highly impacted by the type of teratology information they receive, for example, deciding to terminate a wanted pregnancy, or discontinue a needed pharmacotherapy.

OBJECTIVES OF THE THESIS

The objectives of this thesis are: (1) to determine how knowledge is created about the safety/risk of antidepressant use in pregnancy, (2) to describe different research models and statistical analysis that have been used, so as to critically evaluate the results, and (3) to identify how the information currently is disseminated and how the gaps in KT can be filled.

OUTLINE OF THE THESIS

Chapter 1: Introduction: What is Knowledge Transfer and Translation (KT) and how is it important regarding dissemination of information about the safety of medication use in pregnancy. This introductory chapter gives an overview of knowledge transfer and translation and how it relates to providing women and their healthcare providers with evidence-based information, regarding the safety/risk of drugs during pregnancy.

Chapter 2: The creation of knowledge; researching the safety of antidepressant medication use in pregnancy. This chapter describes how research is conducted when examining the safety of antidepressant use in pregnancy. Included is a description of the types of studies that are conducted, the type of data that is used and what statistical analyses have been utilized. Included are four examples of studies using different methodologies: 2.1 the first study is a meta-analysis that was conducted using published data, evaluating rates of spontaneous abortions following exposure to antidepressants in the first trimester of pregnancy. 2.2 The second study is a collaborative prospective comparative cohort, using data from eight international Teratogen Information Services(TIS) to specifically examine the incidence of heart defects in infants exposed to paroxetine during pregnancy. 2.3 The third study is a prospective comparative cohort, examining fetal growth and preterm birth, using data from Motherisk's prospectively collected pregnancy outcomes of infants whose mothers were exposed to antidepressants during pregnancy. 2.4 The fourth study is also comprised of data from the previously mentioned Motherisk database; in this case outcomes were examined of women who took multiple antidepressants during pregnancy.

Chapter 3: Critical evaluation of studies regarding the safety of antidepressant use in pregnancy. This chapter describes how to understand the results of published studies, using various examples, by carefully examining the authors' objectives and conclusions. It also includes a description of basic statistics, such as what does an odds ratio really mean, so as to be able to understand the difference between statistical significance and clinical

relevance of the results. This chapter included four studies; 3.1 The first study involves a critical evaluation of abstracts of studies that had been published regarding the safety of antidepressants use in pregnancy, specifically addressing the quality and content of the abstracts. 3.2 The second study focuses on publishing statistically significant results with questionable clinical importance, using antidepressant use in pregnancy as an example. 3.3 The third study focuses on the importance of critical evaluation of the literature regarding safety of antidepressant use in pregnancy, including how to understand the difference between statistical significance and clinical relevance of the results. 3.4 The fourth study discusses the question of do findings differ across research design? The case of antidepressant use in pregnancy and malformations.

Chapter 4: How current dissemination of information regarding the safety of antidepressants in pregnancy, impacts both health care providers and pregnant women. This chapter describes how information received and from whom, affects both women and their health care providers in their decision-making regarding taking an antidepressant in pregnancy. The influence of friends, family and the media on risk perception and determinants of decision-making is discussed. This chapter includes four studies that focus on how information has been disseminated and the impact on both health care providers and pregnant women. 4.1 The first study discusses the impact of a public health advisory regarding SSRIs and other antidepressant use during pregnancy regarding potential neonatal adverse effects, with subsequent reports in the news media. 4.2 The second study focuses on the influence of the media on women taking antidepressants during pregnancy and how this information affects their decision-making regarding taking an antidepressant during pregnancy. 4.3 The third study examines the negative impact of non-evidence-based information received by women taking antidepressants during pregnancy from health care providers and others.

4.4 The fourth study examines barriers to the pharmacological treatment of women with psychiatric disorders during pregnancy and breastfeeding.

Chapter 5: General Discussion. In this chapter, the individual studies are put in a broader context. The enhanced role of the pharmacist in disseminating information regarding the use of antidepressants in pregnancy is discussed. In addition, some implications for clinical practice and future research are provided.

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CHAPTER 2

THE CREATION OF KNOWLEDGE; RESEARCHING THE SAFETY OF ANTIDEPRESSANT MEDICATION USE IN PREGNANCY

2.1 Antidepressant use during early pregnancy and the rates of spontaneous abortions: a meta-analysis

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Ann Pharmacother. 2005 May;39(5):803-9

Abstract

Objectives*:* To determine baseline rates of spontaneous (SAs) and if antidepressants increase it.

Data sources: MEDLINE, EMBASE, Healthstar, Toxline, Psychlit, Cochrane, and Reprotox databases were searched for cohort studies published 1966-2002 reporting SAs in women taking antidepressants, compared to non-depressed women.

Data synthesis: Results were combined into a relative risk using a random effects model. We tested heterogeneity with χ^2 and quality with a 29-item checklist.

Main findings: Of 15 potential articles, 6 cohort studies of 3567 women (1534 exposed, 2033 non-exposed) provided extractable data. All matched on important confounders. Tests found no heterogeneity (χ^2=3.13; P=0.98); all quality scores were adequate (>50%). Baseline SA rate ($CI_{95\%}$) was 8.7% (7.5%-9.9%, N=2033); antidepressants rate was 12.4% (10.8%-14.1%; N=1534), significantly increased by 3.9% (1.9%-6.0%); RR=1.52 (1.22-1.89, N=3567). No differences were found among antidepressant classes.

Conclusions: Maternal exposure to antidepressants is associated with increased risk for SA, however, depression itself cannot be ruled out.

Introduction

A substantial number of women of childbearing age suffer from depression. Prevalence estimates, which were evaluated by clinical assessment on the basis of structured criteria, vary between 4% and 17.6% [1,2] The most recent prevalence study was published in 2003, which involved screening 3472 pregnant women for depressive symptoms using the Centre for Epidemiologic Studies Depression Scale. The authors found that 20% of the women surveyed scored above the cutoff for depressive symptoms.[3] The incidence of prenatal depression appears to be increased in the first trimester, suggesting that this trimester may be the time of maximum vulnerability to depression.[4]

Untreated depression and depressive symptoms in the mother have been associated with risks for negative pregnancy outcomes in recent studies. These outcomes included major fetal growth retardation, preterm birth, lower birth weight, smaller head circumference, and lower Apgar scores.[5-10] These outcomes, in turn, have been associated with mortality, an increased risk of severe neurologic morbidity, and mental retardation.[11-13] Although there are several possible mechanisms by which depression during pregnancy could affect neonatal outcome, no causal connections have been established.[5] However, increased serum cortisol and catecholamine levels, which are typically observed in patients with depression, may affect placental function by altering uterine blood flow and inducing uterine irritability.[14,15] A dysfunction in mood could lead to disturbances of the hypothalamic-pituitary-adrenal axis, resulting in deficiencies of glucose metabolism, which may also have a direct effect on fetal development.[16,17]

Predisposing factors for depression during pregnancy include personal or family history of affective illness. However, for about one third of the women who become depressed during pregnancy, this depression represents their first episode. Other risk factors include marital dysfunction or dissatisfaction, young age, inadequate psychosocial supports, recent adverse life events, lower socioeconomic status or minimal education, unwanted pregnancy, and larger number of children.[18,19]

In 1993, Pastuszak et al. reported that women exposed to antidepressants incurred higher rates of spontaneous abortions, although the results were not statistically significant.[20] Subsequently, several studies have investigated this topic as a secondary pregnancy outcome and found the same results. However, no conclusive statements have been made, primarily because the increase in rates was not statistically significant due to the small sample sizes in these studies.[21,23]

In a review of the literature, Garcia-Enguidanos et al.[24] estimated that the incidence of spontaneous abortions in clinical pregnancies was about 12-15%. Furthermore, after including early pregnancy losses, the general incidence was about 17%-22%. The authors pointed out that there have been many suggested risk factors. However, two etiologic factors that were acknowledged by all researchers were uterine congenital malformations and parental balanced chromosomal rearrangements such as trisomy.

A thorough literature search failed to identify definitively the baseline risk for spontaneous abortions in healthy pregnant women. In the studies examining antidepressant use during pregnancy, the exposed group was in the range of 12-15% as quoted previously by Garcia-Enguidanos et al. However, the comparison group rates were much lower, in the range of 7-9%.[21-23] One of the reasons for the lack of data for spontaneous abortions may be a lack of control of possible contributing and confounding variables. Possible major confounding variables are caffeine intake, smoking, age, alcohol use, socioeconomic status, stress, and previous spontaneous abortion.[24,25]

Therefore, a need exists to ascertain whether antidepressants are associated with an increased risk for spontaneous abortions when used in early pregnancy. The objective of our study was to combine data from all of the prospective studies to date that examined the rates of spontaneous abortions in pregnant women exposed to antidepressants in a meta-analysis.

Methods

A comprehensive literature search was undertaken to identify all published papers that reported on spontaneous abortions (SAs) in women taking antidepressants. SA was defined as the unwanted loss of a fetus within the first 20 weeks of gestation. Antidepressants were defined as all drugs in category N06A of the Anatomic Therapeutic Classification of the World Health Organisation.[28] Included were the Selective Serotonin Reuptake Inhibitors (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline), drugs with dual actions (nefazodone, trazodone, and venlafaxine), tricyclics (amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, and trimipramine), and Mono-Amine Oxidase inhibitors (moclobemide, phenelzine, and tranylcypromine). Acceptable comparison groups were non-depressed pregnant women who were exposed to any known non-teratogenic agent throughout their pregnancy. The inclusion and exclusion criteria for the articles are presented in Table 1.

Table 1. Inclusion and exclusion criteria for the articles in this research.

Inclusion criteria
Subjects: Pregnant depressed women (18-45 years of age) *Therapy and disease characteristics:* Antidepressants (at any dose) used to treat depression (comorbidities<25% /no co-medications) *Exposure:* Continuous exposure to antidepressant mono-therapy (SSRI or DAA or TCA or MAOI) at any dose, during the first 20 weeks *Comparison group:* Not exposed to antidepressants or drugs that are associated with teratogenicity or possess abortifacient properties. *Outcomes of interest:* Spontaneous abortions *Research design:* Cohort studies - Observational, interview, survey - Database *Publication:* Published between 1966 and 2002, in any language
Exclusion criteria
For exclusion, only one of the following criteria must have been met: *Patients:* suffering of manic and or mixed depression, bipolar disorders (I and II), cyclothymic disorders, or patients who concomitantly suffered from psychotic features. *Study design:* - Abstracts - Reports from proceedings or symposia - Non-original research. *Data availability:* Articles from which data were not extractable *Exposure:* Differences between groups in maternal exposure to other risk factors

SSRIs = Selective Serotonin Reuptake Inhibitors; DAAs = Dual Action Agents; TCAs = tricyclic antidepressants; MAOIs = Monoamine Oxidase Inhibitors.

MEDLINE, EMBASE, Healthstar, Toxline, Cochrane database, and Reprotox were searched for studies published from 1966 to the end of 2002. Keywords used to identify articles included pregnancy outcome, abortion, miscarriage, spontaneous, therapeutic, antidepressant, depression, and the generic names of each antidepressant and class (e.g., tricyclic, SSRI, SNRI, MAOI). Bibliographies, review articles, and reference lists from studies were also used to identify potential articles expected to provide evidence of safety of antidepressants in pregnancy. Abstracts were excluded, as were papers presented only at scientific meetings and symposia.

A stepwise study selection approach was performed. An initial search was done through examination of information in titles and abstracts, comparing against the preset criteria. This selection was followed by a thorough examination of the remainder of the included articles by analysis of the complete article. Possible reasons for rejection were categorized in the following subclasses: (a) non-original research, (b) ineligible outcome measure, (c) no data of interest, (d) non-comparative study, (e) data not extractable, (f) other/miscellaneous. The results were compared with those of a second reviewer, and discrepancies were settled through consensus discussion, with unresolved disputes adjudicated by a third reviewer whose judgment was considered final. After final selection of articles for inclusion in the

meta-analysis, the same two reviewers independently extracted data from the accepted studies onto a collection sheet. Discrepancies in data extraction were resolved in the same manner as for article identification.

After the data from each study were entered into 2x2 tables, risk ratios and 95% confidence intervals ($CI_{95\%}$) were calculated for each study. Before pooling results, we examined for heterogenity of effects by calculating χ^2. Then, results from individual studies were pooled using the random-effects model developed by Cochran.[29] As subgroup analyses, SA rates were determined for individual classes of antidepressants.

Because outputs like RRs may be difficult to interpret, the number needed to treat to harm (NNTH) was also calculated. The NNTH estimates the number of patients that would need to be exposed to an antidepressant to produce one additional SA. The $CI_{95\%}$ was calculated using the limits of the confidence interval on the RR, as described by Bjerre et al.[30]

The presence of publication bias was evaluated with the funnel-plot-based trim and fill method.[31-35] The trim and fill algorithm is based on a formation of the qualitative approach using the funnel plot. The asymmetric outlying part of the funnel is trimmed off after the number of studies that are in the asymmetric part are estimated. The symmetric remainder is then used to estimate the true center of the funnel. Then, the trimmed studies and their (presumed) missing counterparts are replaced around the center. The final estimate of the true mean, and also its variance, are then based on the filled funnel plot and compared with its original value to assess the impact.[34]

Because the funnel plot requires judgement and has no associated statistical test, we also applied the Begg and Mazumdar[36] test. That test complements the funnel graph, examining the agreement between effect estimates and their variances by calculating Kendall's τ. In this way, it exploits the fact that publication bias will tend to induce a correlation between these two factors; thus, a significant τ would indicate the presence of publication bias.

The quality of individual studies may effect the overall interpretation of the results in a meta-analysis. Based on the critical appraisal systems described by Elwood et al.,[37] Lichtenstein et al.,[38] and Feinstein,[39] a scoring sheet was developed as the basis for quality assessment of the articles. The checklist contains 29 questions in total, which requires the reviewer to answer yes or no to each item and score each item with 1 point if the answer is yes and 0 points if the answer is no. Thus, the highest score is 29. If a question was not applicable (NA) to a specific article, the total score would be calculated based on the total answerable questions. The questions in the checklist are separated into 7 categories, with each category representing a section within the article being evaluated. The categories

include Research design, Subjects, Exposure, Analysis, Confounders and bias, Methods, and Results.

It was decided that descriptors would assist in the judging of the quality. The scores were therefore divided into quartiles as follows: a) 25% = very poor, b) 25%-49% = poor, c) 50%-75% = acceptable, and d) >75% = good quality. Descriptive statistics such as the mean and range were used to determine the overall quality of the cohort studies. A copy of the checklist appears in the Appendix. To avoid potential bias, all identifying information (e.g., authors, institutions, journal, and country) was removed from the articles by an independent third party. Two independent, blinded raters performed scoring. Scores were compared between raters, with differences settled through consensus. In the case of disagreement, a third judge was enlisted as adjudicator whose decision was considered final.

To determine the validity of the quality scoring, the interrater reliability between the two reviewers was measured using the kappa statistic with statistical significance set at p-value = 0.05.[40,41] It was decided *a priori* that a kappa value of 0.8 would be deemed satisfactory to establish reliability. Furthermore, to assure the quality of the meta-analysis, a cutoff point in quality score <50% was used to exclude studies from the meta-analysis.

Results

Figure 1 depicts the search results and disposition of those articles. The initial search yielded 156 potential articles, but on reading the titles and abstract, 15 remained. Of those 15, 9 were rejected;[42-50] 3 did not contain pertinent data and we were unable to extract data from the other 6. That left 6 articles that met the inclusion criteria and provided useable data[51-56] with 11 different data sets (i.e., some reported on more than one group tking different drugs or classes of drugs). Table 2 describes the accepted studies and their characteristics.

Figure 1. Literature search strategy, results, and disposition of potential articles identified in the search

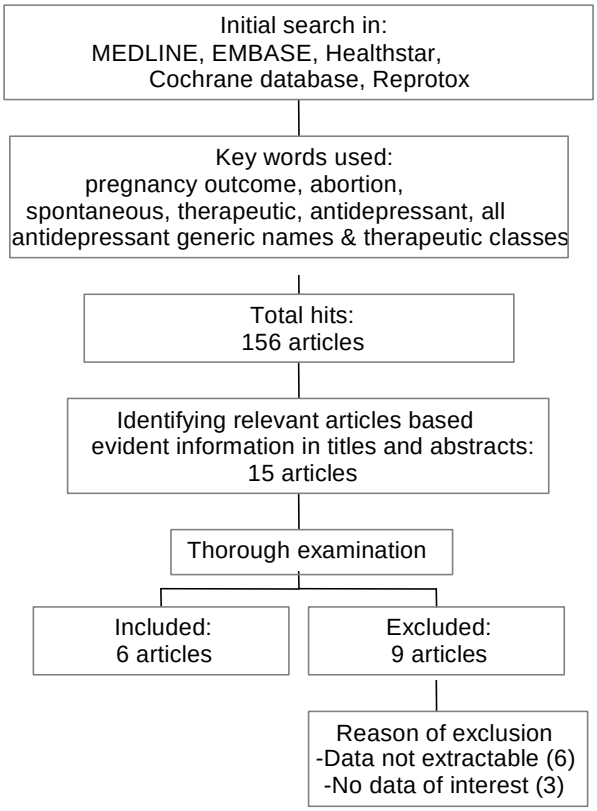

Table 2. Description of included studies and their characteristics.

Author, Year, Country	Quality score	Indication, exposure (dose)	Nonexposed subjects	Primary outcome	Matching variables	Exposure history and patient data obtained	Exposure definition	Outcome verification
Einarson[21], 2003, Canada	66%	Depressed Trazodone/nefazodone (dose: NS)	NT	MM	Disease, age, smoking, alcohol, time of call	Medical indication for drug use, dose, frequency/timing of administration, maternal demographics, obstetrical history	Defined as occurring during organogenesis (4-14th week)	Telephone interview and examination of medical record
Einarson[22], 2001 Canada	69%	Depressed Venlafaxine (75mg/day, range 37.5-300mg/day)	SSRI, depressed NT	MM	Age, smoking status, alcohol use	Medical indication for drug use, dose, frequency/timing of administration, maternal demographics, obstetrical history	Defined as occurring during organogenesis	Telephone interview and examination of medical record
Kulin[23], 1998, Canada	72%	Depressed SSRIs: Sertraline (50mg/day), Paroxetine (30mg/day) Fluvoxamine (50 mg/day)	NT	MM	NS	Medical indication for drug use, SSRI dose schedule and length of therapy, other therapy, smoking and alcohol, medical, obstetric, and genetic history, exposure to environmental toxins	Defined as occurring during first trimester	Telephone interview and examination of medical record
Chambers[51], 1996, USA	83%	Depressed (77%) Fluoxetine (dose: 28mg/day +/- 15mg)	NT	Major and minor structural anomalies or perinatal complications	Age	Dosage, dates, and indications for all medications, caffeine, vitamins, occupational exposures, infectious/chronic disease, prenatal testing, use of recreational drugs, tobacco, alcohol	Defined as occurring during first trimester	Telephone interview and examination of medical record
Pastuszak[20], 1993, Canada	79%	Depressed Fluoxetine (25.8 mg/day, range 10-80mg/day)	TCA NT	BD	Age	Obstetric, medical, genetic and drug exposure history	Defined as occurring during first trimester	Telephone interview and examination of medical record
McElhatton[52], 1996, Europe	66%	Depressed TCA (dose: NS)	Non TCA NT	PO	NS	Medical and obstetric history	Throughout pregnancy	Questionnaire and Telephone interview

BD= Birth Defects; MM= Major Malformations; NS= Not Stated; NT= Non-Teratogenic; PO= Pregnancy Outcomes (Including spontaneous and therapeutic abortions, fetal death, malformations, neonatal disorders); SSRI= Selective Serotonin Reuptake Inhibitor; TCA= Tricyclic antidepressant.

Table 3. All study arms with their number of patients in the exposed, nonexposed group for the SAs, along with their Risk Ratios and $CI_{95\%}$.

Study	Drug Class	Exposed group			Nonexposed group			RR	$CI_{95\%}$
		SA	No SA	Rate	SA	No SA	Rate		
Einarson[21]	DAA	20	127	0.14	12	135	0.08	1.67	0.85-3.28
Einarson[22]	DAA	18	132	0.12	11	139	0.07	1.64	0.80-3.35
Einarson[22]	SSRI	16	134	0.11	11	139	0.07	1.45	0.70-3.03
Kulin[23]	SSRI	30	237	0.11	21	246	0.08	1.43	0.84-2.43
Chambers[51]	SSRI	23	146	0.14	22	232	0.09	1.57	0.91-2.73
Pastuszak[20]	SSRI	10	64	0.14	5	69	0.07	2.00	0.72-5.57
Pastuszak[20]	SSRI	19	109	0.15	10	118	0.08	1.90	0.92-3.93
McElhatton[52]	SSRI	12	80	0.13	28	235	0.11	1.23	0.65-2.31
Pastuszak[20]	TCA	9	65	0.12	5	69	0.07	1.80	0.63-5.12
McElhatton[52]	TCA	12	97	0.11	28	235	0.11	1.03	0.55-1.96
McElhatton[52]	TCA	23	151	0.13	28	235	0.11	1.24	0.74-2.08
Meta-analysis	**All**	**192**	**1342**	**0.124**	**181**	**1852**	**0.087**	**1.45**	**1.19-1.77**

SSRIs = Selective Serotonin Reuptake Inhibitors; DAAs = Dual Action Agents; TCAs = tricyclic antidepressants;
MAOIs = Monoamine Oxidase Inhibitors; SA = Spontaneous abortion; RR = Risk Ratio; $CI_{95\%}$ = 95% confidence interval

Table 4. Meta-analytic risk rates and ratios of spontaneous abortions and the number needed to treat to harm.

Drug Group						Comparison Group			Meta-analytic Risk Ratio			NNTH($CI_{95\%}$)
Class	Studies	N	Rate (N)	$CI_{95\%}$	$\chi^2_{Heterogeneity}$	Rate (n)	$CI_{95\%}$	$\chi^2_{Heterogeneity}$	Rate	$CI_{95\%}$	$\chi^2_{Heterogeneity}$	
Overall	11	3567	12.4% (1534)	10.8-14.1	2.29 (p=0.994)	8.7% (2033)	7.5-9.9	5.31 (p=0.99)	1.45	1.19-1.77	3.13 (p=0.978)	26 (17-53)
SSRIs	6	2016	12.4% (880)	10.2-14.5	1.76 (p=0.881)	8.4% (1136)	6.8-10.0	2.15 (p=0.828)	1.52	1.17-1.98	1.16 (p=0.948)	23 (14-67)
TCAs	3	957	12.3% (357)	8.9-15.7	0.31 (p=0.855)	10.0% (600)	7.6-12.4	1.47 (p=0.481)	1.23	0.84-1.78	0.79 (p=0.672)	43 (NS)
DAAs	2	594	12.8% (297)	9.0-16.5	0.17 (p=0.679)	7.7% (297)	4.7-10.8	0.07 (p=0.789)	1.65	1.02-2.69	0.001 (p=0.971)	20 (10-500)

SSRIs = Selective Serotonin Reuptake Inhibitors; DAAs = Dual Action Agents; TCAs = tricyclic antidepressants; MAOIs = Monoamine Oxidase Inhibitors; N = Number of patients; $CI_{95\%}$ = 95% confidence interval; NNTH = Number Needed to Treat to Harm; NS = Not significant).

The overall test for heterogeneity of effects was non-significant (χ^2 =3.13, p= 0.978), suggesting that results could reasonably be combined. As well, tests for individual classes of antidepressant were not significant (SSRIs: χ^2 = 1.16, p = 0.948; TCAs: χ^2 = 0.79, p = 0.672; DAAs: χ^2 = 0.01, p = 0.971).

The funnel plots for the 11 sets of data showed that there existed a lack of small "negative" studies. The Begg-Mazumdar confirmed this observation that publication bias was present (τ= 0.491; p = 0.04). The meta-analytic RR was 1.45 ($CI_{95\%}$ = 1.19-1.77, N = 3567; Table 3), however, after adjustment, it changed only slightly to was 1.36 ($CI_{95\%}$ = 1.15-1.61). Thus, although publication bias appeared to be present, the results of the meta-analysis were not affected.

Overall, the quality of the included articles was rated as acceptable (Table 2). Kappa between the two raters was 0.86 (Z=11.32, P<0.001), which was considered acceptable. Table 4 summarizes all of the rates of interest. The baseline rate of SAs, as estimated by the group not exposed to antidepressants was 8.7% ($CI_{95\%}$ = 7.5%-9.9%). The risk for SAs in depressed pregnant women who were exposed to antidepressants during the pregnancy was 12.4% ($CI_{95\%}$ = 10.8%-14.1%). Exposure to antidepressants was associated with an average increase from of 3.9% ($CI_{95\%}$ = 1.9%-6.0%), with a corresponding the risk ratio of 1.45 ($CI_{95\%}$ = 1.19-1.77). Non-significant differences were found between antidepressant classes in risk ratios.

Discussion

To our knowledge, this is the first meta-analysis to examine the risk for spontaneous abortion in pregnant women exposed to antidepressants, which included 3567 women. Although this meta-analysis indicates that maternal exposure to antidepressants may be associated with a significantly increased risk for spontaneous abortions and therapeutic abortions, depression per se may also be associated with abortive properties.

Despite a great volume of literature on the subject, we were only able to include a relatively small number of cohort studies. Six studies with a total of 11 treatment arms reporting rates on spontaneous abortions were included in the analysis. Women were exposed to drugs from three therapeutic classes (SSRIs, TCAs, and DAAs). This sample size was considered adequate for the purpose of this analysis.

Because there was sufficient power to detect a difference, one may assume that there is no important clinical difference between spontaneous abortions compared to those women in the non exposed groups.

If these results are compared with the postulated theories (i.e., the serotonin theory and the adrenergic/noradrenergic theory, the following associations could be made: the serotonin theory, which suggested that serotonin possesses abortive properties, may be valid. With respect to the adrenergic/noradrenergic theory, which suggests that catecholamines are associated with tocolytic properties, no significant tocolytic association was observed. The similar results among women who were exposed to different classes makes the immunological theory more plausible.

Some of the studies included in the meta-analysis matched the patients for age, smoking status, alcohol use, and time of the call. None of the studies, however, investigated the patient's reproductive history. Regan et al. followed-up prospectively 630 women to estimate the overall incidence of clinically recognizable spontaneous abortions prior to 20 weeks of gestation. Initially, the overall risk for spontaneous abortions was 12% (50/407 pregnancies). After stratification with respect to the patient's 'reproductive history, this rate was 4% (3/73) for women who had a history of consistently successful pregnancies, and 24% (24/98) among women with unsuccessful histories, whereas the incidence of loss of pregnancy among women whose last pregnancy had aborted was 19% (40/214).[26] Therefore, it may be possible that the results of our studies are biased, however, in which direction remains unknown. The strength of our study was the use of comparative groups which were enrolled in the same fashion, thus eliminating this bias.

A limitation was that institution bias may be present, as two-thirds of the studies were produced by the Motherisk Program at the Hospital for Sick Children in Toronto, Canada. Therefore, it could be possible that methodology-wise, these 4 studies have more in common with each other compared to the other two.

As previously discussed, spontaneous abortion rates in the population range between 12%-15%. According to this meta-analysis, the meta-analytic rate (12.4%) falls within this range of published rates. A few non-controlled prospective studies have been published reporting similar rates in women exposed to antidepressants during their pregnancy. Goldstein et al.[27] evaluated outcomes of pregnancies with confirmed first-trimester fluoxetine exposure in the Eli Lilly and Company pregnancy registry. In this study, spontaneous abortions were reported in 110 of the 796 (13.8%) pregnancies, which is a little higher than our meta-analytic rate of 12.4% for the SSRIs. There are other limitations, most importantly the time of exposure among the studies varied. This is especially true with women identified through teratogen information services, where women initiate a call to the service requesting information regarding a drug use during pregnancy. If a woman taking an antidepressant becomes pregnant and suffers a spontaneous abortion early on, she would not call the service and therefore would not be included in the study, thus lowering the rates. Currently, the

Motherisk Program enrols all women in both groups within 1 week of time of call, however this was only done in the trazodone/nefazodone study. In that study the differences were greater between the exposed and comparison group than in the other studies. Despite this, even in the other studies that did not match for time of call, the comparison group was recruited in the same way as the exposed group and still there were more spontaneous abortions in the exposed group.

We were unable to locate any studies of women who were depressed and not receiving any pharmacotherapy, which may solve the question whether it is the drugs or the depression that is associated with this increase in spontaneous abortion. The ideal study would be to enrol 4 groups of women, including 1) depressed, taking antidepressants, 2) depressed, not taking antidepressants, 3) not depressed, taking antidepressants and 4) not depressed, not taking antidepressants. However, this type of study would be very difficult to carry out at a teratogen information service, because normally women do not call these services unless they are taking a drug and want information on the safety of that drug in pregnancy.

In summary, this meta-analysis indicates that maternal exposure to antidepressants may be associated with a significantly increased risk for spontaneous abortions. However, is important to keep in mind that the underlying depression could also be a contributing factor. Women and their health care providers should be cautious about using this information to decide whether or not to treat their depression pharmacologically during pregnancy. Further research is needed before any definitive conclusion can be made. A pregnant woman with depression should be treated with antidepressants if appropriate, to ensure that she is in optimal mental health for both herself and her baby.

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Appendix. Checklist for quality scoring.

Author and Title of article:

Reviewer:

Questions:	YES	NO	NA
Research Design			
Was research design model stated? (e.g., cohort study)			
Was research question stated explicitly?			
Was exposure mentioned by name/definition?			
Was exposure well described?			
Was the outcome described by diagnostic procedure / definition?			
Was study population described?			
Subjects			
Was source of cohort identified?			
Was study group defined?			
Was outcome defined / described?			
Was follow-up appropriate for study purpose?			
Exposure			
Was duration of exposure described?			
Was quantity/dosage of exposure stated?			
Is the appropriate time of exposure measured?			
Was exposure verified?			
Analysis			
Was method of data-collection mentioned? (Interview, Questionnaire, Record review, etc.)			
If an interviewer or record review was used, information on whether or not these observers were blinded?			
Was there a correct time relationship?			
Was conclusion drawn from data?			
Confounders and bias			
Was information on the presence of possible confounding variables stated?			
Were possible sources of bias investigated?			
Were methods for dealing with confounders used and mentioned?			
Was the influence of bias on the results described?			
Methods			
Were analytic methods described? (statistical methods)			
Did controls undergo the same diagnostic procedures as the cases?			
Results			
Was non-response rate stated?			
Was main result described?			
Was there a dose-response relationship?			
Were appropriate results given? (OR, RR, etc.)			
Was confidence interval stated?			

NA= Not applicable; OR= Odds ratio; RR= Risk ratio

2.2 Evaluation of the risk of congenital cardiovascular defects associated with use of paroxetine during pregnancy

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Am J Psychiatry. 2008;165(6):749-52

Abstract

Objective: In 2005–2006, several studies noted an increased risk of cardiovascular birth defects associated with maternal use of paroxetine compared with other antidepressants in the same class. In this study, the authors sought to determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.

Method: From teratology information services around the world, the authors collected prospectively ascertained, unpublished cases of infants exposed to paroxetine early in the first trimester of pregnancy and compared them with an unexposed cohort. The authors also contacted the authors of published database studies on antidepressants as a class to determine how many of the women in those studies had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Results: The authors were able to ascertain the outcomes of 1,174 infants from eight services. The rates of cardiac defects in the paroxetine group and in the unexposed group were both 0.7%. The rate in the database studies (2,061 cases from four studies) was 1.5%.

Conclusions: Paroxetine does not appear to be associated with an increased risk of cardiovascular defects following use in early pregnancy, as the incidence in more than 3,000 infants was well within the population incidence of approximately 1%.

Introduction

Prior to late 2005, selective serotonin reuptake inhibitor (SSRI) antidepressants as a class were considered relatively safe to take in pregnancy, as they had not been found to be associated with a risk of major malformations above the baseline rate of 1%–3% in the general population. Studies supporting this view included a meta-analysis and two database studies, with a combined total approaching 4,000 pregnancy outcomes [1–3].

In the fall of 2005, GlaxoSmithKline published on its web site the results of a claims database study with the finding that infants exposed in utero to paroxetine may have a higher risk of congenital malformations, in particular cardiovascular defects. The study was based on outcomes of 815 infants, and the reported incidence of cardiovascular malformations, unspecified in terms of severity, was 2% [4]. A more detailed analysis of these data was published recently in which the incidence was adjusted to 1.5% [5]. The latest results of a prospective longitudinal database study in Sweden [6], which included 959 exposures to paroxetine in early pregnancy, indicated an increased risk of cardiovascular defects of relatively mild types after maternal use of paroxetine, at a rate of 2%. Finally, a small prospective comparative study from a teratology information service, presented as an abstract at a meeting, also documented a higher rate of cardiovascular defects associated with use of paroxetine, at 1.9% [7].

Based on these three reports, warnings were posted in late 2005 on the web sites of Health Canada [8] and the U.S. Food and Drug Administration (FDA) [9] advising women to avoid paroxetine if possible during pregnancy. In December 2006, the American College of Obstetricians and Gynecologists published a similar advisory [10]. After these warnings were publicized in the media, a web site was developed that invited women to join a class action suit against GlaxoSmithKline if they had taken paroxetine in pregnancy and delivered a baby with a cardiovascular birth defect [11].

We were concerned that, because 50% of pregnancies are unplanned [12], women who were already pregnant and taking paroxetine might abruptly discontinue their medication. Abrupt discontinuation is generally not wise, although some women may feel that it is the right course to take [13]. Notably, there have been no similar warnings about the risk of cardiovascular birth defects from the psychiatric professional bodies. In a study of 201 pregnant women recently published by a group of psychiatrists [14], 86 (43%) women experienced a relapse of major depression during pregnancy. Among the 82 women who maintained their medication throughout their pregnancy, 21 (26%) relapsed, compared with 44 (68%) of the 65 women who discontinued medication. The authors noted that women

with a history of depression were less likely to relapse if they stayed on their medication during pregnancy and recommended that each case be considered individually.

The primary objective of our study was to collect from teratology information services around the world as many cases as possible of infants who had first-trimester in utero exposure to paroxetine and to calculate the rate of cardiovascular defects in these infants and in a unexposed cohort. The secondary objective was to contact the authors of database studies that had been published on antidepressants as a class to determine how many women in these studies had been exposed to paroxetine and the rates of cardiovascular defects in their infants.

Methods

We identified pregnancy outcomes of infants exposed in utero to paroxetine from two sources: teratology information services and database studies. The Motherisk Program at the Hospital for Sick Children in Toronto is a teratology information service. We provide evidence-based information on the safety of and risks associated with exposures to drugs, chemicals, radiation, and infectious diseases during pregnancy and lactation to pregnant women, lactating mothers, and their health care providers. We also conduct observational studies of drugs and other exposures in pregnancy. We are member of the Organization of Teratology Information Services (OTIS), a group with members in North America. The European Network of Teratology Information Services (ENTIS) is a group based in Europe, and similar services operate in other parts of the world, providing services similar to those we provide and collecting information on women and pregnancy outcomes in the same fashion. We have collaborated on many occasions, including in research on pregnancy outcomes of women who were exposed to various antidepressants [15–20].

At the teratology information services, women are recruited for studies when they call to inquire about the use of a drug they are taking and are currently pregnant. Eligible women are prospectively enrolled in the study after providing informed consent over the telephone. During the initial telephone contact, demographic information, medical and obstetrical histories, and details of exposure and concurrent exposures are recorded on a standardized questionnaire form. Details about the exposure include duration, timing in pregnancy, dose, frequency, and medical indication for use of the drug. Women are informed that they will be contacted after their expected date of delivery for an assessment of pregnancy outcome. At the follow-up interview, gestational findings and fetal outcomes are documented on a

structured, standardized form by telephone interview. With the mother's permission, this report is corroborated with the report of the physician caring for the baby.

This method of data collection by teratology information services involves three critical elements that are not always possible with database studies: personal interviews with the mothers; confirmation of drug exposure, including time and dose; and confirmation of the congenital defect by the child's attending physician. In addition, because all of the women called the teratology information service when they were in early pregnancy and the details of their pregnancy and drug exposure were recorded at that time, the possibility of recall bias is eliminated.

We contacted members of OTIS, ENTIS, and the other services to request available pregnancy outcomes of women who had taken paroxetine in the first trimester of pregnancy. We requested details of their cases, with specific information on the rates of cardiovascular defects and ascertainment of the infant's age at the time of diagnosis. To form a comparison group, we obtained an equal number of pregnancy outcomes of other women who called teratology information services inquiring about exposures to drugs that are considered safe in pregnancy, such as acetaminophen, and calculated the rate of cardiovascular defects in infants of mothers in this group. Women in the comparison group had similar demographic and clinical characteristics to those of the study group, such as smoking, alcohol use, and socioeconomic status, and their infants were not exposed to teratogenic agents or antidepressants. They were not enrolled in any other study.

Subsequently, we identified published database studies of pregnancy outcomes following exposure to antidepressants. Since all of these studies presented SSRI data aggregated by class [21–24], we contacted the authors and requested the same information, specific to paroxetine, as we had from the teratology information services.

The rate of cardiovascular birth defects following exposure to paroxetine in pregnancy was compared with the rate in the comparison group of unexposed women by means of chi-square test and expressed as an odds ratio as well as in percentages.

The study protocol was approved by the Hospital for Sick Children Research Ethics Board as well as by the research ethics boards at the other sites.

Results

We were able to ascertain 1,174 unpublished cases of first-trimester paroxetine exposure from eight teratology information services and 2,061 cases from five previously published

database studies, including the GlaxoSmithKline study [4] (Table 1). One of the groups of authors we contacted to request information from their database [24] was not able to provide details of specific exposure to paroxetine because of the confidentiality policy of the database (although the authors did report that there were 320 cases of women exposed to paroxetine in their study).

Table 1 Paroxetine exposure during pregnancy and cases of cardiovascular birth defects (N=3,379)

Sources of Cases	Exposures	Cases
Teratogen Information Services	300	0
Florence, Italy	170	0
Rome	25	0
Lausanne, Switzerland	17	0
Sidney, Australia	158	2
Toronto, Canada	98	0
Ravensburg, Germany	252	5
Tel Aviv, Israel	143	2
San Diego, USA	11	0
Helsinki, Finland	1,174	9[a]
Previously published cases from database studies		
Malm et al.[22]	149	1
Wilton et al. [21]	63	0
Källén and Olausson [6]	959	20
Wogelius et al. [23]	219	1
GlaxoSmithKline [4]	815	12
Total	2,205	34[b]

[a] incidence=0.7%; 95% CI=0.4-1.4
[b] incidence=1.5%; 95% CI=1.1-2.1

All of the women in the cases we ascertained had been taking paroxetine before they became pregnant and continued well into the first trimester, so their infants were exposed while the fetal heart was developing.

The rates of cardiovascular defects in the teratology information service cohort were 0.7% in the exposed group and 0.7% in the unexposed group (odds ratio=1.1, 95% confidence interval [CI]=0.36–2.78). In the database group, the rate was 1.5%. When the data sets from the teratology information services and from the database studies were combined, the mean rate of cardiovascular defects was 1.2% (95% CI=1.1–2.1).

Discussion

To our knowledge, these data represent the largest documented number of exposures (>3,000) to paroxetine during the first trimester of pregnancy. The rate of cardiovascular

defects falls well within the incidence of cardiovascular defects in the general population, which was documented in Hoffman and Kaplan's landmark study investigating the incidence of congenital heart disease in the population [25]. Hoffman and Kaplan reviewed 62 studies published since 1955 in an attempt to determine the reasons for the variability of the reported incidence of congenital heart disease. After taking into account the timing of diagnosis, their estimate of the incidence of moderate and severe forms of cardiovascular defects was about 6 per 1,000 live births, which increases to 19 per 1,000 with the inclusion of the potentially serious bicuspid aortic valve, and to 75 per 1,000 with the inclusion of tiny muscular ventricular septal defects that are present at birth and may resolve spontaneously and other trivial lesions. Their estimate of the overall incidence was 0.96% (95% CI=0.7–1.2). They also concluded that there is no evidence for differences in incidence among different countries.

Confirmation of the timing of diagnosis was not standardized in either the teratology information services or the database studies, and the timing varied from 1 month to 3 years of age across all studies. Consequently, some defects would not have been detected immediately after birth in the early interviews, and conversely, some would have resolved spontaneously by the time of the later examinations. Källén and Olausson [6], who reported the highest incidence, did state that most of the defects in their cohort were minor, and in a personal communication (January 2007) Källén indicated that his group counted all diagnosed cardiovascular defects, even if they resolved spontaneously. In contrast, the teratology information service groups did not include cardiovascular defects that resolved spontaneously (with the exception of Diav-Citrin et al. [7], who reported a higher rate; personal communication, December 2006), so this would account for their lower rates. The GlaxoSmithKline results did not specify whether the defects were mild, moderate, or severe, so a number of these cases may have resolved spontaneously, and inclusion of these cases could have inflated the rate. However, despite these discrepancies and variations, the overall rate still fell within the limits described in Hoffman and Kaplan's report on population rates of cardiovascular defects [25].

Our study has several limitations. One of these is the sample size, which is relatively small for an epidemiologic study. However, to date the cases we report on constitute the largest number of prospectively ascertained pregnancy outcomes after exposure to paroxetine, including the database studies. If, as reported in the Hoffman and Kaplan review [25], cardiovascular defects occur in approximately 1% of cases, our sample size is large enough to rule out a twofold increased risk. Another limitation may be the combining of cases from different countries. However, as documented in our previous publications, when maternal characteristics were compared among sites, we found no differences [17, 20]. Women who call

teratology information services anywhere in the world tend to be more highly educated, of higher socioeconomic status, and older, with a mean age of 30 years (SD=2). They do not reflect all pregnant women in the general population who use antidepressants, but as a group they are homogeneous. For obvious reasons, it is impossible to conduct a randomized controlled study of women taking drugs during pregnancy.

A recent study by Berard et al. [26] reported an increased risk of cardiac defects (1.7%) associated with paroxetine, but only with dosages above 25 mg/day. In our study, most of the women received paroxetine at a dosage of 20 mg/day or less, and there was not enough variability to conduct a dose-response analysis. The Berard et al. study is the first to report a dose response, although it was based on information from a prescription database, which lacks any confirmation that the women actually took the medication as dispensed. It is conceivable that women stopped taking paroxetine when their pregnancy was diagnosed, or lowered the dose, especially after seeing media reports of concerns about paroxetine use in pregnancy. We reported this phenomenon in a recent publication based on interviews of women after reports in the media of concerns regarding neonatal effects of antidepressants[27].

In summary, our data suggest that paroxetine is not associated with an increased risk of cardiovascular birth defects. The number of cases in our analysis is larger than in other published studies on this topic, which typically have sample sizes in the range of 100–200 cases [17, 19]. With nearly 1,200 cases from teratology information services and over 2,200 cases from previously published database studies, our findings may be considered sufficient evidence to suggest that there is no association between the use of paroxetine in pregnancy and risk of cardiovascular defects in exposed infants.

This is important information for women and their health care providers in their effort to make informed, evidence-based decisions as to whether to take paroxetine during pregnancy. Untreated depression during pregnancy appears to carry substantial perinatal risks, whether they be direct risks to the fetus and infant or risks secondary to unhealthy maternal behaviors arising from depression. These risks include suicidal ideation, an increased risk of miscarriage, hypertension, preeclampsia, and lower birth weight. Moreover, untreated depression in pregnancy is associated with a sixfold increase in the risk of postpartum depression [28, 29]. Consequently, appropriate treatment of depression during pregnancy is essential, and if this includes taking paroxetine, the findings of this study should reassure women and their health care providers. A pregnant woman should always be in the best mental health possible to ensure optimal outcomes for herself and her child.

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2.3 Adverse effects of antidepressant use in pregnancy: an evaluation of fetal growth and preterm birth

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Depress Anxiety. 2010;27(1):35-8

Abstract

Objective: To compare the rates of low birth weight, preterm delivery and small for gestational age (SGA), in pregnancy outcomes among women who were exposed and nonexposed to antidepressants during pregnancy.

Methods: At The Motherisk Program, we analyzed pregnancy outcomes of 1,243 women in our database who took various antidepressants during their pregnancy. Nine hundred and twenty-eight of these women and 928 nonexposed women who delivered a live born infant were matched for age, (±2 years), smoking and alcohol use and specific pregnancy outcomes were compared between the two groups.

Results: There were 82 (8.8%) preterm deliveries in the antidepressant group and 50 (5.4%) in the comparison group. OR: 1.7 (95% CI: 1.18–2.45). There were 89 (9.6%) in the antidepressant group and 76 (8.2%) in the comparison group who delivered babies evaluated as SGA; OR: 1.19 (95% CI: 0.86–1.64). The mean birth weight in the antidepressant group was 3,449±591 g and 3,455±515 g in the comparison group (p=0.8).

Conclusion: The use of antidepressants in pregnancy appears to be associated with a small, but statistically significant increased rate in the incidence of preterm births, confirming results from several other studies. It is difficult to ascertain whether this small increased rate of preterm births is confounded by depression, antidepressants, or both. However, we did not find a statistically significant difference in the incidence of SGA or lower birth weight. This information adds to limited data available in the literature regarding these outcomes following the use of antidepressants in pregnancy. Depression and Anxiety,

Introduction

The use of antidepressants in pregnancy remains a controversial topic; consequently, prescribing them in pregnancy is a complex decision-making process. This is understandable because of the number of conflicting studies published in the literature and lack of practice guidelines. There is also a paucity of information on outcomes other than birth defects, such as preterm births, small for gestational age (SGA), and birth weight.

Preterm birth

The criteria for a diagnosis of preterm birth are delivery at <37 weeks of pregnancy.[1] There is little data regarding this outcome and antidepressant use, especially studies with large cohorts. The most recent and largest study to date was from a group who analyzed data from a large Health Maintenance Organization (HMO). Each woman was administered the CESD once during pregnancy and after controlling for use of antidepressants (85% were not taking an antidepressant); they reported an increased rate for preterm birth. Among the 791 women who completed the study, individuals with CESD scores ≥16 had almost twice the risk of preterm delivery, compared with women without depressive symptoms: adjusted hazard ratio (aHR)=1.9, 95% confidence interval (CI) 1.0–3.7. In addition, the risk for preterm birth increased with severity of illness and appeared to be associated with low educational level, history of fertility problems, obesity, and stressful events. The authors concluded that it was the depression, rather than medication use, that was associated with an increased risk for preterm birth, as only the women who were not taking antidepressants were included in the final analysis.[2] Conversely, several studies have been published that documented an increased risk for preterm birth in infants whose mothers used antidepressants during pregnancy, although the results were not highly significant.[3–6] To further add to the complexity of the situation, other studies that reported on women taking antidepressants during pregnancy did not find an increase in the rates of preterm births (Table 1).[7–10]

SGA is a gender-specific measure that combines both gestational age and birth weight. An infant born SGA is one whose birth weight is below the 10th percentile and is based on reference birth weight curves stratified by infant gender, gestational age, singleton birth status, and country. SGA infants have been shown to suffer from growth restrictions, and are thus at an increased risk of death compared to non-SGA infants. In addition, some of these children may suffer from permanent deficits in growth and neurodevelopment in later childhood.[11,12] We were unable to find any studies in the literature that specifically described SGA associated with depression and/or exposure to antidepressants during pregnancy.

Birth weight

Low birth weight has been defined by the World Health Organization (WHO) as weight at birth of less than 2,500 g (5.5 lbs). This practical cut-off for international comparison is based on epidemiological observations that infants weighing less than 2,500 g are approximately 20 times more likely to die than heavier babies. More common in developing than developed countries, a birth weight below 2,500 g contributes to a range of poor health outcomes.[13] To date, results of studies are conflicting as to whether depression and or antidepressant use during pregnancy increases the risk for low birth weight. It appears that there are a similar number of studies describing an association,[14–16] as ones that did not.[17, 18] Most of the studies have relatively small sample sizes and the odds ratios (OR) in the studies that did find a statistically significant result were not highly significant, as none was higher than 2. The objectives of our study were to compare the incidence of preterm births, SGA, and mean birth weight in two groups of women, exposed and nonexposed to antidepressants

Methods

The Motherisk Program at the Hospital for Sick Children in Toronto, Canada is a Teratology Information Service. We provide evidence-based information on the safety and or risks associated with exposures to drugs, chemicals, radiations, and infectious diseases during pregnancy and lactation to pregnant women, lactating mothers, and their health care providers. Women call us for information regarding the safety of a drug, usually early in gestation, most often following recognition of the pregnancy. During the initial telephone contact, demographics, medical, and obstetrical histories as well as details of drug and concurrent exposures are recorded on a standardized questionnaire. Details include duration, timing in pregnancy, dose, frequency, and indication for drug use. At the follow-up interview, gestational findings, fetal outcomes, and neonatal health are documented on a structured form by telephone interview with each mother, following a detailed explanation of the study and with her consent. The details are then, with her permission, corroborated with a report from the physician caring for the baby.

We used this method to ascertain pregnancy outcomes of women who called us regarding the use of antidepressants in pregnancy and entered the details in an electronic database. We used data from women who were pregnant at the time they contacted us for information regarding antidepressant use in pregnancy, and compared them with an equal

number of women who were not exposed to antidepressants and who had called Motherisk for information regarding nonteratogenic drugs such as acetaminophen. To examine the incidence of preterm births, SGA, and mean birth weight, we included only women who delivered a live born infant. The comparison group was composed of women who also delivered a live born infant and the two groups were matched for maternal age (±2 years), smoking, and alcohol use. We calculated the number of women who delivered an infant who fulfilled the definition of preterm birth and SGA in each group in percentages and then calculated the risk ratio and 95% confidence interval between exposed and nonexposed women. We compared birth weights in the two groups by calculating a mean and standard deviation. This study was approved by The Hospital for Sick Children, Research Ethics Board.

Results

We were able to analyze data from 928 women in each group who fulfilled the inclusion criteria. Of the 1,243 women, 315 were excluded from the analysis because they reported a spontaneous or therapeutic abortion, so did not fulfill the criteria of continuing the pregnancy to term. Due to the matching, there was no difference in maternal characteristics, with 20% of the women in both groups who smoked and less than 1% who used alcohol. The antidepressants taken by the women were: bupropion (113), citalopram (184), escitalopram (21), fluvoxamine (52), fluoxetine (61), mirtazepine (68), nefazodone (49), paroxetine (148), sertraline (61), trazodone(17), and venlafaxine (154).

When we examined the rates of premature delivery (<37 weeks gestation), there were 82/928 (8.8%) among women who took an antidepressant and 50 (5.4%) among the 928 comparison group. The difference was significant (OR=1.70; CI 95%: 1.18–2.45; χ^2=7.84,*P*=.005).

There were 89 (9.6%) in the antidepressant group and 76 (8.2%) in the comparison group who delivered babies evaluated as SGA. The difference was not statistically significant (OR=1.19, 95% CI: 0.86–1.64). The mean birth weight of infants exposed to antidepressants was 3,449±591 g, compared with 3,455±515 g in the comparison group

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Table 1 Comparison of outcomes of infants exposed/nonexposed to antidepressants (N=928 per group)

Outcome	Antidepressants	Nonexposed	Difference	p-value
Premature delivery	82 (8.8%)	50 (5.4%)	3.4%	.005*
Small for gestational age	89 (9.6%)	76 (8.2%)	1.4%	.3
Mean birth weight±SD (g)	3449±591	3455±515	6 g	.8

SD standard deviation, * Statistically significant

Discussion

To our knowledge this is the first study with a large enough sample size (**n**=938) to evaluate a possible association of SGA with the use of antidepressants in pregnancy, which we did not find. In addition, it is one of the few to examine a possible increase risk in preterm births and to examine the mean birth weights of infants born to mothers who had been exposed to an antidepressant during pregnancy. We did not find an increased risk for low birth weight as reported in other studies and we feel that our sample size was large enough to detect even a small difference of 70 g, which it did not.[14–16] The only statistically significant results we documented was a small but statistically increased risk for preterm delivery (OR 1.7). This confirms the findings of previous studies, where researchers documented similar results, also resulting in a small but statistically increased risk, regardless of whether the woman took an antidepressant or not.[2–4] Most recently, a prospective observational study was conducted, in which three groups of pregnant women: (1) depressed and exposed to antidepressants, (2) depressed and unexposed to antidepressants, and (3) nondepressed and nonexposed to antidepressants were followed longitudinally from week 20 through delivery. The only outcome that was statistically significantly different among the three groups was a higher rate of preterm births in both the women who were depressed and took an antidepressant and women who were depressed and did not take an antidepressant. However, the sample size in the depressed nontreated was small (**n**=36) and a larger sample would be required to make a definitive association in this particular study.[19] This most recent report, combined with previous data and the results of our study, appear to suggest that there may be a correlation between a pregnant woman's depression and an increase risk for preterm births.

The main strength of this study is the personal interview with the women, which includes a detailed history of drug use and other maternal demographics. Our pregnancy registry is

designed specifically for collecting pregnancy outcomes, so we are able to collect details of alcohol, tobacco, and concurrent drug use, as well as other potential confounders of pregnancy outcome. Importantly, because all women contacted Motherisk in early pregnancy and the details of their pregnancy and drug exposure was recorded at that time, the possibility of a recall bias is eliminated.

The major limitation, due to the nature of the participants in this study, was that we did not have a comparison group of women who were depressed and not taking antidepressants. The Motherisk Program is a service where women and their health care providers call us for information regarding the safety/risk of the antidepressant medication. Consequently, they do not call us unless they are actually taking a medication, so we were not able to form a comparison group of women who were depressed and untreated. Unfortunately, without this group of women it was not possible to measure whether the increased risk for preterm birth was due to the drug, the underlying depression, or both. We also did not have a measurement of whether the women taking antidepressants were appropriately treated (if they were euthymic) so as to be able to possibly separate the depression from the drug. Another limitation is that we did not receive confirmatory information from all the attending physicians, regarding pregnancy outcomes, despite sending reminders. The reliability of the mother's report regarding some of the outcomes could make a difference. However, this is the same deficiency in both groups and in this study, 70% of the physicians returned the forms. Finally, another limitation is that this is not a randomized sample and may not be extrapolatable to the general population of pregnant women taking antidepressants.

Prematurity is a multi-factorial condition in which in most cases the etiology is unknown. However, women who are depressed may suffer concurrently with stress and anxiety, which appears to be a biologically plausible reason for preterm births. Several studies have been published where the authors attempted to examine a possible association with stress and anxiety and an increased risk for preterm birth. The results have been conflicting with some finding an increased risk and others with no differences in any of the outcomes between women who were stressed and anxious and those who were not.[20, 21]

In one study, the authors reported that raised maternal prenatal cortisol levels played a role in the differences in the gestational age at birth.[22] In another study, it initially appeared that all the women in the stressed and anxious group had an increased risk for preterm delivery. However, when the data were stratified by body weight, only thin women with poor psychosocial background had a higher rate of preterm births.[23]

In summary, it appears that there is a small but significant increase in the incidence of premature births in women exposed to antidepressants during pregnancy. A woman who

requires treatment for depression during pregnancy should discuss the risk/benefit of pharmacological treatment with her physician, as it is important that her depression is treated adequately to ensure the best possible outcome for both her and her baby.

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2.4 Outcomes of infants exposed to multiple antidepressants during pregnancy: results of a cohort study

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J Popul Ther Clin Pharmacol. 2011;18(2):e390-6

ABSTRACT

Background A single study has been published documenting an increased risk for adverse pregnancy outcomes following use of more than one antidepressant during pregnancy.

Objective To examine whether multiple antidepressant use is associated with increased rates of major malformations, spontaneous abortions (SA), therapeutic abortions (TA), stillbirths, preterm birth, low birth weight, small for gestational age (SGA) and admission to the neonatal intensive care unit (NICU).

Methods Information from the Motherisk Program's prospectively collected database of 1243 women with gestational exposure to antidepressants. We compared pregnancy outcomes of 89 women exposed to >1 antidepressants, 89 taking one antidepressant, and 89 women not exposed to antidepressants (n= 267). Women were matched for maternal age, smoking and alcohol use. Groups were compared using odds ratios and ANOVA.

Results 11/89 (12%) took 3 and 78 (88%) took 2 antidepressants. There were no statistically significant differences in any of the outcomes analyzed among the 3 groups except for a lower mean gestational age at birth in the multi-antidepressant group (0.9 week, P=0.036). There were 9 admissions to NICU from the antidepressant groups and 3 from the non-exposed group; but this did not reach statistical significance.

Conclusions There is a small risk of preterm delivery that is associated with exposure to antidepressant therapy, although the clinical relevance remains to be determined

Introduction

In the past five years, epidemiologic studies, including a meta-analysis[1], two large case control studies[2,3] and most recently, a large cohort study[4], have established that overall there is no increase in the rates of major malformations in infants exposed to selective serotonin reuptake inhibitor (SSRI) antidepressants and other antidepressants during pregnancy. Other studies have also been published documenting a slight increased risk for spontaneous abortions[5] and an increase in the rates of preterm births (approximately 1 week preterm).[6] In addition, well defined self-limiting symptoms of abrupt. discontinuation have been identified in newborn infants, although there is no definitive estimate as to their frequency.[7] Several reports, including results from a registry by the manufacturer, suggested that the risk of cardiovascular defects in infants whose mothers had used paroxetine is 1%-2%.[8-10] However, in 2008, a study documented the largest number of exposures to paroxetine (N=1170) during the first trimester of pregnancy, reporting no difference in the rates of cardiovascular defects between paroxetine exposed and unexposed infants, when compared to the rate of cardiovascular defects in the population.[11]

To our knowledge there is only one other published study analyzing outcomes following use of more than one antidepressant during pregnancy. However, the authors did not examine outcomes other than malformations, and reported an increased risk for septal defects, but not for other malformations, including other cardiovascular defects. The prevalence of septal heart defects was 0.5% (2315/493,113) among unexposed children, 0.9% (12/1370) among children whose mothers were prescribed any SSRI, and 2.1% (4/193) among children whose mothers were prescribed more than one type of SSRI.[12]

The objective of this study was to examine infant outcomes of women who were exposed to more than one antidepressant during the course of their pregnancy.

Methods

The Motherisk Program at the Hospital for Sick Children in Toronto, Canada is a Teratology Information Service. It provides evidence-based information on the safety and/ or risks associated with exposures to drugs, chemicals, radiations and infectious diseases during pregnancy and lactation to pregnant women, lactating mothers and their health care providers. Women call for information regarding the safety of a drug, usually early in gestation, most often following recognition of the pregnancy. During the initial telephone contact, demographics, medical and obstetrical histories as well as details of drug and concurrent exposures are recorded on a standardized questionnaire. Details include

duration, timing in pregnancy, dose, frequency and indication for drug use. At the follow up interview, gestational findings, fetal outcomes and neonatal health are documented on a structured form by telephone with each mother, following a detailed explanation of the study and with her consent. The details are then, with the mother's permission, corroborated with a report from the physician caring for the baby.

We used this method to ascertain pregnancy outcomes of women who called the Motherisk Program between 1992 and 2007 regarding the use of antidepressants during pregnancy. These details were entered into an electronic database which when completed, totaled 1245 women exposed to antidepressants and 1245 non-exposed women. For this study, we separated the women who had been exposed to more than one antidepressant during pregnancy. We compared their data with those from an equal number of women who were exposed to a single antidepressant and a third group not exposed to any antidepressants, who had called Motherisk for information regarding nonteratogenic drugs such as acetaminophen. The three groups were matched for maternal age (±2 years), smoking and alcohol use. We also matched for time of call to Motherisk, as this is critical when calculating the incidence of miscarriages (SA). This is important because the observed proportion of pregnancies ending in loss is highly dependent on the gestational age at which pregnancies are recognized, as well as how the losses are identified. Thus, all three groups of women were pregnant at the time of enrollment in the study and had not yet miscarried.

Outcomes of interest were major malformations, spontaneous abortion, therapeutic abortion, stillbirth, preterm birth, small for gestational age, gestational age at birth and birth weight. The latter two were compared across groups using ANOVA. All other outcomes were compared using odds ratios. A level of $P \leq 0.05$ was considered significant for all statistical tests. This study was approved the Research Ethics Board at The Hospital for Sick Children in Toronto, Canada.

Results

Out of 1245 women, 89 (10%) were exposed to more than one antidepressant during pregnancy. Of these women, 78 (88%) took two different antidepressants and 11 (12%) took three. There were 32 different combinations of drugs taken by those women who took 2 antidepressants (Table 1A), and 8 different combinations by the women who took 3 antidepressants (Table 1B). A large number of the women took more than one antidepressant concomitantly (n=66, 74%), while the remainder (n=23, 26%) took a single antidepressant at a time, but switched to a different one at a later stage in the same

pregnancy. All of the women reported that they were treated exclusively for depression and/or anxiety, with none reporting any other psychiatric diagnosis and none taking other psychotropic drugs during pregnancy, such as anti-psychotics or lithium. All of the women took the drug(s) in the first trimester.

Table 1A Exposure to two different antidepressants (n=78)

n	Drug 1	Drug 2
5	bupropion	citalopram
1	bupropion	fluoxetine
1	bupropion	mirtazapine
1	bupropion	nefazodone
1	bupropion	paroxetine
1	bupropion	sertraline
7	bupropion	venlafaxine
2	citalopram	fluoxetine
1	citalopram	mirtazapine
1	citalopram	paroxetine
1	citalopram	sertraline
5	citalopram	trazodone
2	citalopram	venlafaxine
1	citalopram	mirtazapine
2	fluoxetine	fluvoxamine
2	fluoxetine	mirtazapine
6	fluoxetine	nefazodone
1	fluoxetine	paroxetine
3	fluoxetine	trazodone
1	fluoxetine	venlafaxine
1	fluvoxamine	trazodone
3	mirtazepine	sertraline
1	mirtazapine	venlafaxine
3	mirtazapine	venlafaxine
2	nefazodone	paroxetine
1	nefazodone	sertraline
4	paroxetine	trazodone
2	paroxetine	venlafaxine
7	sertraline	trazodone
2	fluoxetine	venlafaxine
4	sertraline	venlafaxine
3	trazodone	venlafaxine
32	**combinations**	

Table 1B Exposure to three different antidepressants (n=11)

n	Drug 1	Drug 2	Drug 3
1	bupropion	Citalopram	Fluvoxamine
3	bupropion	Citalopram	Trazodone
1	bupropion	Citalopram	Venlafaxine
1	bupropion	Fluoxetine	Trazodone
1	bupropion	Mirtazapine	Paroxetine
1	bupropion	Paroxetine	Venlafaxine
1	Fluoxetine	Paroxetine	Trazodone
2	fluoxetine	sertraline	Trazodone
8	**combinations**		

Table 2 Pregnancy outcomes following exposure to multiple/single and no antidepressants (n=89 in each group)

	Antidepressant exposure				
Outcome	**Multiple**	**Single**	**None**	**OR Single (95% CI)**	**OR None (95% CI)**
SA*	8	7	8	1.16 (0.40-3.34)	1.00 (0.36-2.79)
TA*	2	3	2	0.66 (0.11-4.04)	1.00 (0.14-7.26)
Fetal death[1]	3	1	1	3.08 (0.31-30.26)	3.08 (0.31-30.26)
Live birth*	76	78	78	0.82 (0.35-1.95)	0.82 (0.35-1.95)
Malformation†	2	3	2	1.03 (0.14-7.48)	0.68 (0.11-4.16)
Preterm (GA<37 weeks)	11	9	4	1.30 (0.50-3.33)	3.13 (0.95-10.31)
SGA†	2	2	3	1.03 (0.14-7.48)	0.68 (0.11-4.16)
NICU†	9	9	3	1.03 (0.39-2.75)	3.36 (0.87-12.92)

*denominator=all exposures; †denominator=all live births; GA=gestational age; SA=spontaneous abortion; SGA=small for gestational age; TA=therapeutic abortion

Table 2 presents pregnancy outcomes that were measured as discrete events and Table 3 presents those measured as continuous variables. The only statistically significant result was gestational age, which was lower by 0.9 week in the multiple antidepressant group (P=0.032). There were also numerically more infants admitted to NICU in both single and multiple antidepressant groups, 9 in each of the antidepressant groups compared to 3 in the non-exposed group, although this did not reach statistical significance (Fisher's Exact P=0.077 between the multi-antidepressant and no antidepressant groups). Birth weight was numerically lower in the multi-antidepressant group, although the difference was only 172 gm and did not reach statistical significance (P=0.19). Finally, there were more preterm births (<37 weeks GA) in both antidepressant groups, but again, the differences were not statistically different (Table 2).

Table 3 Pregnancy outcomes (continuous) following exposure to multiple/single and no antidepressants

	Antidepressant exposure			
Outcome	**Multiple**	**Single**	**None**	**p-value***
Gestational age at birth (weeks)	38.4±2.4	38.8±2.6	39.3±1.7	0.036
Birth weight mean SD	3291±648	3408±692	3463±577	0.190

*ANOVA. Gestational age differs significantly between Multiple and None using Tukey's post hoc test; others=NS

Discussion

To our knowledge, this is only the second study to report on outcome of infants exposed to more than one antidepressant during pregnancy, either concomitantly or intermittently. We did not find an increase risk for any type of heart defect in our study, unlike the Danish study previously described.[12] The major limitation of that study was that the information came from a database which recorded redeemed prescriptions, with very little other maternal information. Most notably, they did not verify whether the women actually took the drug and did not state whether the women took the antidepressant concomitantly or intermittently. In addition, using this type of data to document psychotropic drug exposure in pregnancy is a flawed methodology, as it has been documented that women and health care providers are more afraid of psychotropics than of other classes of drugs. Consequently, the woman may elect not to take the antidepressant, even after filling the prescription.[13] In addition, if some of these women were anxious/depressed enough to require two antidepressants, they probably sought more prenatal diagnostic testing than other women and consequently more cardiovascular heart defects would have been diagnosed (i.e., detection bias).[14]

The main strength of our model is the personal interview with the woman, which includes a detailed history. Our pregnancy registry is designed specifically for collecting pregnancy outcome data. Consequently, we are able to collect details of alcohol, tobacco and concurrent drug use, as well as other important potential confounders of pregnancy outcomes. Importantly, because all of the women called when they were in early pregnancy and the details of their pregnancy and drug exposure were recorded at that time, the possibility of a recall bias is eliminated or reduced substantially.

The main limitation of this study is the sample size at 89 is relatively small, and there was inadequate power to achieve statistical significance for the observed results. With our sample size, we would be able to detect a 5.4-fold difference in overall malformation rates and a 12- fold increase in cardiac malformations. However, it is the largest sample size to

date with data to control for potentially important confounders, and to examine potential adverse effects of taking more one than one antidepressant during pregnancy.

The only statistically significant result was gestational age at time of birth, which was almost one week earlier in both single and multiple antidepressant groups, compared to the nonexposed women (p=0.036). It is debatable if this difference is clinically important. However, this same observation has been reported in other studies with the same difference. Women had delivered their babies approximately one week earlier than women who were not taking an antidepressant.[15] Another group conducted a population-based study where most of the women (98.5%), who had depressive symptoms and were not taking an antidepressant reported that the risk of preterm delivery increased with increasing severity of depression. However, they also suggested this risk appeared to be exacerbated by low educational level, a history of fertility problems and the presence of obesity and stressful events.[16]

Another difference which did not achieve statistical significance was the number of admissions to NICU - 9 in both single and multiple antidepressant groups compared to only 3 in the non-exposed group. However, some of these admissions were because of hospital policy, to allow closer observation of infants exposed prenatally to antidepressants, not necessarily because they had a problem. It was reassuring to note that none of the infants stayed in the NICU for more than 3-4 days and that there were no differences in length of stay between neonates whose mothers were taking one antidepressant at the time of delivery, to those who were taking two or three. In addition, none of the mothers mentioned any long-term withdrawal effects from the multiple antidepressant exposure prior to delivery in their infants. This confirms the results of our findings from another study we conducted to examine the incidence of poor neonatal adaptation in infants whose mothers took an antidepressant prior to delivery. We compared paroxetine (n=57), venlafaxine (n= 97) and a nonexposed group (n= 64) and did not find a statistically significant difference in the incidence of poor neonatal adaptation syndrome (PNAS) among the three groups (p=0.54). In addition, we did not find a correlation in either the incidence or severity of PNAS when related to the dose of antidepressant a mother was taking prior to delivery, confirming results of a previous Motherisk study.[17]

Severity of depression is most likely a confounding factor, consequently another important limitation was not having a confirmed psychiatric diagnosis or severity of depression, as these were self reports with no confirmation from the attending physician. Ideally, we should have had a fourth group of women who were depressed and unexposed to antidepressants. However, due to the nature of our service, we do not have access to such a group. Women who call Motherisk do so with inquiries regarding the safety of an

antidepressant that they had been taking prior to becoming pregnant. We also did not measure Socioeconomic Status (SES) and differences which may have impacted our findings. What we do know from previous research is that all women who called the Motherisk Program have a higher SES, and are more motivated to do the "right thing," and use less alcohol and tobacco than the general population.[13]

In summary, taking more than one antidepressant during pregnancy does not appear to increase the risk of birth defects, miscarriages, low birth weight or delivery of infants small for gestational age. There does appear to be an increased risk for preterm delivery, (<37 weeks GA), with women giving birth approximately one week earlier than women not exposed to antidepressants. Currently, we do not have a definitive answer as to whether this is the result of the antidepressant, depressive symptoms or a combination of both. If a pregnant woman requires treatment with an antidepressant, this additional information may be of help for her to make an evidence-based decision together with her physician regarding pharmacological treatment.

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CHAPTER 3

CRITICAL EVALUATION OF STUDIES REGARDING THE SAFETY OF ANTIDEPRESSANT USE IN PREGNANCY

3.1 Quality and content of abstracts in papers reporting about drug exposures during pregnancy

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Birth Defects Res A Clin Mol Teratol. 2006;76(8):621-8

Abstract

Background: Most clinicians read only the abstract of papers in scientific journals. Therefore, it is very important that abstracts contain as much information as possible, to summarize the data succinctly. Our objectives were to evaluate the quality of information in abstracts reporting human fetal outcomes following drug exposure during pregnancy.

Methods: We developed quality criteria based on previous work, modifying them for use with pregnancy outcomes. Quality scores were calculated as present/absent for all of the equally weighted criteria, then expressed as percentages (present/[present + absent]). We examined a random sample of 100 abstracts obtained through searches of MEDLINE, EMBASE, and the Web of Science databases from 1990 to 2005. Average quality scores were compared across designs (cohort, case-control, meta-analysis, and mixed design) Using Kruskal-Wallis ANOVA and structured/unstructured formats using Student's t test.

Results: the overall average quality was 59.2% ± 14% (median, 61.5%; range, 15.4–83.3%). Quality was not significantly different across designs (P= .16) or between structured and unstructured abstracts (P = .44). Quality scores increased over time (Rho = 0.23, P = .02). Most frequently absent were baseline risk (94%), drug dose (91%), nonsignificant P values (72%), confounders (69%), significant P values (57%), and risk difference (48%).

Conclusions: Abstracts provide insufficient information, particularly baseline risk values, for readers to make evidence-based decisions regarding drug use during pregnancy. Efforts need to be made to improve the quality of abstracts and include critical information such as baseline risk.

Introduction

Exposing a fetus to a drug during pregnancy continues to be amajor concern for pregnant women and their health care providers (Lenz, 1962). Some medical conditions require that women take drugs throughout pregnancy and even if they do not intend to take anything, 50% of pregnancies are unplanned, so consequently, many women may be inadvertently exposed (Henshaw, 1998; Matteson et al., 2006). Although the prevalence of drug-induced teratogenesis is low, contributing to only 1% of congenital malformations of known etiology, the consequences can be devastating (Koren et al., 2001). It is estimated that the medical care for a child born with a birth defect over the span of his/her lifetime can surpass $500,000 USD (Finnel, 1999). Therefore, current accurate drug safety information is constantly in demand. Information on the fetal effects of drugs during pregnancy in humans usually starts with case reports published in the literature shortly after the introduction of a new drug onto the market (Benke, 1984; De Santis et al., 2004). Later, outcomes of infants of mothers who took a particular drug during pregnancy are examined in the form of prospective cohort studies, case-control studies, pregnancy registries, prescription database studies, and health care insurance data base studies, as well as metaanalyses. Understanding how all these studies are conducted, as well as the often complicated statistical analyses, can be quite bewildering to clinicians, who in the most part do not have a research background and yet are expected to make evidence-based decisions based on this information (Chen et al., 2004).

In recent years, the advent of the Internet has made scientific medical information far more accessible. All that is required is a computer with Internet access and a search engine such as PubMed, which is very simple to use (Pitkin, 1987). A Medline Express search from 1966 to 1998 found a more than doubling of publications, with an average increase of 2.8% annually, resulting in a vast amount of literature to examine (Waheed, 2000). One strategy for staying currently informed is to scan abstracts of original research, which are the most easily accessible sections of these articles (Pitkin, 1987; Haynes et al., 1990a, 1990b; Winker, 1999). Not only is it quicker to read only the abstracts, it is also cheaper, as articles can be costly to purchase (up to $50), while abstracts are usually free of charge. In large institutions at which there is a paid subscription to many journals by the library, researchers have access to the full article; however, in a physician's office or home this is not available. Therefore, it is of the utmost importance that abstracts contain all the necessary information in an understandable format, to allow the health care provider to make an informed decision regarding exposures of pregnant women. Previous research on abstracts have found that quality scores were less than ideal (Taddio et al., 1994; Wong et al., 2005). Others have

found high rates of omissions and deficiencies (Harris et al., 2002; Krzyanowska et al., 2004). To our knowledge, no comparable research has been published that has examined abstracts in the field of birth outcomes. Therefore, we undertook the present study to determine the quality of abstracts in this area.

Methods

Eligible abstracts

A comprehensive literature search was undertaken to identify all published abstracts reporting on safety of drugs in human pregnancy. The National Library of Medicine's MEDLINE database, Elsevier's EMBASE, and the Institute for Scientific Information's (ISI's) Web of Science database were searched for studies published in English from 1990 to 2005. The searches were performed during the last week of September and the first week of October 2005. Key words used to identify articles included teratogenesis (focus on headings for MEDLINE: drug-induced abnormalities, teratogens, and pregnancy), exposure during pregnancy, drug-induced fetal malformations, and abnormalities. Only abstracts that reported outcomes in humans following drug exposure during any stage of pregnancy were included.

Drug exposure was defined as exposure to any prescribed or over-the-counter medication including vitamins. Literature describing the effects of social and recreational drugs (e.g., alcohol, nicotine, caffeine, drugs of abuse) was not included in this study. Our goal was to have a sample size that reflected the population with a reasonable degree of precision. A priori, we chose a precision of 10% as being sufficiently precise. Using the standard formula (Aday, 1996), N ¼ Z2PQ/Pr2, Where Z ¼ the normal curve equivalent (i.e., 1.96 for 5% a error), P ¼ the expected rate in the population (in this case. .5, since the exact rate or quality score is unknown and .5 gives a conservative estimate), q ¼ (1 _ p), and pr ¼ the desired precision (i.e., 0.1, or 10%). That calculation gave a sample size of 97 and allowing for a small degree of error (3%), we arrived at 100 as our target sample size. Abstracts were selected in a stepwise approach.

In a comprehensive initial search, information in the title was compared against preset criteria by 2 independent reviewers. Next, citations selected from the initial search were retrieved and thoroughly examined. Only those meeting our inclusion criteria were further analyzed. Possible reasons for rejection were absence of abstract, animal studies, and no data of interest. The decisions to include or exclude citations were compared with those of a second reviewer for consensus agreement. Discrepancies were settled through consensus

discussion, with unresolved disputes adjudicated by a third reviewer whose judgment was considered final. The next step was to extract the data of interest from all selected abstracts, which were divided among 7 reviewers, with 6 individuals having to analyze 47 abstracts and 1 with 48 abstracts. To minimize bias in selecting and distributing the abstracts, a random number generator was utilized (obtained from http://www.random.org). Since 330 abstracts met initial inclusion criteria, we randomly chose 100 for analysis. In this way, a random sample of 100 abstracts was obtained from the population of abstracts and then distributed to the 7 reviewers.

The data were collected independently by 2 reviewers and entered onto a collection form. Discrepancies in data extraction were resolved in the same manner as for abstract identification.

Evaluation Criteria

For the purposes of this study, an instrument was adapted for recording data and scoring the abstracts, based on previous research on abstracts (Taddio et al., 1994; Wong et al., 2005). On this data form, we recorded the year of publication, journal name, name of authors, and format of abstract (structured or unstructured). Criteria used to calculate quality scores of each abstract included: stated objectives, study design using 4 categories: cohort, casecontrol, meta-analysis, and other (defined as a combination of 2 or more types of these designs), how information was obtained, sample size of exposed group, presence of control group, size of control group, time of drug exposure, drug dose, presence of risk difference (relative risk or odds ratio) with a confidence interval, presence of baseline risk, presence of P values for both significant and nonsignificant findings when findings are reported (i.e., when a difference between groups is reported), conclusions, and confounding factors/limitations. By baseline risk, we refer to the rate of the outcome in the comparison group, since the purpose of a comparison group is to represent the non-exposed groups of comparable patients.

Data collection

A scoring sheet was developed to assess abstract quality in the format of a checklist that contained 16 questions in total. The reviewer was required to answer yes or no to each item, scoring 1 point for each yes and 0 points for each no. One question required an identification of the study design and another one to organize the abstracts into structured or unstructured. Thus, the highest possible score for an abstract was 14. A copy of the checklist

appears in Appendix A. Questions that were not applicable to a specific abstract were eliminated; the total score was calculated based on the total answerable questions.

Calculations and Statistical Analysis

Overall quality scores for each article were obtained by summing all of the yes scores occurring in the abstract divided by the total possible number of relevant outcomes for that abstract. To calculate the observed rates of absence of each criterion evaluated, we counted how many abstracts received a no score for that criterion. Correlation between quality score and year of publication was evaluated using Spearman's rank order correlation coefficient. Differences between quality scores across study designs were contrasted using a Kruskal-Wallis test. Scores were contrasted between structured and nonstructured abstracts using Student's t test. Statistical significance was declared for all values of P <= .05.

Results

Literature Search

Approximately 4870 citations were located from the databases searched. Of those citations, a total of 330 abstracts met the initial acceptance criteria listed in Table 1. A total of 100 abstracts was randomly chosen from that set for review and included in the analysis.

Table 1. Inclusion and Exclusion Criteria Used in Selecting Abstracts for the Sample

Criterion	Included	Excluded
Publication	English language	All others
	Full research articles	Abstracts of posters or papers at meetings
	Publication year, 1990–2005	All others
	Must have an abstract	All without
Research Design	Original research studies	Narrative reviews, letters, editorials, comments
	Cohort studies, case-control studies, meta-analyses	Case reports, case series
Subjects	Human adult females	Animal studies
Exposure	Drug exposure during pregnancy	Alcohol, nicotine, biological preparation, caffeine, narcotic exposure
Outcomes	Pregnancy outcomes reported (e.g., malformations, embryotoxicity, developmental delay)	Maternal outcomes only

Appendix B lists the 100 abstracts that were analyzed. In the sample selected, there were 29 from obstetrics/ gynecology, 18 from reproductive toxicology, 11 general medical journals, 39 specialty medical journals (e.g., infectious diseases, neurology, psychiatry, clinical pharmacology), and 3 from epidemiology/pharmacoepidemiology journals. Thus, a broad range of fields was represented in the sample.

Table 2. Quality Scores of Abstracts of Studies Reporting Drug Exposures in Pregnancy

Study design	No. of abstracts	Average quality score	SD
OVERALL	100	59.2*	14.0
Case-control	24	62.1	10.8
Cohort	53	53.0	13.4
Meta-analysis	10	52.8	16.0
Other†	13	53.0	17.8
Abstract format			
Structured	72	59.9‡	13.5
Unstructured	28	57.4‡	15.3

SD = Standard Deviation.
* Difference between groups not significant (Kruskal-Wallis test, **P** = .16).
† Includes 9 mixed cohort/case-control studies, 3 database studies and 1 utilized patient interview.
‡ Difference between groups not significant (**t** test, **P** = .44).

Quality of Abstracts

The average quality score was 59.2% 6 14% (mean 6 SD) and the median score was 61.5% (range: 15.4–83.3%). Table 2 and Figure 1 summarize the quality score. There was no significant difference found between average quality scores of the 4 study designs (P ¼ .16). Average quality scores were also not significantly different between structured and unstructured abstracts (P ¼ .44; Table 2). There was a significant trend for improvement of quality scores over time (Rho ¼ 0.23; P ¼ .02). We also examined the rate of absence of each evaluation criterion in our sample of abstracts. Most frequently absent was baseline risk (94%), followed by drug dose, P value for nonsignificant results, confounding factors, P value for significant results, and risk difference (see Fig. 2).

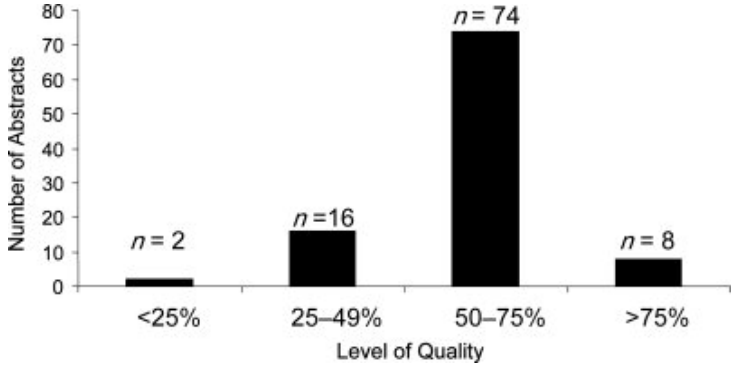

Figure 1. Distribution of scores by quartile. Overall quality scores for each abstract were obtained by summarizing all yes scores occurring in the abstract divided by the total possible number of relevant outcomes for that abstract. Quality scores for all 100 abstracts were divided into the following quartiles: <25% = very poor; 25–49% = poor; 50–75% = fair; and >75% = good.

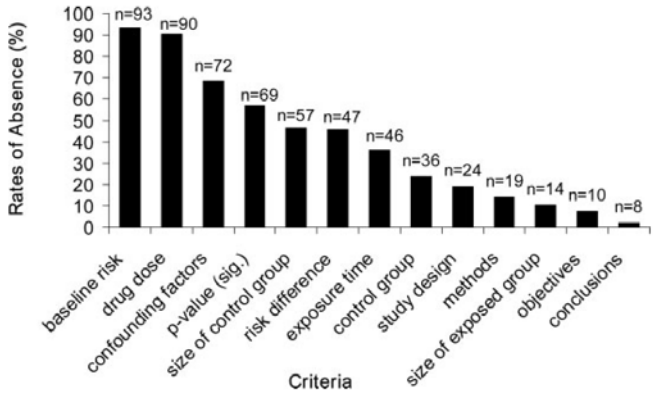

Figure 2. Observed rates of evaluation criteria being absent in the total population of abstracts. To calculate the observed rates of absence of each criterion evaluated we counted how many abstracts received a no score for that criterion.

Discussion

To our knowledge, this is the first study to examine the quality of abstracts reporting fetal outcomes following drug exposure during pregnancy. The evaluation criteria included basic

items commonly found in all abstracts as well as items specific to information regarding the safety of drug use during pregnancy.

The quality of structured versus nonstructured abstracts was also compared. Structured abstracts were introduced in the late 1980s (Ad Hoc Working Group, 1987) and rapidly became the standard format for many prestigious medical journals. The advantage was that the structured abstract provided headings for each section (e.g., Objectives, Methods, Results, etc.), which served as a prompt so that less material was left out. It was expected that structured abstracts would provide authors with better guidelines to convey the most important information to the readers, and this was found in previous research (Taddio et al., 1994). No statistical differences existed between the qualities of structured versus nonstructured abstracts. These results are in agreement with recent findings that a structured format was not associated with an improvement in overall quality of abstracts (Wong et al., 2005), even though previous findings did find a significant difference between the 2 abstract formats (Taddio et al., 1994).

Other studies that have assessed abstracts in the fields of psychology, pharmacoeconomics, oncology, and pharmacy have also found abstract quality and accuracy to be subop timal (Taddio et al., 1994; Trakas et al., 1997; Harris et al., 2002; Krzyanowska et al., 2004; Ward et al., 2004; Wong et al., 2005). One possible explanation for these findings is that the low word limit on abstracts set by many journals may have forced authors to omit important and relevant information from their abstracts. However, proponents of the structured format have demonstrated that a word limit of 250 words is adequate to include all essential information (Ad Hoc Working Group, 1987; Mulrow et al., 1988).

Since it is possible that study design may influence the quality of information obtained and presented in abstracts, the average quality scores for the different study designs (cohort, meta-analysis, case control, and other) were compared. Since meta-analyses comprehensively review and analyze a large pool of data from primary research, we expected that these studies might score higher. However, the average quality scores in our sample were not significantly different among the different study designs.

As well, the trend of quality scores was assessed over time (1990–2005) to determine whether there was a trend for increased quality over the last 15 years. A small but significant correlation was observed between quality scores and year of publication, and such a trend is encouraging.

It was interesting to note that the most commonly missing criteria were those that were especially important for abstracts dealing with drug safety during pregnancy. Of particular importance is the reporting of the baseline risk. In our sample of abstracts, the baseline risk

(i.e., the risk in the nonexposed population of comparable patients), was absent in 94% of the abstracts. Baseline risk is most often the primary endpoint readers want to know, since it serves as a basis of comparison when the risk difference is stated, but of those articles reporting risk difference, only 5.8% also included a baseline risk (i.e., stated the rate that was found in the comparison group).

As well, the risk difference was reported in only 52% of abstracts analyzed. However, the risk difference may be irrelevant without knowledge of the baseline risk in the population of comparable patients. Abstracts that contain the risk difference without the baseline risk can be misleading. For example, in a study comparing 2 groups for a particular outcome, 1 group may have twice the rates of the other, but if both groups have rates that fall below the expected rates in the general population, then it is not very meaningful, and in this case can cause alarm to pregnant women and their health care providers.

One limitation of the study is that we did not assess every abstract, but only a random sample. It is possible that we got a skewed sample, but we found no evidence of that.

The main objective of this study was to examine the overall quality of abstracts reporting on the safety of drug use in pregnancy. We feel that this study gives a good indication of the information contained in abstracts of studies reporting on the safety of drug use during pregnancy. Major critical decisions, such as terminating a wanted pregnancy, are often made based on information gleaned from an abstract in a journal (Koren et al., 2001), so it is vital that an abstract contains all the important information to aid the clinician and their pregnant woman patients, to make empowered evidence-based risk/benefit decisions regarding the use of a drug during pregnancy. It is clear that much room exists for improvement of quality.

A final note is that reading the abstract can never be considered a substitute for reading the entire text. Clinicians treating patients should consult all of the evidence and remember that a considerable amount of important information may not appear in the abstracts.

Conclusions

Current abstracts do not appear to provide all the necessary information on drug safety during pregnancy. Reviewers of journal articles should probably pay more attention to the information contained in the abstract, since this section of the paper is often the only source of information for busy clinicians.

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Appendix A

Checklist Used to Evaluate Each Abstract in the Sample

ARE THE FOLLOWING ITEMS REPORTED/INCLUDED IN THE ABSTRACT?			
1. STATED OBJECTIVE(S)	YES □	NO □	
2. STUDY DESIGN	YES □	NO □	
3. STUDY TYPE	COHORT □	CASE-CONTROL □	
	META-ANALYSIS □		OTHER □
4. METHODS (how information was obtained)	YES □	NO □	
5. SIZE OF EXPOSED GROUP*	YES □	NO □	
6. CONTROL GROUP*	YES □	NO □	
7. SIZE OF CONTROL GROUP*	YES □	NO □	
8. EXPOSURE TIME*	YES □	NO □	
9. DRUG DOSE*	YES □	NO □	
10. RISK DIFFERENCE W/CI*	YES □	NO □	
11. BASELINE RISK* (Risk or level of incidence in the general population)	YES □	NO □	
12. **p** FOR SIGNIFICANT FINDINGS*	YES □	NO □	NO Sig. Findings □
13. **p** FOR NONSIGNIFICANT FINDINGS*	YES □	NO □	NO Nonsig. Findings □
14. CONCLUSION	YES □	NO □	
15. CONFOUNDING FACTORS/LIMITATIONS	YES □	NO □	
16. STRUCTURED	YES □	NO □	
TOTAL SCORE	YES __	NO __	

*Specific criteria (deemed as elements that provide the necessary information to accurately interpret results on drug safety in pregnancy from an abstract. Sig. =significant.

Appendix B

List of the 100 Abstracts That Were Evaluated

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3.2 DO FINDINGS DIFFER ACROSS RESEARCH DESIGN? THE CASE OF ANTIDEPRESSANT USE IN PREGNANCY AND MALFORMATIONS

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J Popul Ther Clin Pharmacol. 2012;19(2):e334-48

ABSTRACT

Background Many studies examining the teratogenic potential of antidepressants have been published. A variety of observational designs have been used with apparent conflicting results, although odds ratios were rarely >2.

Objectives To examine whether these apparent differences were associated with research methods such as model, comparison groups, data source, data collection procedures, definition of malformations, outcome ascertainment or management of confounders.

Methods Medline and Embase were searched using terms: pregnancy, antidepressants, serotonin uptake inhibitors OR SSRI, AND embryonic structures OR congenital malformations OR fetal development for observational studies with original data. Data were analyzed using a structured approach and narrative review. Designs that were compared, included prospective cohort, retrospective cohort, and case-control studies. Rates of major malformations and cardiac malformations were combined by study type using random effects meta-analytic models**.**

Results We identified 150 papers; 127 were rejected, 23 were analyzed: 9 prospective cohort, 8 retrospective cohort, and 6 case-control studies. Sample sizes were large (1,818 exposed in case-control and 16,824 in cohort studies), providing relatively robust findings. Overall Odds Ratio's for major malformations ranged from 1.03-1.24 and 0.81-1.32 for cardiac malformations. No discrepancies among research designs were identified.

Conclusions Diverse observational models with differing strengths and weaknesses produced remarkably similar nonsignificant results. Perceived conflicting results may be due to subsequent dissemination of results with attention given to small statistically differences with negligible clinical importance. Improved methods of knowledge transfer and translation are required to provide sound evidence-based information to assist in decision-making surrounding the use of antidepressants in pregnancy.

Introduction

Prior to 2005, research using observational designs conducted on the use of SSRIs in pregnancy reported no association between SSRI use and congenital malformations.[1] However, in 2005, GlaxoSmithKline conducted a study of outcomes from 815 exposed infants and reported a 2% incidence of cardiovascular malformations (where 1% is expected in the general population), unspecified in terms of severity and unpublished in the peer reviewed literature.[2] That study motivated both the Food and Drug Administration (FDA) and Health Canada, to warn about the use of paroxetine in the first trimester of pregnancy. Since these warnings were issued seven years ago, there has been a sizable increase in the number of studies published on this topic, with some finding evidence of harm and others not. However, despite all of this new information, to date these warnings have not been updated and currently, the information is unchanged from December 2005- Dec 2011.[3,4]

Due to the ethical restrictions of randomized controlled trials (RCTs) in pregnant women, studying the gestational safety of drugs is a complex process. Consequently, observational study designs (i.e., case reports, case series, cohort studies, case-control and nested case-control studies and administrative database studies) are currently used, which obviously have many limitations.[5] Recent years have seen a increase in the number of computerized databases, which were not designed for scientific studies. However, researchers have used these databases to conduct complex analyses of data, resulting in a substantial increase in such studies. This issue was recently raised by the research group of the Organization of Teratogen Information Services (TISs) who issued a call for more complete information from database studies.[6] Together with other observational studies using different data and study designs, conflicting results have been published regarding the safety of antidepressant use in pregnancy. Understandably, this mixed information has caused anxiety for health care providers and their pregnant patients, who may require pharmacological treatment for depression.

To our knowledge, in this field of researching the safety/risk of drugs used during pregnancy, differences in study designs, including data collection, data analysis, managing confounders, and limitations inherent in observational studies have not been closely examined. Therefore, as an example we conducted a systematic review of all studies reporting on antidepressant use in early pregnancy and congenital malformations, with a special focus on cardiovascular malformations, as this has been the most conflicting outcome, in an attempt to answer this question: “Do different research designs produce different estimates of risk for antidepressant exposure in pregnancy?”

Methods

For studies to be included in this review, articles had to report on the use of antidepressants during the first trimester of pregnancy. Included were SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and drugs from other classes of antidepressants, such as bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. The outcomes of interest were major malformations and we examined cardiac malformations separately. Studies were not considered if their focus was on later trimesters or if they investigated other outcomes such as pulmonary hypertension of the newborn (PPHN), low birth weight, or premature delivery.

Since randomized controlled trials of antidepressants are not permitted using pregnant women, we examined only observational studies. We included all types, such as cohort studies, case-control studies, and database studies, providing they had a comparison group that was not exposed to antidepressants. For cohort studies, we accepted those with either prospective or retrospective data collection, but were analyzed separately. For that purpose, data extraction sheets were developed and used to collect and compile data on each of the articles included in the review. Primary data points collected included type of study, location(s), inclusion and exclusion criteria, sample size, drugs reported on, duration of exposure, study outcomes, confounders, limitations, statistical analysis performed and conclusions.

There were no restrictions placed on year or language of publication. Databases searched included MEDLINE, and Embase on the OVID platform from inception to June 2011. Both database specific subject headings and text words were searched using the terms “congenital malformations” OR “prenatal development” OR “embryonic structures” OR “Prenatal Exposure Delayed Effects” AND “Serotonin Uptake Inhibitors” OR “Serotonin Reuptake Inhibitors” OR “SSRI” AND “case-control studies” OR “cohort” OR “registries.

Review articles were retrieved and hand searched to identify additional relevant primary research articles. Screening of articles was performed by three individuals, and discrepancies in agreement regarding inclusion were resolved by consensus.

For the purposes of analysis, studies were divided into prospective cohort studies, retrospective cohort studies, database studies, and case-control studies. Since some designs overlap, we further combined them into cohort studies, regardless of data collection method. Data were combined across studies using a random effects meta-analytic model. For cohort studies, risk ratios with 95% confidence intervals were calculated and for case-control studies, odds ratios were calculated, with 95% confidence intervals. To examine

heterogeneity of effects, we calculated χ^2 and I^2. Other data were summarized descriptively and with a narrative review.

Aspects of research design that were examined were the definition of first trimester, comparison groups used, criteria for identifying congenital malformations, time of follow-up, how confounders were managed, losses to follow-up, and sample size calculations (especially *a priori*).

Results

The search yielded 150 original articles, of which 23 fit our inclusion criteria (Figure 1).[7-29] To evaluate overall rates of malformations, we used 17 cohort studies, including 7 prospective cohort studies[7-13] and 7 retrospective cohort studies[14-20] as well as 3 case-control studies.21-23 The study characteristics are summarized in Table 1. Sample sizes were quite large, with a combined total of more than 20,000 first trimester exposures to antidepressants. We also analyzed 18 studies that specifically reported on the rates of cardiovascular malformations.[19-28] Results are summarized in the Table 2. A single prospective cohort study (7%) reported a significant association between SSRIs and congenital malformations; two cohort studies (14%; one prospective, one retrospective) reported a positive association between antidepressants and cardiovascular malformations. None of the casecontrol studies identified a significant relationship.

Definition of first trimester Some studies incorporated the whole of the preconception period, (especially prescription data base studies). Others considered the first trimester from week 4 to 14 (i.e., mostly studies from TISs), while other studies provided no definition for first trimester (e.g., administrative data bases).

Comparison groups The comparison group was dependent on the data source for the study, for example, studies from the TISs used 2 comparison groups of women: 1) those exposed to a different antidepressant medication and 2) women exposed to drugs known not to be teratogenic. There were equal numbers of exposed and non-exposed. Populationbased registries and/or administrative databases most often used a single comparison group of women who were not exposed to SSRIs.

Criteria to identify congenital malformations*:* Eight out of 23(35%) did not identify the criterion used to define a congenital malformation, while other studies specified the International Classification of Disease (ICD) codes in their analyses. The most notable difference was in the reporting of cardiovascular malformations as major malformations, as most studies included all heart malformations, including ventricular septal defects (VSDs) and atrial septal defects (ASDs), even if they closed spontaneously. When studies in which cardiovascular malformations that resolved spontaneously were excluded, there was no increased risk.[25] In addition, confirmation of the timing of diagnosis was not standardized and appeared to vary from one month to 3 years of age across all studies. Consequently, some heart malformations would not have been detected immediately after birth in the early interviews and conversely, some would have resolved spontaneously by the time the children reached 3 years of age in the later examinations.

Time of follow-up Fourteen out of 23 (61%) studies collected data on congenital malformations at birth or in the neonatal period, while the remainder did not state when follow-up was performed.

Confounders Most of the database studies incorporated multiple linear regressions and calculated adjusted odds ratios to eliminate the effects of potential confounders on their results. For example, in their meta-analysis, Wurst et al. developed a list of key confounders relevant to studying medications and each study in the review was evaluated according to this list.[30] Maternal age and smoking were the most common confounders adjusted for in the analysis. Many of the retrospective registry and database studies were limited by their inability to identify aspects of a women's pregnancy or medical history and most did not adjust for multiple testing.

Loss to follow-up Loss to follow-up information was not reported in any of the studies from TISs.

Lack of a priori sample size calculation Only 2/23 (8%) studies incorporated an *a priori* power calculation, although several studies, did discuss *post hoc* the power of their sample size.

TABLE 1 Studies examining pregnancy outcomes after exposure to antidepressants

CONGENITAL MALFORMATIONS EXAMINED USING PROSPECTIVE COHORT STUDIES WITH EXPOSURE DURING FIRST TRIMESTER

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Chambers[6] 1996	fluoxetine	163	women with NTEs	254	Teratology Information Service Questionnaire completed by mother Questionnaire on birth outcomes Medical records review Infant's MD completed a form Physical exam	Neonatal period	Defined as a structural defect occurring in less < 4 % of the general population that has cosmetic or functional importance.	Determination of the effects of fluoxetine during the first trimester on the frequency of major and minor structural anomalies in infants and the effects of treatment during the third trimester on birth size, gestational age, and neonatal adaptation.
Diav-Citrin[7] 2008	paroxetine fluoxetine	463 346	women with NTEs	1,467	Teratology Information Service Interview at time of inquiry f/u questionnaire to woman or physician or one month post delivery date	To 6 years but mostly 2 years	Major anomalies were defined as structural abnormalities in the offspring that have serious medical, surgical or cosmetic consequences. Ventricular septal defects (VSDs) are structural anomalies of the heart. Significant neurodevelop-mental or functional problems also considered major anomalies	The primary was to evaluate prospectively the rate of major congenital anomalies after pregnancy exposure to paroxetine compared with fluoxetine.
Einarson[8] 2009	bupropion citalopram escitalopram fluoxetine fluvoxmine mirtazapine nefazodone paroxetine	928	women who were not exposed to antidepressants	928	Teratology Information Service Interview at time of inquiry Follow-up questionnaire to woman after delivery date Confirmation with infant's MD	Not specified	Not specified	Determine whether antidepressant as a group representative an increase risk for major malformations

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
	sertraline trazodone venlafaxine							
Klieger-Grossmann[9] 2012	escitalopram	213	mothers with exposure to (1) other antidepressants (SSRIs, venlafaxine, bupropion, trazodone/ nefazodone, and mirtazapine) or (2) NTEs	212 212	The Motherisk Program in Toronto Swiss Teratogen Information Service The Florence Teratogen Information Service	Within 3 months of estimated delivery date	Not specified	Determine whether the use of escitalopram during pregnancy is associated with an increased risk for major malformations above the baseline of 1% to 3%.
Kulin[10] 1998	fluvoxamine paroxetine sertraline	267	Random selection of women with NTEs.	267	Teratology Information Service Interview with mother f/u questionnaire to woman after delivery date corroboration with medical records	6 – 9 months after delivery	Presence of any anomaly that has an adverse effect on either the function or the social acceptability of the individual	To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline
Nordeng[11] 2012	citalopram escitalopram sertraline paroxetine fluoxetine fluvoxamine TCAs	699	no reported use of any antidepressants in the 6 months prior to or during pregnancy	65,751	Meciical Birth Registry of Norway Two questionnaires during pregnancy	Not stated	Malformations were defined as any birth defect, Malformations according to the International Clearinghouse for Birth Defects definition. ICD-10 code Q20-28	The primary aim was to investigate whether exposure to antidepressants, and specifically SSRIs, during the first trimester was associated with the occurrence of congenital malformations above the baseline risk.
Pastuszak[12] 1993	fluoxetine	128	2 groups: women exposed to TCAs during first trimester and women with NTEs	128 128	Teratology Information Service Interview – prenatal Interview - post natal Infant's physician completed a form	8-12 months	Not defined	To compare pregnancy outcome following first-trimester fluoxetine exposure with pregnancy outcome in two matched control groups.

Congenital malformations examined using a retrospective cohort study design (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Cole[13] 2007	Bupropion	1,213	2 groups bupropion within 18 months of delivery or after 1st trimester and other antidepressants during 1st trimester	1,049 4,743	Ingenix Research Data Mart containing medical and pharmacy claims data	Not specified	a structural abnormality with surgical, medical, or cosmetic significance	To determine whether first trimester bupropion exposure maybe associated with cardiovascular or congenital malformations
Davis[14] 2007	SSRIs	1,047 exposed to SSRIs	mothers of infants not prescribed antidepressants during pregnancy, but who may have had other medications prescribed	49,663	HMO Research Network's with data from: Group Health Cooperative Harvard Pilgrim Health Care Henry Ford Health System Kaiser Permanente Colorado Kaiser Permanente Northwest	1 year	ICD 9, codes not specified	Evaluate the risk for congenital anomalies and adverse perinatal events among infants exposed to antidepressants during pregnancy
Malm[15] 2005	citalopram, fluoxetine fluvoxamine paroxetine sertraline	1,782	women with no drug purchases from 1 month prior to and during pregnancy	1,782	4 registries from Finland: Medical Birth Register, National Register of Congenital Malformations, Hospital Discharge Register, Cause-of-Death Register	Up to 1 year of age	ICD-9 for major congenital malformations	Determine whether exposure to SSRIs during early pregnancy is associated with an increased risk of major malformations.
Oberlander[16] 2008	citalopram fluoxetine fluvoxamine paroxetine sertraline venlafaxine	SSRIs: 2,625 BZ: 968 SRI+BZ: 359	women with no exposure to SSRIs	107,320	BC Linked Health Database hospital separation records; PharmaCare registry of subsidized prescriptions; the Medical Services Plan physician billing records; the registry of Medical Services Plan subscribers	Not specified	ICD-9 codes for major anomalies + VSD and ASD	To study whether the risk for major congenital malformations and congenital heart defects differs between first trimester SRI+ BZ exposure and no exposure at all.
Pedersen[17] 2009	citalopram fluoxetine paroxetine sertraline bupropion	1,370	mothers of infants not exposed to SSRIs	493,113	4 Danish registries: Medical birth registry, National register of medicinal product statistics, Fertility database National hospital register	2 years	Eurocat categorization	To investigate any association between selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy and congenital major malformations

Simon[18] 2002	fluoxetine, fluvoxamine, paroxetine sertraline TCAs	185	women with no exposure to SSRIs	185	Group Health Cooperative database	Up to 2 years	Not defined	To evaluate the effects of prenatal antidepressant exposure on perinatal outcomes, congenital malformations, and early growth and development.
Wen[19] 2006	SSRIs	972	women who did not receive SSRIs	3,878	The Saskatchewan Health databases	Up to 1 year of age	ICD-9, codes not specified	The objective of the current study was to make a comprehensive assessment of the safety of prescription SSRIs in pregnancy (including periconception period), with the use of a large population database.

Congenital malformations examined using case-control studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Alwan[20] 2007	paroxetine sertraline, fluoxetine	9,622	random selection of mothers of infants born with no major birth defects	4,092	Infant cases identified from National Birth defects Prevention study Pregnancy information via structured interview of the mother	Not specified	Not specified	To determine the relationship between SSRI exposure and major malformations
Louik[21] 2007	paroxetine sertraline fluoxetine citalopram	9,849	women not exposed to anti-depressants 56 days prior to LMP to end of pregnancy	5,860	Infants identified from Slone Epidemiology Center Birth Defects Study Questionnaire completed by mother via in person interview or over the telephone.	Not specified	ICD 9, codes not specified	Evaluate whether there is an increased risk of omphalocele, craniosynostosis and congenital heart defects and also considered other specific birth defects in relation to first-trimester use of specific SSRIs.
Ramos[22] 2008	citalopram fluoxetine fluvoxamine paroxetine sertraline escitalopram bupropion mirtazapine	189	mothers of infants born with no major birth defects	2,140	Medication and pregnancy Registry data Self-administered questionnaire	12 months after birth	ICD-9 codes, codes not specified	To determine whether duration of antidepressant use during the first trimester increases the risk of major congenital malformations in offspring of women diagnosed with psychiatric disorders

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
	moclobemide nefazodone trazodone venlafaxine TCAs							

Cardiovascular malformations examined using prospective cohort studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Einarson[23] 2008	paroxetine	1,174	women exposed to drugs considered safe in pregnancy	1,174	Teratology Information Service Interview at time of inquiry f/u questionnaire to woman or physician or one month post delivery date	Not specified	Not specified	Determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.
Merlob[24] 2009	paroxetine fluoxetine citalopram escitalopram sertraline fluvoxamine venlafaxine	235	women with no SSRI exposure	67,871	Standardized pregnancy questionnaire following discharge: medical chart review for medication and cardiovascular malformations	Second or third day of life	Not specified	The aim of the present prospective study was to compare the rate of congenital heart malformations in SSRI-exposed versus non-exposed newborns.

Cardiovascular malformations examined using retrospective cohort studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Wichman[25] 2009	fluoxetine, paroxetine sertraline citalopram escitalopram venlafaxine	808	women with no exposure to SSRIs	24,406	Mayo Clinic Division of Obstetrics delivery database Review of medical record	At birth	Congenital heart disease: abnormality in cardio circulatory structure or function that is present at birth; includes VSD even if closed prior to discharge	To determine the risk of congenital cardiac malformations with the use of SSRIs during pregnancy.

Cardiovascular malformations examined using case-control studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Alwan[26] 2010	bupropion	6,853	liveborn with no major birth defects, randomly selected from the same geographical populations using either birth hospital or vital records.	5,869	National Birth Defects Prevention Study Standardized telephone interviews of mothers of either case or control infants regarding demographics and pregnancy exposures.	Interviews were conducted 6 weeks to 2 years after the estimated date of delivery	Classification system developed for NBDP, incorporating three dimensions of cardiac phenotype, cardiac complexity, and extra cardiac anomalies	Association between bupropion exposure and congenital cardiac defects
Bakker[27]	paroxetine	678	children with	1,293	Eurocat Northern Netherlands	Not specified	ICD-9 and 10,	Association between use of

2010			chromosomal or single gene disorders		database, from voluntary reports review of medical charts		codes not specified	paroxetine in early pregnancy and the occurrence of specific heart defects.
Bérard[28] 2007	paroxetine Other SSRIs	Major malformations = 101 Major cardiac malformations=24	women exposed to other antidepressants, not SSRIs	1,302	3 administrative databases from Quebec: La Regie de l'Assurance Maladie du Quebec (RAMQ), Med-Echo, Le fichier des evenements demographiques du Quebec (birth and death registries) of l'Institut de la Statistique du Quebec (ISQ) Databases	12 months	ICD-9, codes not specified	Quantification of the association between exclusive first trimester exposure to paroxetine and occurrence of any major congenital malformations, and more specifically, major cardiac malformations, as compared with exclusive first trimester exposure to other selective serotonin reuptake inhibitors (SSRIs) or other antidepressants.

Abbreviations: BZ: benzodiazepines; ICD: International Classification of Diseases; NTE: nonteratogenic exposures; SSRI: Selective Serotonin Uptake Inhibitor; TCA: Tricyclic antidepressants

TABLE 2 Summary statistics (N=23 studies)*

Malformation	Model	Studies	N	Exposed	RR/OR	LL	UL	$\chi^2_{homogeneity}$	P	I^2
All	All cohort studies	14	737,929	18,824	1.10	0.97	1.18	15.73	0.264	17.3%
	Prospective cohort	7	67,729	2,982	1.24	0.95	1.62	6.00	0.423	0
	Retrospective cohort	7	670,200	13,842	1.03	0.93	1.15	5.77	0.449	0
	Case-control studies	3	30,362	1,818	1.09	0.95	1.25	0.49	0.782	0
Cardiac	All cohort studies	14	823,752	15,872	1.11	0.76	1.62	34.13	<0.001	61.9%
	Prospective cohort	8	135,962	3,389	1.32	0.71	2.46	12.14	0.096	42.3%
	Retrospective cohort	6	687,792	12,484	0.96	0.59	1.57	19.97	0.001	75.0%
	Case-control studies	4	26,177	390	0.81	0.36	1.82	26.06	<0.001	88.5%

*Data were obtained from 23 individual studies, including 9 prospective cohort, 8 retrospective cohort, and 6 case-control studies.
Where more than one control group was reported, non-teratogenic or non-exposed groups were used in these analyses.

Discussion

To our knowledge, this is the first systematic review to specifically examine differences in study design among observational studies that were conducted to assess the safety/risk of antidepressant use in pregnancy. Each type of study had its own limitations, which was not always stated clearly by the authors. The prospective detailed history taking method employed at the TIS is considered a strength as it is possible to clearly ascertain that the medication was actually taken, when and for how long, while population-based studies do not always have this information. In addition, TIS studies for the most part corroborate the outcome by following up with the infant's physician. However, the two main weaknesses in using this data source are the inability to compile a large enough sample size to make a definitive conclusion, and the selection bias due to the nature of the women choosing to call a TIS.[5] In database studies, the major strength is the much larger sample sizes which provide a better representation of the population. The limitations include for example, no knowledge of confounders for alcohol and cigarette smoking, which are known to affect pregnancy outcome.[31] In addition, as Andrews and Tennis identified in their commentary on the pitfalls of administrative databases, there is often a poor degree of correlation between actual medical diagnosis and the outcomes coded for the infant in the database.31 In our review, in the studies that used information from a database, only half tried to overcome this limitation by incorporating a review of the medical chart into their data collection protocol. In addition, it is not known if the women in prescription databases actually took the drug, only that a prescription was redeemed. A recent study of pregnant women compared information recorded in a database with data obtained from actual patient interviews. The authors reported that in women who filled prescriptions 1 to 3 months before their last menstrual period (a commonly used time frame), as many as 43% did not use the drugs in the first trimester.[32] What strengthens this particular finding is, in our experience at Motherisk during many years of conducting these studies, a large number of women discontinued their chronic medications (especially antidepressants) prior to pregnancy, as they had been informed that pregnant women should not take any medication.[33]

This research has highlighted the inconsistencies in the methods used in this area of research, which may affect study results. However, the answer to the research question (Do results differ across research designs and methods?) appears to be "no", with the exception of reported rates of cardiac malformations. On the other hand, those results can mostly be explained by differences in time of diagnosis following birth and inclusion/exclusion of minor malformations which resolved spontaneously. For example, in a study specifically examining

whether there was an association between cardiovascular malformations and SSRIs, every infant born at a center during an 8 year period was examined on the first day of life for a cardiac murmur.[25] Infants with a persistent murmur on the second or third day of life were examined by a pediatric cardiologist and referred for electrocardiography and echocardiography. The authors reported that 8/235 newborns (3.4%) were found to have had cardiovascular malformations following first-trimester exposure to SSRIs. Four of the infants had been exposed to paroxetine, two to fluoxetine, one to citalopram and one to sertraline, and all were identified as having ventricular septal defects (VSDs), the most frequent cardiac malformation. If minor malformations which resolved spontaneously were removed from both groups, the absolute risk in both groups would be less than 1%, which is the rate expected in the general population. Moreover, there is disagreement regarding the safety of paroxetine among researchers and experts. For example, in 2010, a meta-analysis was conducted in an attempt to resolve the issue of whether paroxetine does in fact increase the risk for cardiovascular malformations.[30] The authors had concluded that there was an increased prevalence of combined cardiac defects with first trimester exposure to paroxetine. They calculated their summary estimate as a prevalence odds ratio [POR]. For combined cardiac defects, the POR was 1.46 (CI95%:1.17-1.82), for aggregated congenital defects, the POR was 1.24 (CI95%:1.08- 1.43). Two commentaries were published along with that analysis presenting opposing opinions. Scialli concluded that "the scientific evidence does not support the conclusion that paroxetine causes cardiovascular defects "[34], while Bérard stated that "evidence-based literature shows consistent epidemiologic evidence that paroxetine use during pregnancy increases the risk of cardiac malformations in newborns".[35] From these statements, one is prompted to question how it could be that two experts in the same field have offered such opposing conclusions based on their evaluation of the same data.

Another important question concerns how these results are disseminated to the scientific community and the public. When individual studies are published, much is made of very small increased ORs, which have often been <2 and explained in a way that that it appears much more important than it really is. Small but statistically significant risks are important at the population level, but may be less so when considering an individual, such as a woman who is planning pregnancy or who is currently pregnant and taking a medication such as an antidepressant.[36] Conversely, studies that did not find any adverse effects are frequently ignored by the media. Subsequently, results of these studies can have a far reaching impact on events such as precedent setting lawsuits, as in the case of GlaxoSmithKline, resulting in the company ordered to pay $1.5 million to a couple whose baby was born with a heart defect following exposure to Paxil® in pregnancy. The jurors reached this conclusion

following examination of only selected studies that reported an increased risk, therefore creating a huge potential bias.[37] In addition, widely disseminated results in the media of studies reporting even a marginally increased risk also can cause women to stop taking a needed antidepressant during pregnancy, sometimes with adverse consequences.[39,40] It is extremely important that such decisions be informed with balanced evidence based information.

Conclusions

We found that different research designs do not produce conflicting results per se and apparent differences appear to have been probably due to the way selected results were disseminated. We did note some design deficiencies among the studies examined and these findings reinforce the need to improve the rigor of study methods, which is in the most part achievable. This includes standardizing definitions for evaluation criteria for major malformations and the associated follow up period. In addition, a need exists for universally accepted definition of first trimester, with key confounders to include in regression analysis, adjusted odd ratios or relative risk calculations and very importantly, caution when performing multiple testing. Finally and of great importance, improved knowledge transfer and translation will ensure that pregnant women and their health care providers receive the most accurate evidencebased information, for decision-making regarding the use of antidepressants during pregnancy.

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3.3 Publishing Statistically Significant Results With Questionable Clinical Importance: Focus on Antidepressant Use in Pregnancy

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J Clin Psychiatry. 2012;73(11):1443-6

Many more women than men are diagnosed with depression, most often between 25 and 44 years of age when women are of childbearing age,[1] and approximately 10% to 15% will experience depression during pregnancy.[2] Therefore, a substantial number of women could be taking an antidepressant when they become pregnant.

The use of antidepressants has increased in the past decade, as reported by a group using data from the National Birth Defects Prevention Study,[3] an ongoing case-control study of risk factors for birth defects covering 10 US states. The frequency of reported antidepressant use at any time during pregnancy increased from 2.5% in 1998 to 8.1% in 2005 ($P < .001$) in 4 states. Among 6,582 mothers included in the study, 298 (4.5%) reported use of an antidepressant from 3 months before pregnancy through the end of pregnancy.[3] A statistically significant decline, from 3.1% to 2.3% ($P <.001$), was observed in reported use of antidepressants between the first and second month after conception. This decline in use between the first and second trimester is not because pregnancy caused these women to become euthymic and no longer require antidepressants, but because of fear of teratogenicity associated with fetal exposure to antidepressants, perpetuated by both health care providers and the general public (personal communication with Motherisk callers, unpublished data, 2012).

As there are no randomized controlled trials conducted on pregnant women for obvious ethical reasons, they and their health care providers rely on observational studies published in the peer-reviewed literature to evaluate the safety of antidepressant medication use during pregnancy. Prior to 2005, research using observational designs conducted on the use of selective serotonin reuptake inhibitors (SSRIs) in pregnancy reported no association between SSRI use and congenital malformations. A meta-analysis was conducted of the available literature in 2005, with only 18 identified studies (1,774 outcomes) that met the inclusion criteria (relative risk = 1.01 [95% CI, 0.57–1.80]).[4] At that time, antidepressants were considered relatively safe to take in pregnancy and no one appeared to be unduly concerned judging from the lack of warnings in either the scientific literature or lay press. In December 2005, the US Food and Drug Administration (FDA), on the basis of unpublished data from GlaxoSmithKline[5] and preliminary data from 2 abstracts presented at conferences, published a warning on their Web site that paroxetine use in pregnant women may increase the risk for fetal heart defects by 2-fold, which has not been updated despite the numerous studies that have been published in the ensuing 7 years.[6] However, an update on SSRIs and persistent pulmonary hypertension in newborns (PPHN) stated: “There have been conflicting findings from new studies evaluating this potential risk, making it unclear whether use of SSRIs during pregnancy can cause PPHN. FDA has reviewed new study results and has concluded that it is premature to reach any conclusion about a possible link between SSRI

use in pregnancy and PPHN. FDA will update the SSRI drug labels to reflect the new data and the conflicting results."[7]

It is unfortunate that the FDA did not reexamine the paroxetine and cardiovascular defect studies since this association has not been proven and even "experts" in the field disagree as to whether the association is real. Two commentaries were published along with a meta-analysis presenting opposing opinions.[8,9] Scialli[8] concluded that the scientific evidence does not support the conclusion that paroxetine causes cardiovascular defects, while Bérard[9] maintained that evidence-based literature shows consistent epidemiologic evidence that paroxetine use during pregnancy increases the risk of cardiac malformations in newborns. From these statements, one is prompted to question how it could be that 2 experts in the same field have offered such opposing conclusions based on their evaluation of the same data. In addition, cardiovascular malformations occur in 1/100 live births in the general population, so some women gave birth to an infant with a cardiovascular malformation that would have occurred whether or not the mother took paroxetine in her pregnancy. Subsequently, lawyers encouraged these women to sue the manufacturer by advertising on numerous Web sites.[10] In October 2009, a jury awarded a family $2.5 million in the first Paxil lawsuit filed against the drug manufacturer GlaxoSmithKline, alleging that the drug was responsible for their son's cardiovascular malformations due to exposure during pregnancy. By July 2010, the company reportedly settled about 800 Paxil birth defect lawsuits for approximately $1 billion.[11]

With the use of large administrative databases such as prescription databases, which were for the most part not designed for research since it is unknown if the woman actually took the drug, the number of studies has increased exponentially and currently totals more than 30,000 pregnancy outcomes following exposure to antidepressants during pregnancy.[12] There would seem to be enough evidence-based information accumulated by now, but apparently this is not so, and studies are continuing to be conducted and sent to peer-reviewed journals for publication on the topic of antidepressant use during pregnancy. The probable reason is that, despite this sizeable number of studies and by far the most information on any drug taken in pregnancy, there remains the perception that these results are conflicting, when in reality they are not. When individual studies are published, much is made of very small increased odds ratios (ORs), usually less than 2 (which most epidemiologists consider relatively unimportant). The ORs are frequently explained in a way that they appear much more significant than they really are, and it is rare to see a statement regarding the absolute risk, especially in abstracts,[13] when, in realistic terms, the abstract is often the only part of the article that most clinicians read.

These studies are frequently picked up by the lay media and much is made of these marginally significant results, especially in headlines. In addition, it is uncommon to see studies that found no increased risk reported in the media, an inconsistency that creates a substantial bias in favor of studies associated with adverse effects. Small but statistically significant risks are important at the population level but may be less so when considering an individual, such as a woman who is pregnant and taking an antidepressant. However, many health care providers and their pregnant patients do not understand this concept and use these results to influence their treatment choices.[14] Thus, some women may be influenced to abruptly discontinue their medication, which may have serious consequences to both the mother and her unborn child, or terminate a wanted pregnancy.[15]

The peer-review process

The aim of peer-reviewed research is to publish results of studies that have been conducted using the most rigorous methodology in order to add to the evidence-based information to assist in the treatment of patients. It should be noted that the review process for publication of scientific papers started not long after Johannes Gutenberg invented the printing press in 1440, when a universal method for the generation and assessment of new science was announced by Francis Bacon in the early 1600s. However, it was not until academic societies were founded in the 1700s that a more formal approach was initiated. In 1752, the Royal Society of London took over the editorial responsibility for the production of the *Philosophical Transactions*, at which time it adopted a review procedure that had been used previously by the Royal Society of Edinburgh as early as 1731. Manuscripts sent to the Society for publication were now subject to inspection by a hand-picked group of members who were considered to be knowledgeable in the subject matter and whose recommendation to the editor was influential in the possible publication of the manuscript. Many scholars consider this the beginning of the peer-review process, which is basically still in practice today. This process continued almost to the mid-19th century, when due to the increasing specialization of medicine and the diversity of scientific studies sent to journals, it was necessary for journal editors to seek assistance outside the group of knowledgeable reviewers who could be found in their individual academic societies.[16]

Use of outside experts occurred at different times at different journals. For example, *The Journal of the American Medical Association* did not use outside reviewers until after 1940, which was facilitated by another machine, the Xerox, commercially available in 1959 and used to make multiple copies of papers to be sent out for peer review.[12] Prior to the advent of the Internet, older individuals may remember when one had to send 5 copies of their

manuscript by mail to the journal for consideration. In those days, the average time from sending the manuscript to a journal to eventual print publication if accepted was at minimum a year. As authors are allowed to send a manuscript to only one journal at a time, and, if there are several rejections, by the time the article is finally accepted and in print, it could be several years after the study was completed and the information could be out of date.

With the advent of the computer and Internet technology, the process has accelerated at an amazing rate, to the extent that today, at some of the larger journals, a manuscript can be reviewed, revised, accepted, and published online ahead of print within 6 to 8 weeks. The number of medical journals has also increased to more than 20,000, which means there is a requirement for a huge number of reviewers with scientific expertise who are able to critically evaluate manuscripts and pass on their comments to assist the editor in determining whether or not the journal should publish the manuscript.

As peer review is usually an unpaid task that can be very time consuming, it is prudent to ask where all these “experts” are coming from. How and from where do journals recruit reviewers and what are their qualifications? In researching for this commentary, I could find no documentation of how reviewers are recruited and what qualifies them as experts. As an individual who is frequently asked to be a reviewer, I have never been asked by any journal to state how I am qualified to be an expert. Conversely, as a frequently published author, many times I have been amazed at how totally opposite the opinions of 2 reviewers can be, as it appears that sometimes they have not evaluated the same manuscript. In scientific journals, the decision to publish studies with marginally significant results and questionable clinical significance is the domain of the editors and their editorial boards. These individuals rely heavily on the opinions of their reviewers, who are chosen for their “expertise” in the field, so as to make a decision whether to accept a particular manuscript for publication.

Studies reporting on safety of antidepressant use in pregnancy

Perinatal mental health research is a subspecialty, and studying the use of antidepressants in pregnancy is an even smaller subspecialty. However, information disseminated regarding results of studies conducted on the safety of antidepressants in pregnancy can have a huge impact on a vulnerable population. In addition, pregnancy stories are interesting reading for the general public, and, as everyone knows, “medications should not be taken during pregnancy,” it makes interesting reading when some women do and a study is published associating harm with the drug. Unfortunately, stories about psychotropic drugs are especially interesting, as there continues to be stigma surrounding mental illness,

especially when pregnancy is supposed to be the happiest time in a woman's life. The truth is some women do require pharmacologic treatment for depression in this period. However, many discontinue their medication following pregnancy diagnosis for reasons that include negative information they have heard from their health care providers, who have informed them of studies that have been published without a thorough understanding of the data and results.[13]

Many of the studies published recently regarding antidepressant use in pregnancy that report an association with adverse effects, albeit with small increased ORs, have been conducted using large administrative databases and involve extremely complex statistics, which often only an epidemiologic expert is able to understand. As many reviewers are clinicians, it behooves editors to recruit not only clinical experts in the field, but also someone with statistical skills and knowledge. This recruitment may at times involve sending the manuscript to a statistical expert, which some journals do, but as far as I know, statistical review is not a common practice in all fields. I am considered an expert in the use of psychotropic drugs during pregnancy (probably because I have published many research papers on this topic in the peer-reviewed literature) and consequently am sent many manuscripts to review. However, I am not a statistician and, at times, do ask the editor to send a paper with extremely complex methodology and statistical analysis to someone who is.

In conclusion, with the use of highly advanced computer technology, the process of conducting epidemiologic studies has become so complex that editors of scientific journals have to rely on their reviewers more than ever. Judicious use of both clinical and statistical experts will ensure that the primary focus is on not only the statistical significance, particularly if marginal, but also the clinical importance, if any, of the study results. This will allow empowered decision making on the part of women and their health care providers when deciding whether or not to take an antidepressant during pregnancy.

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3.4 The importance of critical evaluation of the literature regarding safety of antidepressant use in pregnancy

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Acta Psychiatr Scand. 2013;127(2):115-6

Introduction

The important question about antidepressant use in pregnancy is reviewed by Byatt and colleagues in this issue of Acta Psychiatrica Scandinavica[1]. The authors' main conclusions following a review of the literature focusing on controversial results, including 44 studies with (n = 18) reporting on major malformations, (n = 18) on neonatal behavioral symptoms, and (n = 8) on persistent pulmonary hypertension of the newborn (PPHN), are that while some studies suggest an increased risk of specific major malformations, the findings are inconsistent, although the overall risks appear to be small. Neonatal behavioral symptoms can occur in up to 30% of neonates exposed to antidepressants, and in some studies, PPHN has been weakly associated with in utero antidepressant exposure. They also recommend taking into account untreated maternal illness, as this may also exert its own adverse effects on the infant. In addition, they offer some valuable advice in interpreting results of studies, so as to assist the clinician in the treatment of a pregnant and depressed woman.

Pregnancy and antidepressant research

A substantial number of women will become pregnant while taking an antidepressant and may require pharmacological treatment throughout their pregnancy. As almost half of all pregnancies are unintended, this represents a large number of pregnant women taking an antidepressant. Prior to 2005, research using observational designs conducted on the use of SSRIs (Serotonin Reuptake Inhibitors) in pregnancy reported no association between SSRI use and congenital malformations [2], which was based on a meta-analysis of the current data at that time. They appeared to be relatively safe to take during pregnancy and there was no evidence of concern in both the scientific literature and the media. However, this all changed in late 2005, when GlaxoSmithKline (GSK) published on their website, pregnancy outcomes of 815 infants exposed to paroxetine during pregnancy and reported a 2% incidence of cardiovascular malformations (where 1% is expected in the general population). Subsequently, based on this report and data from two unpublished abstracts presented at scientific meetings, The Food and Drug Administration (FDA) issued a warning about the possible adverse effects associated with paroxetine in the first trimester of pregnancy. Subsequently, as Byatt et.al [1] reported, many studies and reviews have been published with 'conflicting results' reporting on thousands of pregnancy outcomes. A recent (August 2nd 2012) GOOGLE search using the keywords 'antidepressants, pregnancy, birth defects' revealed 1 550 000 results, many describing how 'dangerous/ harmful' antidepressants are to take in pregnancy and warning women 'not to take them if they are pregnant.' In addition, there are many websites encouraging women who had a baby who had PPHN or a

birth defect and took an antidepressant during pregnancy, to seek the advice of a lawyer to sue the drug company. Even 'experts' disagree regarding the teratogenicity of antidepressants, most notably paroxetine as illustrated by 2 commentaries in a prominent teratology journal, which were published along with a meta-analysis and presented opposing opinions. Scialli concluded that 'the scientific evidence does not support the conclusion that paroxetine causes cardiovascular defects,' while Bérard stated that 'evidence- based literature shows consistent epidemiologic evidence that paroxetine use during pregnancy increases the risk of cardiac malformations in newborns.'[3] From these statements, one is prompted to question how it is that two experts in the same field have offered such opposing conclusions based on their evaluation of the same data. Understandably, this mixed information has caused anxiety for pregnant women, who may require pharmacological treatment for the depression and for their healthcare providers from whom they seek advice.

Studies conducted on the safety of drugs in pregnancy

Due to the ethical restrictions of randomized controlled trials (RCTs) in pregnant women, studying the safety of drugs in pregnancy is a complex process. Consequently, observational study designs (i.e., case reports, case series, cohort studies, case –control and nested case–control studies and administrative database studies) are currently used, which have many limitations. Recent years have seen an increase in the number of computerized databases, which were not designed for scientific studies, especially prescription databases, where it is only known if the woman redeemed the prescription, not if she actually took the drug. Nevertheless, researchers have used these databases to conduct complex analyses of data, resulting in a substantial increase in such studies. Together with other observational studies using different methodologies, seemingly conflicting results have been published in the peer-reviewed literature and subsequently in the media regarding the safety of antidepressant use in pregnancy.

Knowledge transfer and translation

This brings up a very important question of how are these results disseminated to the scientific community and subsequently to their patients. Most clinicians have a very rudimentary knowledge of epidemiology and statistics, so do not have the skills to carefully examine the often complex methodology of these studies, so rely on the conclusions of the authors, which do not always match their results, most often just from reading the abstract in the journal. When individual studies regarding the safety of antidepressants in pregnancy

are published, much is made of very small increased odds ratios (OR), usually <2 (which most epidemiologists consider relatively unimportant) and are explained in a way that it appears much more significant than it really is. Small but statistically significant risks are the key at the population level, but most often are not clinically important, which is the information that a clinician requires to inform the patient of their individual risk. In addition, studies that did not find an increased risk are frequently ignored by both the scientific literature and in the media. It is rare to see in the media that a new study reporting on the safety/risk of an antidepressant did not find an increased risk for birth defects or other adverse outcomes. Consequently, studies with marginally significant results can have a far-reaching impact on events such as precedent setting lawsuits. In the case of GlaxoSmithKline, the company was ordered to pay $1.5 million to a couple whose baby was born with a heart defect following exposure to Paxil® in pregnancy. By July 2010, the company reportedly settled about 800 Paxil® birth defects lawsuits for approximately $1 billion [4]. In addition, widely disseminated frightening headlines in the media can also cause women to stop taking a needed antidepressant during pregnancy, sometimes with serious consequences, such as contemplating suicide [5]. In summary, this is observational research, and consequently, there are some deficiencies in study design and analysis among all of the studies. However, this does not mean that the information provided from the results of these studies is not valuable, as long as the methodology and analysis are critically evaluated. It is unlikely that in the near future, pregnant women will be included in randomized controlled trials, so this reinforces the need to improve the rigor of the available study methods. However, the bottom line is that current differing research designs regarding the safety of antidepressants in pregnancy did not produce conflicting results per se. Apparent small differences appear to have been likely because of the way selected results were disseminated. Finally and of great importance, improved knowledge transfer and translation will ensure that pregnant women and their healthcare providers receive the most accurate evidence-based information, for decisionmaking regarding the use of antidepressants during pregnancy.

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CHAPTER 4

HOW CURRENT DISSEMINATION OF INFORMATION REGARDING THE SAFETY OF ANTIDEPRESSANTS IN PREGNANCY, IMPACTS BOTH HEALTH CARE PROVIDERS AND PREGNANT WOMEN

4.1 SSRIs and other antidepressant use during pregnancy and potential neonatal adverse effects: impact of a public health advisory and subsequent reports in the news media

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BMC Pregnancy Childbirth. 2005 May 20;5:11

Abstract

Background: On Aug 9th 2004 Health Canada released an advisory, which followed a similar one from the FDA regarding the use of SSRI's and other antidepressants during pregnancy and potential adverse effects on newborns. In neither advisory was it stated that women should discontinue their antidepressant. In the seven days following the release of this advisory, The Motherisk Program received 49 calls from anxious women in response to the media reporting of this information.

Objective: To examine the impact of the advisory and subsequent reporting in the media, on the decision -making of women, currently taking an antidepressant, who called The Motherisk Program after becoming aware of this information.

Methods: We attempted to follow up all the women who had called us who were alarmed by this advisory and asked them to complete a specially designed questionnaire.

Results: We were able to complete 43/49 (88%) follow-ups of the women who contacted us. All of the callers reported that the messages in the media caused a great deal of anxiety. Seven misunderstood the advisory, ie their children were more than 1 year old, five had discontinued their antidepressant (3 abruptly (2 later restarted after speaking with Motherisk counsellors)and 2 with some form of tapering off) and(6) were considering discontinuation, but decided to continue following reassurance from Motherisk

Conclusion: Medical information regarding fetal and infant safety, disseminated in the public domain, should be transferred in a way that does not influence a pregnant woman to make decisions that may not be in the best interest of hers or her child's health.

Introduction

The media plays a significant role in the dissemination of medical information to the general public, through newspapers, television, magazines and more recently through the internet. While it is important to get these messages to the public, at times it appears that the media may have a different agenda, such as selling newspapers or widening their TV audiences. They seem to prefer alarmist headlines and display a preference for stories that catch attention, rather than to inform the public of new scientific data that has both positive and negative results. For example, stories describing safe products are often unreported, or reported in small print, whereas unsafe products usually make headlines. [1] Since the thalidomide scare in the sixties, this has been especially true of stories concerning the safety/risk of exposures during pregnancy.

A recent example in another field, can be found in the study of the use of hormone replacement therapy (HRT) following the release of The Women's Health Initiative (WHI) which was widely publicized in the lay press. [2] A recent survey, completed by more than 1000 women, that examined their opinions and understanding from the lay press of this study, found that women dramatically overestimated the risks of HRT.[3] Another study found that information on the benefits of HRT was mainly provided by health care professionals, whereas information on the risks was provided mainly by the mass media. [4]

The Motherisk Program, at the Hospital for Sick Children in Toronto, is a counseling service that provides pregnant, breastfeeding women, and health care providers with evidence-based information on the safety and risks of exposures to prescription and over-the-counter (OTC) medications, natural health products, chemicals, radiation, and infectious agents. Women and their health care professionals often call us when alarming stories regarding pregnancy exposures are reported in the media. Consequently, we receive a dramatic increase in the number of calls to our service following a report in the media that involves a study that has produced results that are distressing to a pregnant woman.

On June 9th 2004 the FDA(Food and Drug Administration) instructed the manufacturers of antidepressants to issue warnings about perinatal complications associated with their products. FDA: Medwatch Drug Alert. June 03/2004) . On Aug 9th 2004, Health Canada, followed suit and released on their website (http://www.hc-sc.gc.ca/) an advisory warning of the potential adverse effects of Selective Serotonin Reuptake Inhibitors (SSRI's) and other antidepressants on newborns. It was stated that the advisory was intended to increase awareness among mothers and physicians of the possible symptoms that may occur in the newborn, so that they can be recognized and addressed quickly. Some of the symptoms listed were from reports describing feeding and/or breathing difficulties, seizures, muscle

rigidity, jitteriness and constant crying. The advisory also stated that if a woman is pregnant and taking an antidepressant she should discuss with her health care professional the potential benefits and risks of treatment options. It was also stated that it is very important that women do NOT stop these medications without consulting their doctor, however, physicians may consider slowly decreasing the dose in the third trimester of pregnancy. It must be noted, that nowhere in this advisory was it stated that women should avoid taking antidepressants during pregnancy. [5]

This advisory was reported in all forms of the media. Table 1 shows some examples, which were selected both randomly and from the women's reports.

Table 1 Samples of media reporting of advisory (headlines)

Radio: (Ottawa) "Antidepressants pose risk to unborn babies"
Internet: (Canada.com News) "Depression drugs can hurt babies"
Newspaper: (The Toronto Star)"Avoid antidepressants in pregnancy"
Television: (CTV) Antidepressants may put unborn babies at risk
Magazine: (Health and Wellness) "Pregnant women warned about antidepressants"

In the seven days following the media reports, we received 49 calls to the Motherisk line from anxious women. This number was in addition to the already substantial number of calls regarding the use of antidepressants we receive each day. We were not surprised that there was this sudden influx of calls, as we felt that this advisory was clearly ambiguous and it was understandable that the media may have misinterpreted some of the intended message.

The objective of this study was to examine the impact of the media translation of this advisory, on the decision-making of women who were currently taking an antidepressant and called Motherisk for information.

Methods

Researchers at the Motherisk Program developed a questionnaire that consisted of 4 questions, (Appendix). Potential participants were women currently treated with an antidepressant who had contacted the Motherisk Program after hearing about the Health Canada advisory in the media and becoming alarmed.

Table 2 Evidence-based information given by Motherisk counsellors

1. Antidepressants are an important pharmacological tool in the treatment of depression, including during pregnancy.
2. Based on epidemiologic studies they are considered an exposure that would not harm the fetus.
3. Untreated maternal depression is associated with adverse effects on both the mother and the fetus.
4. In a minority of infants there is a mostly self limited but if required, treatable discontinuation syndrome. Consequently, the baby should be observed carefully after birth for signs of withdrawal.
5. If a woman has discussed the benefits and risks of taking an antidepressant during pregnancy with her physician and if the decision is to be pharmacologic treatment, based on current epidemiologic data, there is no reason to discontinue or decrease the drug anytime during pregnancy.

After receiving evidence based information provided by a Motherisk counselor, (Table 2) each woman was followed up by phone within one week of their initial call. Upon contact, she was asked if she would be willing to participate in a telephone survey to be conducted by a student. Oral consent was obtained from each participant after the survey was fully explained over the telephone. If the interviewer was unable to reach the women on the first contact, two more attempts were made before giving up. The data were analyzed by descriptive statistics.

Results

A total of 49 women agreed to participate and 43 completed the survey, a response rate of 88%. Of the women who agreed to participate but were lost to follow-up; 2 had incorrect telephone numbers (either because they had given the wrong number or it had been noted incorrectly) and 4 of the women were unavailable to complete the questionnaire. All of the callers reported that the information they received from the media caused a great deal of anxiety. They all felt that this was important information to know, however would not have been so alarmed if it had been translated by the media in a less “scary” fashion.

Table 3 Background of the women who called Motherisk

N = 43	
Retrospective	**7**
Planning	**4**
Not in 3rd trimester	**32**
Discontinued drug (3 abruptly)	**5**
Considered discontinuing	**6**
Recommendations to discontinue (MD)	**5**

The following results underscore how the information was translated in such a misleading fashion. This information was specifically aimed at women taking an antidepressant in late pregnancy. Thirty-two of the women were not in the third trimester at the time they called the Motherisk Program and eleven were not even pregnant. Four of them were planning a pregnancy and seven had taken an antidepressant when they were pregnant and their children were now more than one year old. Three of the women who stopped taking their antidepressant, discontinued it abruptly, although two restarted following reassurance from Motherisk. Six women were considering discontinuing their medication, but were reassured by Motherisk and decided to continue.

Discussion

To our knowledge, this is the first survey of it's kind that has been conducted to examine the impact of public health advisories and the subsequent reports in the media on the decision-making of pregnant women regarding taking antidepressants during pregnancy. We were able to interview a convenience sample of 43 women who had called our line following the dissemination of this information in the media. We did not set out to conduct a randomized controlled study, we simply wanted to document in an observational fashion , how the women who called our program felt about the information they had received. As such, we were unable to ascertain how many other women in the general population were also possibly negatively affected by rash decision-making prompted by these stories in the media. Conversely, we were also unable to examine how many women were unaffected by the media attention to this advisory, as they did not call us.

To date, based on a fairly substantial body of epidemiologic data, there is no evidence that antidepressants are not safe to take during pregnancy [6,] in fact, emerging data in the literature documents evidence that not taking an antidepressant if it is warranted may be

more harmful. The decision to discontinue taking an antidepressant during pregnancy can have deleterious effects on both the health of the mother and her baby as untreated depression during pregnancy carries its own risks. These include adverse maternal outcomes such as: poor compliance with prenatal care, inadequate nutrition, poor pregnancy outcomes including increased risk of preterm delivery and importantly, an increase risk of post partum depression.[7] Additionally, abrupt discontinuation of antidepressant medication during pregnancy can result in serious physical and psychological adverse effects, which may include substitution of alcohol for medication, acute onset of a major depressive episode and suicidal ideation. [8] Furthermore, studies of infants born to depressed mothers have reported that these infants exhibit "depression –like behavior, demonstrated by decreased facial expressions, inferior orientation skills, excitability and abnormal reflexes.[9] Conversely, the neonatal SSRI poor adaptation syndrome occurs in a minority of cases, is usually self-limited and to date there is no evidence to suggest that a woman should discontinue her antidepressant in late pregnancy.[10] However, the research is ongoing ,so it is not possible to say definitively how often this occurs or that there are no long term adverse effects on the child whose mother was exposed to an antidepressant in late pregnancy. A woman and her physician should always discuss the evidence-based information on both the positive and negative effects of treatment with an antidepressant in pregnancy before making a decision, which will ensure the best possible outcome for the mother and child.

It is important that scientific information is disseminated to the public to empower them to take care of their health. Paternalistic models of health care delivery have been replaced by a more balanced approach, which includes both patient and provider goals Today, patients are encouraged to actively participate in the decision-making regarding management and treatment of their health and the various forms of the news media particularly the Internet are powerful tools to facilitate this process. However, the way in which this information is translated from scientific data and disseminated to the public must be carried out in a responsible and circumspect fashion. Shuchman et al. documented the four problem areas in the reporting of medical information to the public by journalists: sensationalism, biases and conflicts of interest, lack of follow-up and stories that are not covered. [11] Motherisk has previously shown that studies reporting results that showed no harmful effects, were underreported as compared to studies that reported results that showed harmful effects, for example, the use of cocaine in pregnancy.[12]

The major limitation of this study, is that we do not know how this media translation of scientific information affected the general population of pregnant women who are taking antidepressants during pregnancy for example, women who did not call Motherisk. It remains unclear how many women may have suffered from preventable adverse events

secondary to abrupt discontinuation of their antidepressant as a result of these news stories, as we only have information regarding the women who did call The Motherisk Program. On the other hand some women may have been unaffected by these stories and continued to take their medication without any concerns.

In summary, this is an example of how the news media in their misguided reporting of information from a Health Canada Advisory, which in itself was rather ambiguous, influenced a number of pregnant women to make decisions that may not have been in the best interests of their health or the health of their unborn child.

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Appendix

Questionnaire

1. Were you taking an antidepressant when you called Motherisk for information?

YES NO

2. If no:

1) Did you stop taking the medicine:

Abruptly Gradually (i.e. taper off)

2) After speaking with Motherisk, did you restart the antidepressant?

YES NO

3. After speaking with Motherisk, did you speak with your MD?

1) YES NO

2) If Yes:

Did your MD recommend you continue to take the antidepressant?

YES NO

3) If No, why?_____

4) If Yes:

Did you continue to take the antidepressant?

YES No

4. In your own words, “what impact do you feel that the media stories had on your decision making regarding whether you took the antidepressant or not”?

4.2 Influence of the media on women taking antidepressants during pregnancy

Adrienne Einarson

J Clin Psychiatry. 2009;70(9):1313-4

Many more women than men suffer from depression, with up to 20% of women of childbearing age diagnosed with the condition, most often between 25 and 44 years of age.[1] Approximately 10% to 15% of these women experience depression during pregnancy and the postpartum period.[2] Prior to late 2005, there was no evidence that the newer antidepressants, as a group, increased the incidence of major malformations above the expected 1% to 3% in the general population.[3,4] At that time, physicians and their pregnant patients appeared to be relatively comfortable with prescribing and taking these drugs (personal experience from The Motherisk Program). However, in December 2005, GlaxoSmithKline (GSK) published on their Web site preliminary results of a study documenting an increased risk for cardiac malformations (2 per 100 versus 1 per 100) in infants whose mothers took paroxetine in early pregnancy.[5] These data were supported by 2 other studies,[6,7] presented at meetings and at that time published only in abstract form. Subsequently, on the basis of these 3 preliminary reports, the US Food and Drug Administration (FDA)[8] and Health Canada[9] posted warnings (which have not been updated, despite several large studies that have been published in the past 5 years) on their Web sites advising women to avoid paroxetine if possible during pregnancy. This information was quickly picked up by the media and widely published in the print media, on television, and on the Internet. In the 7 days following the release of these advisories, The Motherisk Program received 49 calls for information from anxious women, currently pregnant or planning a pregnancy and taking paroxetine. [10]

In December 2006, the American College of Obstetricians and Gynecologists published a similar advisory (not yet updated with the new information), which also quickly made it to the media, causing further concern among women and their health care providers.[11] Warnings such as these, describing adverse effects of exposures in pregnancy, are almost always widely cited by the media and subsequently make their way to the Internet. A recent Google search (June 23, 2009) using the keywords "*antidepressants*, *pregnancy*" revealed 1,420,000 results, many describing how "dangerous/harmful" antidepressants are to take in pregnancy with many sites warning women not to take antidepressants if they are pregnant. Studies that do not find evidence for harm[12] more often than not are ignored by the media, such as in the recent *Vogue* article that focused only on studies that reported adverse effects.[13] In addition, a number of Web sites have been developed that invite women to join a class action suit against GSK if they took Paxil in pregnancy and delivered a baby with a cardiovascular birth defect.[14]

A survey of community pharmacists in 3 countries reported that pharmacists do not always use evidence-based information, but instead, often refer to the product monograph, which is not an appropriate resource to dispense information regarding the safety of drugs during

pregnancy and breastfeeding.[15] For example, the 2009 product monograph information on Prozac states the following: “The safety of this drug during pregnancy and lactation has not been established, therefore it should not be administered to women of childbearing potential unless the benefit clearly outweighs the possible hazards to the fetus or child.”[16] This despite evidence based on thousands of women exposed to this drug during pregnancy with no evidence of harm to the fetus.[17]

Currently, even though mental illness is more widely accepted, especially owing to famous people talking about their disease, there continues to be a certain amount of stigma, which was documented in a Canadian survey conducted last year that reported 1 in 4 Canadians is fearful of being around those who suffer from serious mental illness.[18] In addition, a group who conducted a worldwide study regarding perceived stigma among people with mental disorders confirmed this general fear and stigma surrounding mental illness.[19] Another group reported that less personal exposure to depression equaled higher personal stigma.[20] Another group who used the same questionnaire used by Griffiths et al20 reported the same results for some of the statements but, for others, found the opposite, ie, that there was a trend between more exposure and higher personal stigma.[21]

For women who require pharmacologic treatment for depression during pregnancy and their health care providers, it is understandable that after reviewing all, or even some of this information, making the decision to prescribe or continue taking an antidepressant during pregnancy would be very difficult. However, somehow amid all of this conflicting information and continued stigma surrounding mental illness, as well as previous information a woman has received, a psychiatrist is expected to assist the pregnant woman in making a decision as to whether she should take an antidepressant and, if so, which one. In conclusion, any decision to take an antidepressant in pregnancy should be made between the woman and her physician after weighing the risks and benefits of the medication using evidence-based information. This standard of care will ensure the best outcome for both mother and infant, which should be the primary endpoint.

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4.3 Negative impact of non-evidence-based information received by women taking antidepressants during pregnancy from health care providers and others

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J Obstet Gynaecol Can. 2012;34(1):66-71

Abstract

Objectives: The use of antidepressants by women during pregnancy continues to be a controversial subject, with conflicting information regarding the safety of this group of drugs. We sought (1) to determine the impact of information, advice, and comments women received from health care providers, family, and media about use of antidepressants during pregnancy, and (2) to compare experiences regarding the psychosocial impact of women who continued and discontinued antidepressant therapy during pregnancy.

Methods: Women who had taken an antidepressant at some point during pregnancy were interviewed. The responses of women who continued antidepressant therapy throughout pregnancy were compared with those of women who discontinued therapy at some point in the pregnancy. A questionnaire with questions pertaining to information women had received from various individuals regarding the use of an antidepressant while pregnant was administered to both groups.

Results: Ninety-four interviews were completed; 78 were with women who continued antidepressant therapy throughout pregnancy, and 16 were with women who discontinued therapy. The small number of women in the discontinuation group was a result of many women declining to participate. More than one half of the women who continued the medication throughout pregnancy had frequently considered discontinuing, despite reassurance that continuation would cause no harm to their baby. Negative information was recalled far more often than reassuring information.

Conclusion: Information from friends, family, and health care providers can have a negative impact on decision-making regarding pharmacotherapy for depression during pregnancy. Health care providers should be cognizant of this when counselling patients who require antidepressant therapy during pregnancy.

Introduction

Many more women than men suffer from depression; up to 20% of women of childbearing age develop this condition, which is most prevalent between ages 25 and 44.[1] Approximately 10% to 15% of these women experience depression during pregnancy and the postpartum period.[2] Consequently, a substantial number of women will become pregnant while taking an antidepressant and will be faced with the decision of whether they should continue the medication throughout pregnancy or not. At this time they are likely to reach out to their friends, family, and health care providers for information to assist them in this decision-making process.[3]

Before 2005, there was no evidence that the newer antidepressants, as a group, increased the incidence of major malformations above the 1% to 3% found in the general population.[4] However, in 2005–2006 GlaxoSmithKline published (on their website) preliminary results of a study documenting an increased risk for cardiac malformations (2% vs. 1%) in infants whose mothers took paroxetine in early pregnancy. The type of cardiac defects were not specified; some could have been minor and may have resolved spontaneously.[5] Later, the data were reanalyzed and the incidence was revised to 1.5%, with these findings published in a peer reviewed journal.[6] These data were supported by two other studies,[7,8] in which investigators also found a small increased risk for cardiovascular defect in infants associated only with paroxetine, and not with other selective serotonin re-uptake inhibitors. However, a recent study with more than 1100 prospectively collected cases of women exposed to paroxetine in the first trimester of pregnancy did not find an increased risk for cardiac defects.[9]

Subsequently, on the basis of the three alarming reports on paroxetine, the United States Food and Drug Administration[10] and Health Canada[11] posted warnings on their websites (which have not been updated with the new reassuring information) advising women not to use paroxetine if possible during pregnancy. In the seven days following the release of these advisories, The Motherisk Program received 49 calls from anxious women in response to the media reporting of this information.[12] In December 2006, the American College of Obstetricians and Gynecologists published a similar advisory, causing pregnant women and women planning pregnancy further concern.[13]

Health care professionals also do not necessarily disseminate evidence-based information, which was made clear by the results of a survey of community pharmacists in three countries. This reported that pharmacists do not always use adequate evidence-based information. Instead, they refer to the product monograph, which does not include

evidence-based pregnancy data, or even give their own personal opinion such as "I would not let my wife take antidepressants in pregnancy."[14]

In August 2008 a news item in the media reported that "one in four Canadians is fearful of being around those who suffer from serious mental illness,"[15] which was based on a report by the Canadian Medical Association.[16] Another group, who conducted a worldwide study regarding perceived stigma among people with mental disorders, confirmed this general fear and stigma surrounding mental illness.[17] Other authors reported that less personal exposure to depression resulted in more personal stigma,[18] and another group who used the same questionnaire reported the same results for some of the statements but opposing results for others, i.e., that there was a trend between more exposure and increased personal stigma.[19]

A study from Motherisk, examining determinants of decision-making regarding the pharmacological treatment of nausea and vomiting, found that women are generally afraid of taking any medications in pregnancy, regardless of the indication. Women were worried about harming their baby by taking Diclectin, despite the fact that this is a drug indicated for pregnant women with safety data involving more than 30 000 women. Although they received detailed information and were informed that it was safe to take in pregnancy, 30% of the women decided not to take the medication.[20] It is therefore not surprising that health care providers are hesitant to prescribe antidepressants during pregnancy and women are hesitant to take them.

Our primary objective for this study was to determine the psychosocial impact of information, advice, and comments women received from health care providers, family, and media sources. Our secondary objective was to compare differences in experiences between women who discontinued antidepressant therapy during pregnancy and women who continued therapy.

Methods

We conducted a semi-qualitative study in a convenience sample of women from Saskatchewan and Ontario.

At The Motherisk Program, we recontacted women from our prospectively collected database of 1245 cases, in which we had completed pregnancy outcome data regarding the safety of antidepressant use during pregnancy. [21–23] We randomly selected 200 women and compiled two comparison groups:

1. women who took their antidepressant throughout pregnancy, and
2. women who discontinued their antidepressant at some time during pregnancy.

Participants from Saskatoon had been enrolled in the Maternal Mental Health Program, a multidisciplinary program that provides consultation and care to preconception, pregnant, and postpartum women within a primary health clinic. Women who had agreed to further follow-up subsequent to a previous antidepressant study during pregnancy were invited to participate in this study.

Women from both provinces were contacted by telephone and were asked to participate in the study. Following oral consent, the same detailed questionnaire was administered. Women were excluded if there was comorbidity other than anxiety (such as bipolar disorder), if the pregnancy had resulted in miscarriage, stillbirth, or birth of twins, or if they reported use of illicit drugs or more than five alcohol units daily.

The questionnaire was divided into six sections:

1. Experiences with depression and general views on taking antidepressants during pregnancy.
2. Attitudes and beliefs about statements concerning health, pregnancy, and medication use.
3. Individuals with whom the women spoke about taking antidepressants during pregnancy and the advice they received.
4. A description of how the need to take antidepressants while pregnant affected them emotionally.
5. Reported comments from friends, family, and co-workers about taking antidepressants during pregnancy.
6. Demographics.

The questionnaire contained a total of 67 questions and required approximately 30 minutes to complete. Information from the initial analysis was reported in descriptive statistics. The responses from those who continued and those who discontinued were then compared using a Mann–Whitney *U* test. Oral consent was given after the study protocol was explained to potential participants in detail. This study was approved by the Ethics Board at The Hospital for Sick Children in Toronto, Ontario, and by the Behavioural Ethics Board, University of Saskatchewan.

Results

From 374 attempted phone calls, we were able to complete 94 questionnaires with participants, 78 of whom were "continuers" and 16 "discontinuers." The maternal demographics did not differ between the Saskatchewan and the Ontario group. Of the continuers, 67 (86%) were married and of the discontinuers 14 (88%) were married. The education level was high: 35 continuers (45%) and 11 discontinuers (69%) had at least a bachelor's degree. However, more continuers (51, 65%) were not employed than discontinuers (13, 81%). The majority of the participants, 51 continuers (65%) and 11 discontinuers (69%), had a combined family income of at least $51 000. The mean age of participants was 33 ± 5 years (Table 1).

Table 1 Characteristics of the participants

	Continuers (n=79)	Discontinuers (n=14)	Total (n=93)
Education > high school, %	76	79	78
Married, %	88	79	85
Caucasian, %	86	93	88
Employed, %	70	86	73
Household income >$50,000, %	83	82	83
Depression (self-reported severity of depression on scale of 0-10)	6.3	6.4	6.3

When asked to describe the chance of having a baby with a major birth defect due to antidepressant use, 38 continuers (49%) and eight discontinuers (50%) felt that the risk was higher than the population baseline risk of 1% to 3%. The remaining women were unable to answer the question. Their answers were based upon different information they had received from sources that included their physician, Motherisk, their own (positive or negative) experience, and someone they knew who may or may not have had a healthy baby and who had taken medication during pregnancy (but not necessarily antidepressants) (Table 2).

Table 2 Exploring women's feelings

	Continuers (n=79) %	Discontinuers (n=14) %
Did you feel guilty?	65	100
Despite reassurance did you still worry that you may be harming your baby?	77	100
Did you consider quitting?	62	100
Despite reassurance, did you have the feeling that you had to choose between your baby or your own health by taking the medication?	37	33
Where there any comments from friends, family, health care professionals, co-workers, or even strangers that upset you?	22	21

Physician Interaction

All participants had asked their physician about taking antidepressants during pregnancy, and all but two continuers and two discontinuers could remember what their physician had said in response (Appendix). The majority of physicians (58 physicians of continuers [75%] and 8 physicians of discontinuers [50%]) were relatively reassuring about taking the medication, although some advised lowering the dose and others reasoned that there were some risks but that the risks were outweighed by the benefits. Many physicians, even if they felt relatively comfortable with the patient taking the medication, advised the woman to call Motherisk to obtain a second opinion. Other physicians (11 physicians of continuers [14%] and 2 physicians of discontinuers [13%]) were clearly not comfortable with the patient taking the medication and advised the patient to call Motherisk. A minority of physicians (4 physicians of continuers and 3 physicians of discontinuers) advised women not to take the antidepressant at all or to discontinue use immediately. Both groups of women felt their physicians were generally not very reassuring and appeared to be uncomfortable about discussing the situation.

Advice From Other Health Care Professionals

In addition to speaking to their physicians, 47 continuers (60%) and 11 discontinuers (69%) spoke with other health care professionals. Most women spoke with a pharmacist, a psychiatrist, a psychologist, or Motherisk. Many of the women who spoke with other health care providers received reassuring information similar to that received from their physician (30 continuers [64%] and 3 discontinuers [27%]). Seven continuers (15%) and one discontinuer (9%) received both positive and negative opinions from physicians and health care providers. Some of the women could not remember who said what and were quite confused about the information.

Internet

Three quarters of the women sought information on the Internet at least once (31 continuers [74%] and 6 discontinuers [60%]), although 12 continuers (39%) and one discontinuer (17%) could not remember what information they had found on the Internet.

Discussion

To our knowledge, this is the first study to examine the impact of information given to pregnant women who require pharmacological treatment for depression in pregnancy. We

feel that one of the key messages from this study, illustrated by the one third of women who did not feel comfortable in confiding in their friends and family that they were pregnant and taking an antidepressant, is confirmation of the continued stigma attached to mental illness. Negative information from friends and family (62%) and from health care providers (12%) about the dangers of taking an antidepressant during pregnancy was recalled in far more detail, and for longer, than reassuring information.

One of the most interesting findings, which we did not anticipate, was that discontinuers did not receive any more negative information prompting them to discontinue the antidepressant than continuers. However, many discontinuers (81) refused to participate in the survey, so some of these women could have received more negative information than we were unable to elicit from them. The few discontinuers who did participate tended to have a more negative attitude than continuers towards use of antidepressants in pregnancy, and in general.

With respect to media sources, 65% of the women retrieved information from the Internet. This is an increasing trend, and many women stated that the Internet was often the first place they turned to for information. Government health warnings, especially when they relate to adverse effects of exposures in pregnancy, are almost always widely cited by the media and subsequently make their way to the Internet. A Canadian website called *BREATH, The Official Blog of Mothers Against Drugging the Nursing And Pregnant* targets psychiatric drug use during pregnancy. Pregnant women are advised that they should not take an antidepressant and instead use nonpharmacological, non evidence-based treatments. Most recently, they are advocating for Canadian regulation on fetal exposure to psychotropic drugs, but do not give any suggestions on how this would transpire.[24]

Health care professionals were generally more reassuring than family and friends. However, if a woman received negative information from a health care provider, especially a physician, this was more upsetting because these individuals are usually trusted to provide correct information. In addition, after receiving negative information from a health care provider, it was difficult for women to accept that the reassuring information provided when they called Motherisk was evidence-based. Consequently, despite reassurance, continuers remained worried and felt guilty because they could not forget the initial (negative) information they received.

There are several limitations to this study. Most importantly, this was a convenience sample, not a population-based sample. The second important limitation was the lack of a sufficiently large sample of discontinuers who agreed to participate. However, because this was a semi-qualitative study, we feel that the sample size overall was sufficient to meet our

objectives. Finally, this survey was conducted in Canada, and the findings may not be extrapolated to other countries, although it is evident from global Internet websites that these attitudes and practices do occur worldwide.

Conclusion

When giving advice regarding taking antidepressants during pregnancy, health care providers should be aware that negative or frightening information from media sources, health care providers (especially physicians), and social contacts can have a major effect on well-being, despite subsequent provision of reassuring information. Even when a woman decides to continue medication, she may still be concerned about risk and she may decide to discontinue treatment without having received any negative information. Women should be provided with unambiguous evidence-based information about the risks and benefits of any medication they use to allow them to make an informed decision about taking a medication they may require during pregnancy.

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APPENDIX

Comments from health care providers reported by participants

"None of them said explicitly if it was safe or not."

"None said it was unsafe but the psychiatrist had some cautions."

"The physician didn't say it was safe but advised me to continue."

"Nobody said it wasn't safe. They were more concerned about my well-being."

"Nobody said it wasn't safe. It was somewhere in between safe or not safe."

"Nobody said it was not safe. Everyone I spoke with encouraged me to get more information."

"There was a bit of a risk (in using Zoloft), but there were not really studies done at the time."

4.4 Barriers to the pharmacological treatment of women with psychiatric disorders during pregnancy and breastfeeding: results of a survey

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J Obstet Gynaecol Can. 2013;35(6):504-5

Psychiatric disorders are relatively common among women of childbearing age; consequently, a substantial number may require pharmacological treatment during the perinatal period.[1] To date, few guidelines exist for treatment of pregnant and/or lactating women with a psychiatric disorder. We could find only two guidelines that were specifically designed for pregnant women with depression and other psychiatric disorders. However, these guidelines (NICE[2] and Psychiatry Online[3]) are very broad and conservative regarding the use of psychotropic drugs in pregnancy and breastfeeding, and are intended primarily for a woman who is planning a pregnancy. As almost half of all pregnancies are unintended,[4] many women approach their health care providers when they are already pregnant and taking a medication, requesting information regarding drug safety.

In 2008, a worldwide group of health care providers involved in the care of pregnant and breastfeeding women with psychiatric disorders formed the Reproductive Psychiatry Group, and provided an email forum to discuss the challenges of treating these women. We wanted to evaluate the perceived barriers in caring for this group of women.

In April 2012, a survey containing demographics questions and open and closed questions about participants' personal attitudes and practices was sent to the Group's listserv. Respondents were also asked to give their opinions regarding possible treatment of women with psychiatric disorders who were pregnant and/or breastfeeding with the use of hypothetical scenarios.

Before the survey was sent out, an email was sent to all the members of the listserv alerting them to the survey, so that consent was implicit in completing the survey. The results were descriptive, and were analyzed using percentages.

One hundred thirty-three of 179 questionnaires were completed for a response rate of 74%. Of the participants, 81% defined themselves as perinatal psychiatrists, while the remainder were obstetricians, family physicians, psychologists, social workers, psychiatric nurses, lactation consultants, pharmacists, and researchers. Most of the respondents were women (93%). Our main findings were that health care providers, especially perinatal psychiatrists who prescribe psychotropic drugs, perceive many barriers related to pharmacologic treatment during pregnancy and breastfeeding. The most prominent barriers were general stigma attached to mental health (45%), women's fear and anxiety about use of medications during pregnancy (70%), conflicting evidence-based information on the safety of psychotropic drugs in pregnancy (50%), biased media reporting about harm of drugs, (50%), difficulty with understanding complex disseminated scientific information (50%), fear of legal ramifications (25%), other health care providers' misperception of the risk of drugs and other misunderstandings about mental health (55%), concern about women seeing

advertisements by lawyers encouraging them to sue drug companies if they took a psychiatric medication during pregnancy and had a baby with a birth defect (35%), lack of professional guidelines for treating women with mental illness during pregnancy (20%), and all of the above (30%).

It is apparent that health care providers (especially perinatal psychiatrists, who are confronted daily with the need to make decisions about treatment options) face many barriers when treating women with a psychiatric diagnosis during pregnancy and breastfeeding. More “real world” evidence-based guidelines for both the health care providers and their perinatal patients are required to assist in decision-making with respect to taking a psychotropic drug in pregnancy or when breastfeeding.

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CHAPTER 5

GENERAL DISCUSSION

Introduction

Traditionally, dissemination of knowledge derived from results of studies, has been carried out through peer reviewed scientific journals and at scientific conferences, with a minimal amount reaching the clinician and patient, who require the information to promote appropriate healthcare behavior. For research to have an impact that will improve the health of the population, it is critical that both the creators and the consumers of knowledge take steps to bridge these gaps. Knowledge translation strategies address this conundrum by bridging the gap between information creation, dissemination and uptake.

Table 1 Information seekers and sources of information used

Information seekers	Sources of information
Physicians	Physician's Desk Reference (PDR), textbooks, PubMed, clinical guidelines
Pharmacists	Same as physicians
Allied health care practitioners	Same as physicians
Pregnant women	Health care providers, websites, media
Law firms	Government websites, media outlets
Teratogen information services	Conduct own research, peer reviewed literature, PubMed
Government organizations	Scientific literature, funded research
Media outlets	Government websites with warnings, scientific literature, press releases

Currently, Knowledge Transfer (KT) is considered a very important component of modern science and health care management. A widely used definition is that of the Canadian Institutes for Health Research (CIHR) who describe KT as "the exchange, synthesis, and ethically sound application of knowledge – within a complex system of interactions among researchers and users to accelerate the capture of the benefits of research through improved health, more effective services and products, and a strengthened health care system".[1] KT may vary in intensity, complexity and level of engagement depending on the nature of the research and the findings, as well as the needs of the particular knowledge user. The transfer of knowledge from the research community to clinical decision-makers should be understood as a two-layered process that includes the exchange of information

among various stakeholders as well as the appropriate cognitive processing. In the current era of evidence-based medicine, it is imperative that clinical decisions be based on up-to-date, scientifically accurate information.

Antidepressant use in pregnancy has become a controversial subject, largely due to inconsistent results from studies and subsequent dissemination of conflicting information in both the scientific and lay press. Users of this information are healthcare providers who are involved with and including the women themselves who may require an antidepressant while pregnant, as well as other information seekers. These include clinicians who are confronted with a woman requiring information about the safety of antidepressants during pregnancy, as well as committees who are attempting to construct specific clinical guidelines (Table 1). In addition, mental illness continues to be surrounded by controversy and stigma, with the lay press frequently using this information, as it has become a “hot topic”.

The objectives of this thesis were: (1) to determine how knowledge about the safety/risk of antidepressant use in pregnancy is created, (2) to describe different research models and statistical analyses that have been used, so as to critically evaluate the results, and (3) to identify how the information is currently disseminated and how the gaps in KT can be filled. The body of the thesis consists of four parts:

1: gives an overview of knowledge transfer and translation and how it relates to providing women and their healthcare providers with evidence-based information, regarding the safety/risk of drugs and other exposures during pregnancy.

2: describes how research is conducted when examining the safety of antidepressant use in pregnancy, which includes a description of the types of studies that are conducted, the type of data that is used and what statistical analyses have been utilized.

3: describes how to understand the results of published studies, using various examples, by carefully examining the authors’ objectives and conclusions. It also includes a description of basic statistics, such as what does an OR really mean, so as to be able to understand the difference between statistical significance and clinical relevance of the results.

4. describes how information received and from whom, affects both women and their health care providers in their decision-making regarding taking an antidepressant in pregnancy. The influence of friends, family and the media on risk perception and determinants of decision-making is also discussed.

In this general discussion I will put the individual studies in a broader context and will discuss the following topics:

- The creation of knowledge
- Critical evaluation of the literature
- How current dissemination of information regarding the safety of antidepressants in pregnancy, impacts both pregnant women and health care providers

In addition, I will provide some implications for clinical practice and future research

The creation of knowledge

Studying the safety of drugs used in pregnancy, especially psychotropics, is a complicated process with currently no "gold standard" for conducting studies. Because of the ethical issues surrounding studying pregnant women, it is highly unlikely that randomized controlled trials (RCTs) will ever be conducted. Consequently, observational studies are used and all of the models have their limitations, such as small sample size, bias, inability to know exactly if the women took their medication in pregnancy and missing data. Currently, there is no specific organization that has been directed to take on the responsibility of conducting these studies, and it appears that if researchers have an interest in this field, have the data and the resources, a study will be conducted. An exception is that in the USA, drug companies are now required to conduct and maintain a post marketing pregnancy registry of a new product, following release on the market.[2] Other data sources typically come from patient charts, insurance claims pharmacy records, physician practices, health databases, hospital records, and teratogen information services.

The following research methodology has been used for studying drug safety in pregnancy:

1) The Case Report is a signal generator, which may identify a potential problem and can prompt a more formal investigation. The earliest teratology studies began appearing in the late 1800s, however, the study of drug safety in pregnancy, began following Dr. W McBride's letter in the Lancet in 1961, stating that he had seen several cases of exposure to a sleeping pill,(thalidomide) in early pregnancy, resulting in polydactyly, syndactyly and failure of development of long bones (abnormally short femora and radii).[3]

Typically the main limitation of case reports is that they cannot determine causation, unless many other cases describe the same defect with the same exposure. However, this was not the case with thalidomide, as many cases were subsequently reported with similar malformations. In the more than 50 years following this discovery, only one other drug has been found to cause major abnormalities to an infant exposed during pregnancy which is the vitamin A derivative isotretinoin used for severe acne (Accutane®). However, because of the

heightened awareness due to the thalidomide tragedy, it was known to be a teratogen in a much shorter time than thalidomide, due to the many case reports published in the literature, reporting on infants exposed in utero to the drug who exhibited the same pattern of malformations. Consequently, guidelines were rapidly put in place to prevent women from taking this particular drug during pregnancy.[4]

2) Case series: are usually more than one case and could be hundreds, occasionally thousands as in some drug company pregnancy registries and other registries from academic organizations. They can be presented as cases of exposure or cases of outcome. However, the main limitation of these studies is that there is no comparison group to examine variables, which may affect outcomes.

3) Prospective comparative cohort studies: which are commonly used when examining the safety of drug exposures in pregnancy and are considered a relatively high level of evidence, mainly because there is a comparison group. They are often conducted by Teratology Information Services (TIS), by a single service or in collaboration from around the world. I, in collaboration with my colleagues at The Motherisk Program and other TIS worldwide, have generated a substantial amount of information derived from studies regarding the safety/risk of antidepressants in pregnancy.[5-16]

4) Case control studies: are retrospective studies where the outcome is known and the group with a given outcome (e.g., major malformation) is compared to another group who did not have that outcome with respect to the exposure of interest. This methodology is often used in teratology studies because far fewer cases are required to examine rare birth defects, compared to prospective comparative cohorts.

5) Meta-analysis: can be a very useful method when studying drug use in pregnancy, as discussed previously, most observational pregnancy outcome studies have small sample sizes. Meta-analysis is a way of combining results across different studies, enlarging the sample size, so as to make a more definitive statement regarding safety/risk of the drug.

With the advent of electronic data bases containing large amounts of patient healthcare information, a new source of data became available for research.

1) Administrative databases: Although commonly used, they are not typically set up for pharmacoepidemiologic research as they are primarily developed for various administrative claims payments. For this reason, important data are often missing, especially for studies of drug use and pregnancy outcomes. However, they often contain data from large numbers of

individuals with important information, so have been increasingly used in research, most frequently to conduct post marketing surveillance.

2) National birth registries: Some European countries operate government supported registries where data from the mother and child pairs are entered after birth and are followed up prospectively.

When practicing evidence-based medicine, all of these methodologies loosely fit into the category Level 2: “Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group”.

Critical evaluation of studies regarding the safety of antidepressant use in pregnancy.

Understanding the strengths and limitations of study designs, data sources and data analyses are essential when evaluating or interpreting published studies , as all study designs have limitations and authors do not always fully disclose details, such as dosing, adherence concomitant medications and other risk factors of importance, such as levels of depression. This is especially critical when examining studies that have been conducted regarding the safety/risk of antidepressants, due to the controversy and subjectivity surrounding this field. In addition, exposure measurements are not always exact an details of concomitant medications are often missing, as well as other risk factors/confounders and it is difficult to exclude confounding by indication.

When evaluating the literature, one should always examine if the results appear to be valid, based on the authors conclusions. In one example, the authors reported an increase risk for major malformation (RR = 1.84) in women taking antidepressants. The validity of these results was questionable for the following reasons: 1) There was no pattern of specific defects 2) There was no separation of major versus minor malformations, 3) As this was a prescription event monitoring study, it was not known whether the medications were actually taken and 4) Psychiatrically ill patients frequently use other psychotropic medications, alcohol and illicit drugs and these potential confounders were not addressed.[17] In another study the authors conducted a large number of tests, but made no adjustment for multiple testing, without acknowledging that their results could all be random error. They also attempted to identify depressed untreated pregnant women, but provided no solid evidence that they actually succeeded in doing so. They also found two very trivial differences in birth weights (30 gm difference between groups) and stated they had found an increased risk for low birth weight.[18]

In another study (meta-analysis) the authors pooled the results of 12 studies that examined poor neonatal adaptation syndrome PNAS. There was a significant association between exposure to antidepressants during pregnancy and overall occurrence of poor neonatal adaptation syndrome PNAS (odds ratio [OR] = 5.07; 95% CI, 3.25-7.90; P<0.0001) However, the reporting of these ORs was not really helpful to the reader, because it is already known that PNAS occurs in up to 30% of neonates and the important statistic in this case, would have been the frequency of occurrence, which was not analyzed.[19]

Finally, in another study (meta-analysis) the authors concluded that the summary estimate indicated an increased prevalence of combined cardiac defects with first trimester paroxetine use. The limitation with this analyses was that the authors opted to exclude the Motherisk study n=1174 cases with no increased risk for cardiovascular defects, for unknown reasons, that probably would have lowered the OR.[20]

It is also likely, for a variety of reasons, that many clinicians only read the abstract of a paper in a scientific journal. Therefore, it is very important that abstracts contain as much information about the study as possible, especially the results and conclusions**.** Most journals have reduced the number of words in their abstracts from 300-350 to 200-250 maximum and some do not include an introduction, simply an objective, the study design, results and conclusions. In one study where we evaluated the quality of information included in abstracts, we found that that details frequently absent included: baseline risk (94%), drug dose (91%), non-significant p-values (72%), significant p-values (57%), confounders (69%), and risk difference (48%).[21] Two examples of why one should not only read the abstract are; (1) (a case control study), where the authors examined whether taking an antidepressant in pregnancy was associated an increased risk of Persistent Pulmonary Hypertension in the Newborn (PPHN). Infants with PPHN who had been exposed to an SSRI in late pregnancy were compared with unexposed infants, and revealed an OR 6.1, which is a significantly increased risk, and which was presented in the abstract. However, in the conclusion of the main text, these results were clearly put into perspective, stating “on the assumption that the relative risk of 6.1 is true and that the relationship is causal, the absolute risk for PPHN in their infants among women who use SSRI’s in late pregnancy is relatively low (about 6-12 per 1000), put in other terms, about 99% of these women will deliver a baby unaffected by PPHN”.[22] This study caused a great deal of angst among both pregnant women and their health care providers, especially because it was published in the prestigious New England Journal of Medicine. The aim of the second (an observational cohort) was to determine the association of maternal psychotropic medication use during pregnancy with preterm delivery and other adverse perinatal outcomes using a cohort of 2793 pregnant women. In the abstract, the authors reported that the maternal use of

benzodiazepine during pregnancy was associated with an increased risk of preterm delivery (adjusted odds ratio, 6.79; 95% confidence interval, 4.01-11.5) and an increased risk of low birth weight, low Apgar score, higher neonatal intensive care unit admissions, and respiratory distress syndrome. The authors' conclusion was that benzodiazepine use in pregnancy was associated highly with preterm delivery and other adverse perinatal outcomes. However, when reading the full text, their conclusions simply did not match the results. The reporting in the abstract suggested that the entire cohort were psychotropic medication users, while in the text, the sample size of psychotropic medication users was only 10.7% (300/2793) of their cohort. Although the authors reported that benzodiazepine was highly associated increased risk of preterm delivery, the sample size was actually very small; N= 85. In addition, decreasing the overall sample size further, hydroxyzine an antihistamine, was listed inaccurately as a psychotropic drug (n=107), making the final sample size of psychotropic drug exposures only (N=193), or 6.9% of 2793 women. Consequently, this sample size was too small to make a definitive conclusion, which was not stated in the abstract.[23] This is observational research, and consequently, there are some deficiencies in study design and analysis among all of the studies. However, this does not mean that the information provided from the results of these studies is not valuable, as long as the methodology and analyses are critically evaluated. It is unlikely that in the near future, pregnant women will be included in randomized controlled trials, so this reinforces the need to improve the rigor of the available study methods.

It should not be assumed that high impact journals, renowned authors, and prestigious institutions automatically publish high quality research. Application of results requires careful interpretation, most importantly, to consider when confronted with marginally increased ORs to examine whether the results have any real clinical significance.

How current dissemination of information regarding the safety of antidepressants in pregnancy, impacts both pregnant women and health care providers

Government health warnings, especially when they are regarding adverse effects of medications in pregnancy, are almost always widely cited by the media and subsequently make their way to the Internet, which is currently available in the majority of homes and workplaces around the world. Recently, (Nov 2014), a GOOGLE search using the keywords "antidepressants pregnancy" revealed 479,000 results, many describing how "dangerous/harmful" antidepressants are to take in pregnancy and warning women "not to take them if they are pregnant." Consequently, some of the information from these sites, as well as from other media outlets, can cause a great deal of stress and anxiety for both

pregnant women who require an antidepressant and their health care providers. Information from scientific sources can also be worrisome, if the results of studies are not clearly understood by the reader.

A study I conducted with colleagues, aimed to determine the impact of information, advice, and comments women received from health care providers, family, and media about use of antidepressants during pregnancy, and (2) to compare experiences regarding the psychosocial impact of women who continued and discontinued antidepressant therapy during pregnancy, because of non-evidence-based information they had received.

We interviewed almost 100 women who had taken an antidepressant at some point during pregnancy and compared responses of women who had either continued or discontinued the antidepressant they were taking. One of the main messages from this study, illustrated by the one-third of women who did not feel comfortable in confiding in their friends and family that they were pregnant and taking an antidepressant, is confirmation of the continued stigma surrounding mental illness. In addition, negative information from friends and family about the dangers of taking an antidepressant during pregnancy, were recalled in far more detail and for longer, than reassuring information and even women who decided to remain on their antidepressant, expressed continued guilt feelings about taking a medication during pregnancy.

Our conclusions were, non-evidence based information, especially negative, from friends and family and healthcare providers, highly impacted women when making decisions regarding pharmacotherapy for depression during pregnancy. [24]

In a recent survey I conducted with perinatal mental health specialists, the main findings, were that health care providers, most especially psychiatrists who are the prescribers of psychotropic drugs, perceive that there are many barriers surrounding pharmacologic treatment during pregnancy and breastfeeding. The foremost reasons included, general stigma surrounding mental health (45%), women's fear and anxiety regarding use of medications during pregnancy (70%), conflicting evidence-based information on the safety of psychotropic drugs in pregnancy (50%), biased media reporting towards harm of drugs (50%), difficulty with understanding complex disseminated scientific information (50%), fear of legal ramifications (25%),other health care providers misperception of the risk of drugs, misunderstanding surrounding mental health (55%), women seeing lawyer advertisements recruiting them to sue drug companies if they had a baby with a birth defect and took a psychiatric medication during pregnancy (35%), lack of professional guidelines for treating women with mental illness during pregnancy (20%) and all of the above (30%).[25]

Implications for clinical practice

The role of the pharmacist has been through many changes over the years and more than 30 years ago, a leader in the field projected the role of the pharmacist in the future in the following statement.

“Historically, the societal purpose of pharmacy has been to make drugs and medicines available. While this core function of pharmacy remains unchanged, the profession's purpose has evolved with new medical and pharmaceutical knowledge and technological advancements. The traditional role of dispensing medications has been expanded to include developing and managing drug distribution systems that provide access points to consumers and assure drug safety and compliance with legal and professional standards. These new responsibilities have required pharmacists to acquire expertise in the storage of data, distribution, and inventory control functions, and the management of data for drug histories, patient records, quality assurance programs, and drug information services. Pharmacists and support personnel who are qualified to perform the physical and scientific aspects of drug distribution and control must also be able to handle the interpersonal relationships required at the interface of the pharmacy system and the ultimate consumer. Today's pharmacists must provide services that transmit the knowledge and skills they have at their command to physicians, other pharmacists, and patients.”[26]

More recently, another individual commented that “while there is an understandable desire to move away from the traditional subservient role in relation to the medical profession, there remains a substantial challenge facing the pharmacy profession to attest its self-declared professional role of providing optimal health care for patients”.[27]

However, despite these recommendations, according to the results of a recent British survey of pharmacists and how they spent their time, the authors found that overall, they spent only 46% of their time on cognitive patient-centred tasks. Their conclusion was that community pharmacists continue to spend the majority of their time on technical dispensing and other activities, not related to pharmaceutical care.[28]

Currently, since the advent of the computerized era and the enormous amount of knowledge that is available, The pharmacist, as a front-line health care provider, plays a pivotal role, as much of their practice, especially in the community, includes the dispensing, not only of medicines, but also of information. In addition, they also interact with other health care providers, most frequently the physician, but also with nurses and midwives, in the synthesis and transfer of information and knowledge. This may be a relatively simple task with the general population, however, with pregnant women, the availability of evidence-based information regarding the safety/risk of medication use in pregnancy, is

often scarce or sometimes non-existent. In addition, studies that are accessible, are often complex, conflicting and rarely have a definitive conclusion that the pharmacist can transfer to the woman. This is especially the case in studies that have been published regarding the safety of antidepressants in pregnancy.

Around the world pharmacists are frequently the first health care professional that a woman encounters after finding out she is pregnant and more often than not, is already taking an antidepressant. In the first of two surveys I conducted with colleagues, in three countries, (Canada, The Netherlands and Iceland), we found that few community pharmacists provided evidence-based information regarding the safety of drugs in pregnancy, especially antidepressants. Only 14% consulted the current medical literature, while 60% referred to the product monograph. In all three countries more than 90% of pharmacists referred the woman directly to her physician, without providing any information.[29] In the second survey using the same questionnaire conducted in Argentina, the results proved to be strikingly similar.[30]

As documented in the results of these surveys, where the participating pharmacists were given case scenarios describing the use of an antidepressant during pregnancy, it was clear they are not comfortable giving advice on this subject. However, it is simply not sufficient to advise the woman to "go ask your physician" as was reported by the vast majority of the participants. It is also apparent, that there does not appear to be a direct line of communication among pharmacists and physicians, which results in conflicting information, often because of the use of different resources of information.[31]

Although this thesis and the findings were not about pharmacy practice *per se* , it would seem appropriate, that all pharmacy schools adopt a compulsory course in their curriculum, entitled "Critical evaluation of the scientific literature ". Modern pharmacists are expected to do much more than fill prescriptions, and those who are armed with a thorough understanding of the literature, will feel more empowered to disseminate evidence-based information. In addition, communication between other healthcare providers needs improvement, as the pharmacist, as a dispenser of information is an integral part of the healthcare team, in this instance providing information about antidepressant use in pregnancy.

Future research

Currently, as many government funding bodies are making it a requirement to include a KT component in a grant proposal, it would important to evaluate if and how the investigators have undertaken this task. In addition, it would be useful to examine the health professional

teaching programs in universities, including pharmacy, to determine if this model has been incorporated in the curriculum, in both a didactic and experiential level. It appears that all healthcare providers, researchers and government bodies, as well as the patients who require the information, need to be involved in the KT process. This will be an important undertaking for all stakeholders who are involved, but it is one that has to be implemented. This will bridge the gaps between the knowledge creators through to the patients, in this case, women who require information regarding the safety of antidepressants in pregnancy.

Conclusions

It is unlikely that in the near future, pregnant women will be included in randomized controlled trials, so studying the safety/risk of antidepressants in pregnancy is observational research, All of the methods used have some deficiencies in study design and analysis and thus reinforcing the need for improved rigor. However, this does not mean that the information provided from the results of these studies is not valuable, as long as the methodology and analysis are critically evaluated and understood by the reader.

It is clear from this research, that KT has become an important component in the health care system. Consequently, it is critical that the current gaps between the creation of knowledge and ultimately to translating and transferring information to the patient are closed. This includes improving the methodology of the studies and unambiguous, dissemination of the results, so clinicians should be capable of evaluating whether the results have clinical significance or not. Pharmacists can and should play an important role in this process, by providing women who is taking an antidepressant in pregnancy with comprehensive, and understandable, evidence-based information. Armed with this knowledge, women will be empowered to make a rational evidence-based decision regarding whether or not she should take an antidepressant during pregnancy.

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SUMMARY

Since the thalidomide tragedy of the 1960's, there exists the general view that every drug has teratogenic potential, and that women should refrain from taking any medications during pregnancy if at all possible. As a result, health care professionals commonly advise pregnant women to avoid pharmacotherapy for fear of causing fetal malformations. However, recent epidemiologic studies have shown that many drugs are safe and viable options during pregnancy, including antidepressants. It is not always feasible that antidepressant drugs can be avoided during this period in a woman's life for several reasons. First, up to 25% of women of childbearing age suffer from depression. Secondly, up to half of all pregnancies are unplanned and because most women are taking an antidepressant prior to becoming pregnant, the fetus has already been exposed before the woman knows that she is pregnant. In addition, depending on the severity of the depression, some women do require pharmacological treatment and discontinuing the drug may put both themselves and their unborn child in jeopardy by committing suicide, which is very tragic case scenario.

An important question then arises as to how knowledge derived from studies is effectively disseminated to the stakeholders who need this information to be able to use and apply in various situations. A relatively new field in science has been emerging, that addresses the issue of ensuring that information generated from research, reaches the right people in the right format. This has been coined knowledge transfer and exchange or knowledge translation (KT). Although KT is now accepted practice among many public health leaders internationally, its potential to advance the quality of health of women during the perinatal period has not been fully examined.

The objectives of this thesis are: (1) to determine how knowledge is created regarding the safety/risk of antidepressant use in pregnancy, (2) to describe different research models and statistical analysis that have been used, so as to critically evaluate the results, and (3) to identify how the information currently is disseminated and how the gaps in KT can be filled.

In Chapter 1, knowledge Transfer and Translation (KT) is described and how is it important regarding dissemination of information about the safety of medication use in pregnancy. This introductory chapter gives an overview of knowledge transfer and translation and how it relates to providing women and their healthcare providers with evidence-based information, regarding the safety/risk of drugs during pregnancy.

Chapter 2: describes how research is conducted when examining the safety of antidepressant use in pregnancy. Included is a description of the types of studies that are conducted, the type of data that is used and what statistical analyses have been utilized. Included are four examples of studies using different methodologies: 2.1 the first study is a meta-analysis that was conducted using published data, evaluating rates of spontaneous

abortions following exposure to antidepressants in the first trimester of pregnancy. 2.2 The second study is a collaborative prospective comparative cohort, using data from eight international Teratogen Information Services(TIS) to specifically examine the incidence of heart defects in infants exposed to paroxetine during pregnancy. 2.3 The third study is a prospective comparative cohort, examining fetal growth and preterm birth, using data from Motherisk's prospectively collected pregnancy outcomes of infants whose mothers were exposed to antidepressants during pregnancy. 2.4 The fourth study is also comprised of data from the previously mentioned Motherisk database; in this case outcomes were examined of women who took multiple antidepressants during pregnancy.

In Chapter 3, critical evaluation of studies regarding the safety of antidepressant use in pregnancy which describes how to understand the results of published studies, using various examples, by carefully examining the authors' objectives and conclusions. It also includes a description of basic statistics, such as what does an odds ratio really mean, so as to be able to understand the difference between statistical significance and clinical relevance of the results. This chapter included four studies; 3.1 The first study involves a critical evaluation of abstracts of studies that had been published regarding the safety of antidepressants use in pregnancy, specifically addressing the quality and content of the abstracts. 3.2 The second study focuses on publishing statistically significant results with questionable clinical importance, using antidepressant use in pregnancy as an example. 3.3 The third study focuses on the importance of critical evaluation of the literature regarding safety of antidepressant use in pregnancy, including how to understand the difference between statistical significance and clinical relevance of the results. 3.4 The fourth study discusses the question of do findings differ across research design? The case of antidepressant use in pregnancy and malformations.

Chapter 4 describes how current dissemination of information regarding the safety of antidepressants in pregnancy, impacts both health care providers and pregnant women. This includes how information received and from whom, affects both women and their health care providers in their decision-making regarding taking an antidepressant in pregnancy. The influence of friends, family and the media on risk perception and determinants of decision-making is discussed. This chapter includes four studies that focus on how information has been disseminated and the impact on both health care providers and pregnant women. 4.1 The first study discusses the impact of a public health advisory regarding SSRIs and other antidepressant use during pregnancy regarding potential neonatal adverse effects, with subsequent reports in the news media. 4.2 The second study focuses on the influence of the media on women taking antidepressants during pregnancy and how this information affects their decision-making regarding taking an antidepressant during pregnancy. 4.3 The third

study examines the negative impact of non-evidence-based information received by women taking antidepressants during pregnancy from health care providers and others.

4.4 The fourth study examines barriers to the pharmacological treatment of women with psychiatric disorders during pregnancy and breastfeeding.

Chapter 5 describes the pivotal role of the pharmacist in KT. In this chapter, the enhanced role of the pharmacist in disseminating information regarding the use of antidepressants in pregnancy is discussed. This includes becoming more comfortable with dispensing not only drugs, but also information, as well as improving their communication with physicians. This chapter includes three studies regarding pharmacists and dissemination of information. 5.1 The first study is a survey of community pharmacists in three countries, examining their use of evidence-based information regarding the safety of medications used in pregnancy. 5.2 The second study is a follow up of the previous survey, using the same questionnaire in a different country 5.3 The third publication is an examination of the role of the pharmacist in medication management during pregnancy, focusing on how pharmacists can optimize their position in the health care team, when disseminating teratology information.

In conclusion;

It is unlikely that in the near future, pregnant women will be included in randomized controlled trials, so studying the safety/risk of antidepressants in pregnancy is observational research. All of the methods used have some deficiencies in study design and analysis, thus reinforcing the need for improved rigor.. However, this does not mean that the information provided from the results of these studies is not valuable, as long as the methodology and analysis are critically evaluated and understood by the reader.

It is apparent from this research, that (KT) has become an important component in the health care system. Consequently, it is critical that the current gaps between the creation of knowledge and ultimately to translating and transferring information to the patient are closed. This includes improving the methodology of the studies and unambiguous, dissemination of the results, so clinicians are capable of evaluating whether the results have clinical significance or not.

Currently, as many government funding bodies are making it a requirement to include a KT component in a research grant proposal, it is important to evaluate if and how the investigators have undertaken this task. In addition, it is important to examine the health professional teaching programs in universities, to determine if this model has been incorporated in the curriculum, in both a didactic and experiential level. It appears that all

healthcare providers, researchers and government bodies, as well as the patients who require the information, need to be involved in the KT process. This will be an important undertaking for all stakeholders who are involved, but it is one that requires implementation. This will bridge the gaps between the knowledge creators through to the patients, in this case, women who require information regarding the safety of antidepressant use in pregnancy.

SAMENVATTING

Sinds de thalidomide-tragedie in de jaren 60, heerst het algemene beeld dat ieder geneesmiddel potentieel teratogeneen is en dat vrouwen waar mogelijk gebruik van geneesmiddelen moeten vermijden tijdens de zwangerschap. Dit heeft als gevolg dat zorgverleners zwangere vrouwen vaak adviseren farmacotherapie te vermijden, uit angst voor afwijkingen bij de foetus. Recent epidemiologisch onderzoek heeft echter aangetoond dat vele geneesmiddelen, zoals antidepressiva, veilig te gebruiken zijn tijdens de zwangerschap. Het is door verschillende reden niet altijd mogelijk om antidepressiva te vermijden rondom een zwangerschap. Ten eerste lijden tot 25% van de vrouwen in de vruchtbare leeftijd aan een depressie. Ten tweede, tot de helft van de zwangerschappen is ongepland en omdat de meeste vrouwen die antidepressiva gebruiken dat al deden voor de zwangerschap, is de foetus al blootgesteld voordat de vrouw weet dat ze zwanger is. Daarnaast is behandeling met geneesmiddelen bij sommige vrouwen noodzakelijk, afhankelijk van de ernst van de depressie en zou staken van de behandeling tot suïcide-gevaar kunnen leiden, met mogelijk ernstige gevolgen voor haarzelf en haar ongeboren kind.

Een belangrijke vraag is hoe kennis vanuit wetenschappelijk onderzoek vertaald en verspreid wordt naar belanghebbenden die deze informatie nodig hebben in diverse situaties. Er is een relatief nieuw interessegebied in opkomst in de wetenschap, gericht op het overbrengen van informatie uit wetenschappelijk onderzoek naar de juiste personen op de juiste manier. De Engelstalige term die hiervoor wordt gebruikt is ‘Knowledge transfer and exhange’ of ‘Knowledge Translation (KT)’. Dit is te vertalen met kennisoverdracht en –uitwisseling. KT wordt wereldwijd gezien als de standaard manier van werken in de volksgezondheid. Er is echter nog maar weinig onderzoek gedaan naar het potentieel van KT om de gezondheidskwaliteit van vrouwen in de perinatale periode te verbeteren.

De doelstellingen van dit proefschrift waren: (1) om te bepalen hoe kennis over de veilgheid / risico’s van het gebruik van antidepressiva tijdens de zwangerschap wordt gecreëerd (2) verschillende onderzoeksmodellen en statistische analyse die gebruikt worden te beschrijven, om de resultaten kritisch te kunnen evalueren en (3) identificeren hoe de informatie momenteel wordt verspreid en hoe de lacunes in KT kunnen worden ingevuld.

In Hoofdstuk 1, wordt Knowledge Transfer (KT) beschreven met betrekking tot het verspreiden van informatie over de veiligheid van medicijngebruik tijdens de zwangerschap. Dit inleidende hoofdstuk geeft een overzicht van kennisoverdracht en hoe het zich verhoudt tot het verstrekken evidence-based informatie aan vrouwen en zorgverleners met betrekking tot de veiligheid en de risico’s van geneesmiddelengebruik tijdens de zwangerschap.

Hoofdstuk 2 beschrijft hoe onderzoek wordt uitgevoerd naar de veiligheid van het gebruik van antidepressiva tijdens de zwangerschap. De soorten onderzoeken die zijn uitgevoerd worden beschreven, het type gegevens dat wordt gebruikt en welke statistische analyses worden gebruikt. Vier voorbeelden van onderzoek met verschillende methoden worden nader beschreven: in Hoofdstuk 2.1 wordt een meta-analyse beschreven die werd uitgevoerd met behulp van gepubliceerde gegevens. Hierin worden de percentages spontane abortus na blootstelling aan antidepressiva in het eerste trimester van de zwangerschap geëvalueerd. Het tweede onderzoek (2.2) betreft een prospectief vergelijkend cohort door een internationaal samenwerkingsverband van 8 teratologie informatie services (TIS) om specifiek de incidentie van hartafwijkingen bij baby's die waren blootgesteld aan paroxetine tijdens de zwangerschap vast te stellen. De derde studie (2.3) is een prospectief vergelijkend cohort-onderzoek gericht op foetale groei en vroeggeboorte, met behulp van gegevens uit Motherisk over zwangerschapsuitkomsten van baby's waarvan de moeders werden blootgesteld aan antidepressiva tijdens de zwangerschap. In de vierde studie (2.4) werden ook gegevens uit de eerder genoemde Motherisk databank gebruikt. In dit geval werden uitkomsten onderzocht van vrouwen die meerdere antidepressiva tijdens de zwangerschap gebruikten.

Hoofdstuk 3 bevat een kritische evaluatie van studies met betrekking tot de veiligheid van het gebruik van antidepressiva tijdens de zwangerschap waarin aan de hand van voorbeelden wordt beschreven hoe resultaten van gepubliceerde studies te interpreteren, door doelstellingen en conclusies van de auteurs zorgvuldig onderzoek. Het bevat ook een beschrijving van de basisstatistiek, de interpretatie van een odds ratio, oen het onderscheid tussen statistische significantie en klinische relevantie. Dit hoofdstuk bevat vier delen; Het eerste onderzoek (3.1) betreft een kritische evaluatie van de samenvattingen van studies die waren gepubliceerd over de veiligheid van het gebruik van antidepressiva tijdens de zwangerschap, specifiek gericht op de kwaliteit en inhoud van de samenvattingen. Het tweede onderzoek (3.2) richt zich op het publiceren van statistisch significante resultaten met twijfelachtige klinische betekenis, waarbij het gebruik van antidepressiva tijdens de zwangerschap als een voorbeeld is gebruikt. De derde studie (3.3) richt zich op het belang van een kritische evaluatie van de literatuur met betrekking tot de veiligheid van het gebruik van antidepressiva tijdens de zwangerschap, met inbegrip van hoe het verschil tussen statistische significantie en klinische relevantie te begrijpen. De vierde studie (3.4) gaat over de verschillen in bevindingen bij verschillende onderzoeksopzetten.

Hoofdstuk 4 beschrijft hoe de huidige verspreiding van informatie over de veiligheid van antidepressiva tijdens de zwangerschap, gevolgen heeft voor zowel zorgverleners als zwangere vrouwen. Dit geldt ook voor de wijze waarop informatie ontvangen wordt en van

wie, en hoe dit vrouwen en hun zorgverleners beïnvloedt in hun besluitvorming over het nemen van een antidepressivum tijdens de zwangerschap. De invloed van vrienden, familie en de media over risicoperceptie en mogelijke determinanten van de besluitvorming wordt besproken. Dit hoofdstuk bestaat uit vier studies die zich richten op hoe de informatie wordt verspreid en wat de impact is op zowel zorgverleners als zwangere vrouwen. De eerste studie (4.1) bespreekt de impact van een gezondheidsadvies over mogelijke neonatale bijwerkingen met betrekking tot SSRI's en andere antidepressiva tijdens de zwangerschap, gevolgd door de berichtgeving hierover in de media. Het tweede onderzoek (4.2) richt zich op de invloed van de media op vrouwen die antidepressiva tijdens de zwangerschap gebruiken en hoe deze informatie van invloed is op de besluitvorming met betrekking tot het gebruik van medicatie tijdens de zwangerschap. De derde studie (4.3) onderzoekt de negatieve impact van niet-evidence-based informatie die vrouwen van zorgverleners en anderen ontvangen over het gebruik van antidepressiva tijdens de zwangerschap. De vierde studie (4.4) onderzoekt de belemmeringen voor de farmacologische behandeling van vrouwen met psychiatrische aandoeningen tijdens de zwangerschap en tijdens het geven van borstvoeding.

Hoofdstuk 5 beschrijft de centrale rol van de apotheker in KT. In dit hoofdstuk wordt de veranderende rol van de apotheker bij het geven van informatie over het gebruik van antidepressiva tijdens de zwangerschap besproken. Dit omvat het afleveren van de geneesmiddelen, maar ook relevante informatie aan patiënten, en het verbeteren van de communicatie met artsen. Dit hoofdstuk bevat drie studies over dit onderwerp. Het eerste onderzoek (5.1) is een enquête onder apothekers in drie landen, over het gebruik van evidence-based informatie met betrekking tot de veiligheid van de medicijnen die worden gebruikt tijdens de zwangerschap. De tweede studie (5.2) is een vervolg op de vorige enquête, met behulp van dezelfde vragenlijst in een ander land. De derde studie betreft een onderzoek naar de rol van de apotheker bij farmaceutische zorg tijdens de zwangerschap, met de nadruk op hoe apothekers hun positie kunnen optimaliseren bij het verspreiden van teratologie informatie.

Tot slot;

Het is onwaarschijnlijk dat in de nabije toekomst zwangere vrouwen zullen worden geïncludeerd in gerandomiseerde gecontroleerde studies. Het bestuderen van de veiligheid en risico’s van het gebruik van antidepressiva tijdens de zwangerschap zal dus met observationeel onderzoek moeten gebeuren. Alle beschikbare methoden hebben een aantal tekortkomingen in onderzoeksopzet en analyse, waardoor er behoefte is aan methodologie-

ontwikkeling. Echter, dit betekent niet dat de resultaten en conclusies van de huidige studies niet waardevol is, mits de methodologie en analyse kritisch worden geëvalueerd en begrepen door de lezer.

Uit het hier gepresenteerde onderzoek blijkt dat KT is uitgegroeid tot een belangrijk onderdeel van de gezondheidszorg. Daarom is het essentieel dat de huidige kloof tussen kenniscreatie en het uiteindelijk vertalen en overdragen van informatie aan de patiënt wordt verkleind. Dit omvat het verbeteren van de methodologie van de studies en ondubbelzinnige verspreiding van de resultaten, zodat clinici in staat zijn om na te gaan of de resultaten klinische betekenis hebben of niet.

Tegenwoordig is bij door overheden gefinancierd onderzoek, een KT component in een onderzoeksvoorstel meestal verplicht. Het is belangrijk om te evalueren of en hoe onderzoekers dit hebben geëffectueerd. Daarnaast is het belangrijk om gezondheids-onderwijsprogramma's op universiteiten te onderzoeken, om te bepalen of dit model is opgenomen in het curriculum, zowel op didactisch als ervaringsniveau. Het blijkt dat alle zorgverleners, onderzoekers en overheden, evenals patiënten die de informatie nodig hebben, moeten worden betrokken bij het proces. Dit zal een veeleisende taak zijn voor alle belanghebbenden, maar het is er een die implementatie vereist. Hierdoor wordt de ruimte overbrugt tussen degenen die de kennis creëren en de patiënten: de vrouwen die informatie over de veiligheid van antidepressiva bij zwangerschap nodig hebben.

ACKNOWLEDGEMENTS

It is difficult to know where to begin, as there are so many individuals who assisted and supported me on this journey.

My colleagues

Dr Toine Egberts and **Dr Rob Heerdink:** my promoters, who had faith in an old lady, who was not a pharmacist or from The Netherlands and definitely was not their typical PhD student! They have supported and encouraged me in every way and I would like to thank them both from the bottom of my heart.

Dr Gideon Koren: the director of The Motherisk Program, who gave me an opportunity 25 years ago and encouraged me to achieve goals of which I often did not feel capable. When I started at Motherisk, in 1990, I had been practicing as a psychiatric nurse and had no background in the fields of teratology, pharmacology, epidemiology, conducting studies and publishing results in peer reviewed journals. He is a skillful educator and was great mentor to me, always supporting me in every way he could. Even though I have since retired from Motherisk, we will be friends for the rest of our lives.

Dr Saskia DeWildt: from Rotterdam, who spent time at Motherisk as a fellow, where we became more than colleagues. She first suggested to me that it could be possible that I could enroll in a PhD in the Netherlands, and pushed me to apply. I would never have made the first step if it had not been for her faith in me that I could pursue and achieve a PhD

Students from Utrecht University, Faculty of Pharmacy:

Michiel Hemels, Suzanne Gerichhausen, Anne –Marie Schachtschneider (deceased) and Eva Mulder. They all spent time at Motherisk as 4th pharmacy students and co-authored published papers under my supervision in the peer reviewed literature. This was a great experience for me and started my involvement with Rob Heerdink, who supervised the students who studied with me .

The Motherisk team at The Hospital for Sick Children, Toronto, Ontario, Canada. Motherisk Counselors past and present:

Michael Gallo, Samar Shuhaiber, Yvette Navoiz, Michael Chan, Pina Bozzo, Aida Erebara, Angela Chua, Kamelia Mirdamadi, Caroline Maltepe and Eunji Kim

Each one of them has always been supportive of me, in whatever my path in life has taken, even though they were not happy when I retired for the second time.

Graduate students:

Heather Bennet, MSc,PhD, Lori Bonari,MSc,MD, Michiel Hemels, MSc, Moumita Sarkar, MSc, PhD, Brian Chan MSc, Lisa O'Brien, MSC, Sami Gill, MSc, PhD, Kate McKenna, MSc, Samar Shuhaiber MSC, Anna Sivojelezova, MSc, Sanjog Kalra, MSc,MD, Rebecca Hancock, MSc, PhD, Patricia Nguyen, MSc, Neda Ebrahimi MSc, PhD(cand)

I was privileged to be involved in a supervisory capacity with these students as they studied for their post-graduate degrees and was proud to be a co-author with each one of them, when they published their thesis findings in the peer reviewed literature.

I truly believe that I learned more from them, than they from me and all inspired me to take this step, even though they are probably not aware of it..

My collaborators and co-authors

There are too many to list individually, as over the years I have collaborated with many colleagues, from all over the world, in many different projects. However, they are all duly noted in the list of my published papers and it was great to work with each and everyone of them. I would not have been able to accomplish this task if not for all my publications, which was definitely a group effort.

My colleagues in Perinatal Psychiatry

Founding and coordinating the reproductive psychiatry group has been one of the highlights of my career and I will continue to lead this group for as long as they want me to. Pregnant and breastfeeding women with psychiatric disorders deserve to be treated when necessary and I hope that I have contributed in some useful way for these women, with compassion and my research. Thanks to everyone in the group who has supported me, with a special mention of my friend **Vivien Burt, MD,PhD** who has had such unwavering faith in me.

My family:

Thomas Einarson PhD: my husband of 25 years who has supported me throughout this whole process, with encouragement every step of the way. He was the one who encouraged me to change careers mid-life when heard about the opening for a teratology information specialist at The Motherisk Program, when I had no experience in this field. He told me that you can learn, which I did, subsequently realizing that being researcher was what I really wanted to achieve. To help me reach this goal, he taught me, among many things, about study design, epidemiology, statistics and critical evaluation of the literature, in such a way, that even I could understand, who had no background in any of these subjects... He is a great teacher and no-one can teach a difficult subject like statistics, as well as he can. I love you.

David Baines: my son, **Rachael Scutt:** my daughter, **Kristjana Einarson**: my step-daughter, **Michael Einarson**: my step-son and **Sharon Kempel**: my foster daughter: my children

I hope that you are as proud of me, as I am of you. I love you all.

Jazzlyn, Riley, Ryan, Evan, Joshua and **Utah.** My grandchildren..

I hope you will always be proud of what your grandma/"ninna" has accomplished in her life. I love you all

Frances Pairaudeau: my " baby" sister who knew more than anyone how much I wanted to do this and never stopped encouraging me to go forward.. I love you..

List of Publications (relevant to this thesis)

Selected publications in the past 9 years focused primarily on psychiatry and psychotropic drugs in pregnancy, including health behaviours:

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The CNS clinical pharmacoepidemiology research group

Background

Central Nervous System Clinical Pharmacoepidemiology is one of the research themes of the division of Pharmacoepidemiology & Clinical Pharmacology of the Utrecht Institute for Pharmaceutical Sciences (UIPS). The division of Pharmacoepidemiology & Clinical Pharmacology consists of a multidisciplinary team of young and internationally oriented researchers. The research program is directed at the epidemiological, therapeutic and policy aspects of drug use and their effects. The mission of the research program is to contribute to the knowledge of and decision-making in the effectiveness, safety and economics of drug usage. In bridging the gap between the science of pharmacoepidemiology and the 'real world' of patients' drug usage and public health, the program covers a variety of methods and approaches from (molecular) epidemiology, pharmacovigilance, practice research and policy analysis. The myriad of research strategies provides an excellent environment for thoughtful learning and innovation in system therapeutics.

The Central Nervous System Clinical Pharmacoepidemiology research group focuses on the use and effects of psychotropic drugs in psychiatry and neurology, both in ambulatory care and in clinical settings. Principle investigators of this research group are Dr Eibert R Heerdink and Prof dr Toine CG Egberts. There is close collaboration with psychiatric hospitals including Altrecht and GGZ Centraal and with the University Medical Centre Utrecht.
Contact: www.uu.nl/science/pharmacoepidemiology

Theses from the CNS clinical pharmacoepidemiology research group:

Dr Els van den Ban (2014)

ADHD medication use and long-term consequences. (Co)promotores: Prof dr ACG Egberts, Prof dr H Swaab, Dr ER Heerdink.

Dr Jochem Gregoor (2013)

Genetic Determinants of Antipsychotic Drug Response. (Co)promotores: Prof dr ACG Egberts, Dr J van de Weide, Dr ER Heerdink.

Dr Arne Risselada (2012)

Genetic determinants for metabolic abnormalities. (Co)promotores: Prof dr ACG Egberts, Dr H Mulder, Dr ER Heerdink.

Dr Bart Kleijer (2011)

Balancing the benefits and risks of antipsychotics. (Co)promotores: Prof dr ACG Egberts, Prof dr MW Ribbe, Dr ER Heerdink, Dr R van Marum.

Dr Wilma Knol (2011)

Antipsychotic induced parkinsonism in the elderly: assessment, causes and consequences. (Co)promotores: Prof dr AFAM Schobben, Prof dr ACG Egberts, Dr PAF Jansen, Dr R van Marum.

Dr Inge van Geijlswijk (2011)

Melatonin in sleepless children. Everything has a rhythm? (Co)promotores: Prof dr ACG Egberts, Prof dr H Vaarkamp, Dr M Smits.

Dr Maurits Arbouw (2010)

Assessment of pharmacotherapy in Parkinson's disease. (Co)promotores: Prof dr ACG Egberts, Prof dr HJ Guchelaar, Prof dr C Neef, Dr KLL Movig.

Dr Laurette Goedhard (2010)

Pharmacotherapy and aggressive behaviour in psychiatric patients. (Co)promotores: Prof dr ACG Egberts, Prof dr H Nijman, Dr ER Heerdink, Dr JJ Stolker.

Dr Jeroen Derijks (2009)

Effects of antidepressants on glucose homeostasis. Effects and mechanisms. (Co)promotores: Prof dr ACG Egberts, Dr ER Heerdink, Dr GHP de Koning, Dr R Janknegt.

Dr Helga Gardarsdottir (2009)

Drug treatment episodes in pharmacoepidemiology: antidepressant use as a model. (Co)promotores: Prof dr ACG Egberts, Dr ER Heerdink.

Dr Kim Gombert - Handoko (2009)

Treatment failure in epilepsy: exploring causes of ineffectiveness and adverse effects. (Co)promotores: Prof dr ACG Egberts, Prof dr YA Hekster, Dr J Zwart-van Rijkom, Dr W Hermens.

Dr Tessa Ververs (2009)

Antidepressants during pregnancy, risks for mother and child. (Co)promotores: Prof dr GH Visser, Prof dr AFAM Schobben, Dr E Mulder.

Dr Emmeke Wammes – van der Heijden (2009)

Migraine and ischemia. (Co)promotores: Prof dr ACG Egberts, Dr C Tijssen.

Dr Katja van Geffen (2008)

Initiation, execution and discontinuation of antidepressant therapy: considerations and decisions of patients. (Co)promotores: Prof dr ACG Egberts, Dr E Heerdink, Dr R van Hulten.

Dr Mirjam Knol (2008, summa cum laude)

Depression and diabetes. Methodological issues in etiologic research. (Co)promotores: Prof dr DE Grobbee, Prof dr ACG Egberts, Dr M Geerlings, Dr ER Heerdink.

Dr Ingeborg Wilting (2008)

Patterns and clinical outcomes of lithium treatment. (Co)promotores: Prof dr ACG Egberts, Prof dr WA Nolen, Dr ER Heerdink.

Dr Hans Mulder (2007)

CYP2D6 and 5HT2c polymorphisms in psychiatric pharmacotherapy. (Co)promotores: Prof dr ACG Egberts, Dr FFW Wilmink.

Dr Gerard Hugenholtz (2005)

Antipsychotics in daily clinical practice: patterns, choices and consequences. (Co)promotores: Prof dr ACG Egberts, Prof dr WA Nolen, Dr ER Heerdink.

Dr Hamid Rahimtoola (2003)

Transitions in migraine treatment. (Co)promotores: Prof dr ACG Egberts, Prof dr HGM Leufkens, Dr CC Tijssen.

Dr Igor Schillevoort (2002)

Drug-induced extrapyramidal syndromes. (Co)promotores: Prof dr HGM Leufkens, Prof dr RAC Roos, Dr RMC Herings.

Dr David van de Vijver (2002)

Quality of the pharmacological treatment of patients with Parkinson's disease. (Co)promotores: Prof dr AJ Porsius, Prof dr RAC Roos, Prof dr A de Boer.

Dr Joostjan Stolker (2002)

Struggles in prescribing: determinants of psychotropic drug use in multiple clinical settings. (Co)promotores: Prof dr WA Nolen, Prof dr HGM Leufkens, Dr ER Heerdink.

Dr Welmoed Meijer (2002)

The value of observational research on antidepressant use: a broadened perspective. (Co)promotores: Prof dr HGM Leufkens, Prof dr WA Nolen, Dr ER Heerdink.

Dr Kris Movig (2002)

Detection and elucidation of adverse neuropsychiatric adverse effects. (Co)promotores: Prof dr ACG Egberts, Prof dr HGM Leufkens.

Dr Rolf van Hulten (1998)

Blue boy – why not? (Co)promotores: Prof dr A Bakker, Prof dr HGM Leufkens, Dr KB Teeuw.

Dr Toine Egberts (1997)

Pharmacoepidemiologic approaches to the evaluation of antidepressant drugs. (Co)promotores: Prof dr A Bakker, Prof dr HGM Leufkens, Dr GHP de Koning.

Curriculum Vitae

Adrienne (Pairaudeau, Baines, Yoder) Einarson was born in London, England, UK. October 1st 1945. She graduated as a registered nurse in 1966, followed by midwifery training and in 1967 emigrated to Canada, where she continues to reside.

From 1967 -1990: held a number of nursing positions, and found her niche specializing in psychiatry.

In 1990 her career changed dramatically as she accepted a position at The Motherisk Program at The Hospital for Sick Children, Toronto, as a teratogen information counselor. She held this position until she was promoted to Assistant Director of the program in 1996, until her initial retirement in 2011. She continued to be a consultant for the program, until she retired from that position in 2014.

She has conducted many research projects on the safety of medications used in pregnancy, specializing in psychiatric drugs, as well as perception of risk and determinants of decision-making. She has published almost 200 papers in the peer reviewed literature and has given more than 100 international oral and poster presentations, both invited and from submitted abstracts at conferences.

She has held many academic appointments, as supervisor of students from various faculties of health education, including medicine, pharmacy, clinical pharmacology, midwifery, genetics and naturopathic medicine. She has also been a reviewer for numerous peer reviewed journals.

She is currently the founder and coordinator of the Reproductive Psychiatry listserve which is devoted to all aspects of perinatal mental health, with 350 members worldwide.

She is married to Thomas Einarson PhD and resides in Barrie, Ontario, Canada.

They have a blended family of four children; David(Usha), Rachael(Chris), Krisjtana(Dan) and Michael, as well as four grandsons, Ryan, Evan, Joshua and Utah.