Mental Health and Pregnancy: An Exploration of Issues Regarding the Use of Prescription Medications

A summary of findings from

A 3-part project conducted by Women and Health Protection (at the National Network on Environments and Women's Health) 2010

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Introduction

Drug use in pregnancy has a legacy in regulatory history globally, including in Canada. The two best-known examples are thalidomide,and DES (diethylstilboestrol). Thalidomide was approved for morning sickness in Canada in 1959 and removed from the market in 1962, when it was found to cause severe malformations in exposed babies, including limb reductions. DES (diethylstilbestrol) was prescribed to prevent miscarriage for close to three decades until it was banned for use in pregnancy in 1971 when it was found to cause cancer in women who had been exposed prenatally. The experience with thalidomide led to the introduction of modern drug regulation, with systematic evidence of effectiveness and safety needed before a medicine could be marketed. DES brought home the need for longer-term follow-up of drug safety because unexpected longer-term effects could occur, including cancer 20 years or more after exposure.[1]

Antidepressants are often used during pregnancy. Between 1998 and 2001 selective serotonin reuptake inhibitor (SSRI) antidepressant use in British Columbia, Canada, doubled from 2.3 per cent to 5.0 per cent among pregnant women.[2] However, their use constitutes unapproved "off-label" use and there is controversy regarding their benefits, harms, and appropriateness of prescribing, both within pregnancy and more broadly in treatment of non-pregnant adults. In 2004, the National Institute for Clinical Excellence (NICE) in the United Kingdom recommended that SSRIs not be used as the first line treatment for mild depression because of their limited effectiveness (NICE 2004), with other NICE advisors questioning even the clinical significance of improvements in more severe depression.[3] Recently, growing evidence questions the efficacy of SSRI medication for the majority of depression cases encountered in clinical practice, from mild to moderate and even severe major depression.[4] Both Kirsch et al.[5] and Fournier et al.[6] report improvements over placebo only for very severe major depression (which is distinguished in clinical studies from severe depression).

Research in British Columbia[7] and Quebec[8] found the rate of SSRI prescriptions to pregnant women doubled between 1998 and 2001 despite warnings issued by Health Canada and a growing body of research documenting harm to the fetus. These include, spontaneous abortion[9],[10], cardiac defects,[11] increase in cardiac malformations, [12] persistent pulmonary hypertension (PPHHN),[13] septal heart

defect,[14] and motor developmental delays at six months.[15] Finally, several studies have demonstrated poor neonatal adaptation including irritability, persistent crying, tremor, restlessness, feeding difficulties and sleep disturbance.[16] It is against this backdrop that we examined the present-day use of psychotropic medications in pregnancy. Specifically, this report is concerned with treatment of depression in pregnancy.

The present report represents the culmination of three phases of work by Women and Health Protection (WHP):

1. An examination of sources of popular information from the mainstream media for pregnant women regarding the treatment of mental health issues
2. A systematic review of the medical literature regarding evidence of benefit of SSRI anti-depressant use in pregnancy
3. An examination of sources consulted by physicians on the use of SSRI anti-depressants in pregnancy

Phase I: Pregnancy Information Sources for Women in Mainstream Media[17]

A review undertaken by Women and Health Protection in 2008-09 examined the main messages that pregnant women are receiving from popular Canadian media on depression and treatment options in pregnancy. Thirty-one English and French-language magazines and ten English and French-language websites, based on circulation rates and relevance, were selected and reviewed. In particular, the research sought to identify information relating to depression and treatment during pregnancy, and to assess any gaps in information or lack of coherence between public information and current medical literature.

The examination revealed a significant lack of substantive information on depression and other mental health problems and treatment options during pregnancy. Pharmacological treatments were most commonly recommended, while more limited and less frequent information was found on alternative options and therapies. The review found a lack of information on risks related to psychotropic drug use in pregnancy, and what risk information was provided was limited and generally not comprehensive. Additionally, the sources surveyed revealed a significant lack of reference to relevant Health Canada safety advisories regarding the risk of cardiac malformations associated with paroxetine exposure during pregnancy, and the risk of persistent pulmonary hypertension of the newborn.[18] Mainstream media sources constitute an important source of information for pregnant women, and this oversight to referencing important national health warnings represents a significant absence.

The findings from the review pointed to the need for greater clarity in public information on depression and other mental health problems. In particular, given concerns relating to the expanding definition of depression, the review identified pregnant women's need for clear information in order to distinguish normal hormonal changes, mood changes, and reactions to life events, from clinical depression. The

review also indicated that information on mental health, treatment options and risks was extremely varied across sources. This wide variation and lack of clarity suggest significant confusion for women seeking information about depression during pregnancy.

Phase II: Systematic Review: Is There Evidence of Benefit from SSRI Use in Pregnancy?

Concurrent with work on the review of media reports and websites for pregnant women, a systematic review of the literature on SSRI use in pregnancy was begun by a research team at the University of British Columbia Therapeutics Initiative.

Pregnant women and the professionals who care for them are often told that the risks of antidepressants in pregnancy need to be balanced against the risks of untreated depression. This presumes that antidepressants are an effective means of preventing this harm. This systematic review was carried out in order to examine the evidence of health benefits from SSRI antidepressants in pregnancy, in comparison with no treatment or non-drug treatments. The researchers in this study asked: Is there evidence of a net benefit to maternal health and quality of life, or to neonatal and infant health, from the use of SSRI antidepressants for the treatment of depression in pregnancy, as compared with placebo, non-drug treatments or no treatment?

A comprehensive literature search was carried out in computerized databases (Medline, EMBASE, and Web of Science, Cochrane database of systematic reviews and Central, CINAHL and PsychInfo), and researchers in the field were contacted. Clinical trials and observational studies were included if they had a comparison group of women with depression that was followed over the same period of time as women taking SSRIs.

The systematic review of the literature revealed no significant benefit to mother or infant in the use of SSRI antidepressants in pregnancy for treatment of depression when compared with placebo, non-drug treatments or no treatment.

No randomized controlled trial has compared SSRIs in pregnancy with non-drug treatments, no treatment or other anti-depressants. Eight observational studies have compared antidepressants to no treatment in women with depression. Three were population-based administrative database analyses, two in British Columbia.[19] The other five studies were smaller studies based on convenience samples, mainly clinic based, and mainly of poor methodological quality.[20] There is no evidence from any of these studies that SSRI use in pregnancy improves infant or maternal health. No study had shown that use of antidepressants in pregnancy prevents postpartum depression, and there is no evidence that effects such as pre-term birth that occur more often among women with depression are prevented if antidepressants are used. There was no evidence to support the idea that untreated depression in pregnancy leads to greater harm than SSRI exposure. In fact, infants generally did worse in the group treated with antidepressants than those with untreated depression, with higher rates of respiratory distress at birth, and more pre-term births.

All of the studies compared SSRIs to no treatment. There were no studies comparing antidepressant treatment with non-drug treatments such as psychotherapy, cognitive behavioural therapy. The review authors note how much of the literature on depression treatment in pregnancy presents a false dichotomy: antidepressant exposure or untreated depression. Much less attention is paid to the option of a third alternative, non-drug treatments, which, by contrast, show no documented harm to mother or infant.

Phase III: Information Sources Consulted by Physicians on SSRI Use in Pregnancy

The three components of this phase of the study (undertaken in the 2009-1010 fiscal year) consisted of a brief review of information sources for physicians, a survey of physicians, and a citation analysis of the literature on SSRI use in pregnancy.

1. REVIEW OF INFORMATION SOURCES FOR PHYSICIANS

In addition to examining the academic literature on SSRIs, we were interested in examining regulatory information (safety advisories and approved product information) and prescribing guides, as these are important resources that inform physicians' prescribing decisions. We were interested in the messages and information sources available both nationally and in the U.S.

Sources from 2004 to the present were examined. These included: product monographs for drugs in this class, regulatory updates (including warnings) from national bodies (Health Canada, the U.S. Food and Drug Administration), frequently consulted on-line information sources ("UpToDate.com", Motherisk), websites of pharmaceutical companies manufacturing SSRI antidepressants, and clinical guidelines from the websites of psychiatric and obstetrics/gynecology associations. The intent with this search was to determine what a practising physician would find on a quick search for information on this topic.

Health Canada Advisories: There were three Health Canada advisories issued in 2004, 2005 and 2006 relating specifically to fetal health risks following exposures of pregnant mothers to SSRIs and venlafaxine.

- August 9th, 2004, Health Canada Advisory: Health Canada advised the public of the potential for neonatal withdrawal syndrome with the use of SSRIs or venlafaxine in the third trimester of pregnancy. The SSRI products affected by this advisory were citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, as well as venlafaxine (SNRI). Following the advisory, Health Canada advised all SSRI and venlafaxine manufacturers to update their product monographs with the confirmed new safety information on the neonatal withdrawal syndrome.[21]
- October 6th, 2005, Health Canada Advisory: Health Canada issued an advisory indicating that paroxetine (specifically, the innovator product Paxil) use in the first trimester of pregnancy increases the risk of cardiac birth defects. Health Canada explicitly ensured that Paxil product monographs reflected this new safety information.[22]
- March 10th, 2006, Health Canada Advisory: Health Canada issued an advisory informing the public that SSRIs (citalopram , escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline)

and venlafaxine were linked to serious and potentially fatal lung disorders in newborns, specifically persistent pulmonary hypertension (PPHN).[23]

Product Monographs: When a drug is approved for marketing, it is accompanied by an approved 'product monograph' that summarizes the scientific evidence on the medicine's characteristics and effects, and sets out conditions for use. Product monographs are prepared by the manufacturer as part of the original drug submission file that is intended for regulatory body review. Health Canada reviews the information and often requires changes to the wording before approval. They include the drug's chemistry and pharmacology, clinical trial results, indications, contraindications, warnings, precautions, conditions of use, drug interactions, and the approved dose and administration schedule.[24] This information is also called the approved "labelling" of a medicine.

Health Canada can ask a manufacturer to revise the product monograph of drugs that have already been approved for marketing when important new evidence on safety and/or effectiveness becomes available, as per Canada's *Food and Drug Regulations*. Regulation C.08.006(f) obliges the sponsor to update their product monograph to reflect the most accurate and newest safety information available. In addition, the sponsor should initiate product monograph revisions upon the new findings that affect the safety and efficacy of the product and justify those revisions to Health Canada.[25]

We examined the wording of product monograph information on the use of SSRIs and venlafaxine during pregnancy for all SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and fluvoxamine) and one SNRI (venlafaxine) approved in Canada, all of which were mentioned in Health Canada safety advisories related to their use in pregnancy. None of these products are approved for use in pregnancy in Canada or in any other country. All of the product monographs include a precaution about use during pregnancy. The precaution information consists of a statement that the safety of these drugs for pregnant women has not been established.[26] In addition to the precautionary statement, paroxetine product monographs include additional warnings.

On August 9th, 2004, a Health Canada Advisory was issued regarding the potential for neonatal withdrawal syndrome with the use of SSRIs or venlafaxine in the third trimester of pregnancy. Following the advisory, Health Canada required all SSRI and venlafaxine manufacturers to update their product monographs with the confirmed new safety information on neonatal syndrome.

Upon further product monograph examinations, we found inconsistencies related to the implementation of the 2004 advisory in different product monograph versions of the same product. These different product monographs exist because the patents for most SSRIs have expired, which allows generic manufacturers to also produce the product. Several versions of the product are therefore available for sale in Canada. Specifically:

- Out of 22 versions of citalopram, 1 generic product (ratio-Citalopram) *does not* have neonatal withdrawal syndrome advisory reflected in its product monograph.

- Escitalopram, which is chemically nearly identical to citalopram (brand name Cipralex, also no generic versions on the market) *does* have neonatal withdrawal syndrome advisory incorporated in its product monograph.
- Out of 16 versions of a fluoxetine drug, 1 generic product (Rhoxal-fluoxetine) *does not* have neonatal withdrawal syndrome advisory reflected in its product monograph.
- Out of 14 versions of paroxetine, 1 generic product (Riva-paroxetine) *does not* have neonatal withdrawal syndrome advisory reflected in its product monograph.
- Out of 15 versions of sertraline, generic Riva-sertraline product has incomplete wording on neonatal withdrawal syndrome.
- Out of 12 fluvoxamine versions, 3 generic brands do not have neonatal withdrawal syndrome advisory reflected in their product monographs (they are Co-fluvoxamine, phl-fluvoxamine and Riva-fluvoxamine).
- All venlafaxine versions have neonatal withdrawal syndrome advisory reflected in their product monographs.

On October 6th, 2005, Health Canada issued an advisory indicating that paroxetine use (specifically, the innovator product Paxil) in the first trimester of pregnancy increases the risk of cardiac birth defects. Health Canada explicitly ensured that Paxil product monographs reflected this new safety information.

While no explicit information was located on the Health Canada website that would urge the generic brand manufacturers to update their product monographs with this new safety information, Health Canada did not state that it considers cardiac birth defect safety information preliminary. We would, thus, expect all paroxetine manufacturers to be required to incorporate this new safety information into their product monographs.

We found that out of 14 available paroxetine products, 3 generic versions do not have cardiac birth defects advisory from 2005 reflected in their product monographs. These generic products are Mylan-paroxetine, Paroxetine (by Pro Doc Limitee) and Riva-paroxetine.

A third Health Canada Advisory was issued on March 10th, 2006, informing the public that SSRIs (citalopram , escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline) and venlafaxine were were linked to serious and potentially fatal lung disorders in newborns, specifically persistent pulmonary hypertension (PPHN). While Health Canada still considers PPHN risk as preliminary information, a number of manufacturers of SSRIs have voluntarily updated their product monographs to reflect this new safety information.

We found that none of the citalopram, fluoxetine and venlafaxine manufacturers chose to update their product monographs with the new PPHN safety information.

Amongst manufacturers of the rest of the SSRIs, escitalopram (brand name Cipralex) included a PPHN advisory in their product monograph. Other SSRI manufacturers that also chose to incorporate the PPHN safety information in their product monographs include 10 paroxetine, 3 sertraline and 2 fluvoxamine manufacturers.

The main prescribing guide in Canada, the CPS (Compendium of Pharmaceuticals and Specialties) and its electronic version, the e-CPS, contain summarized prescribing information based on approved product monographs. Similar inconsistencies regarding neonatal withdrawal syndrome, cardiac birth defects and PPHN advisory inclusions into CPS product monographs are reflected in this briefer prescribing information. CPS (and its electronic version, e-CPS) is a prescribing guide that is produced for practical use by physicians and pharmacists by the Canadian Pharmacists' Association, and is updated annually. It is more accessible to physicians than product monographs, and likely to be consulted more often.

Website of the Public Health Agency of Canada (PHAC): Information about depression in pregnancy on the website of PHAC did not reflect the Health Canada advisories respecting neonatal syndrome, cardiac birth defects and PPHN. The same website also states that new antidepressants are safe to use in pregnancy, without stating which antidepressants they are referring to. In addition, there is no mention on the PHAC website that the use of SSRIs and venlafaxine during pregnancy is an unapproved, off-label use. With the help of the PHAC $298,200 federal grant, the Canadian national program "Beyond the baby blues" has been established to help develop pregnancy depression screening and research tools. The research will be conducted by Mosaic Counselling and Family Services in Kitchener. This project will investigate a number of social circumstances that may contribute to depression in pregnancy, such as teenage pregnancy, family violence, social isolation and poverty.

Motherisk: Motherisk is Canada's teratology information centre, and is a frequently consulted source of information about drugs in pregnancy. The Motherisk website's most recent safety guideline about antidepressant use in pregnancy is from 2005. Here, the authors mention Health Canada's Advisory from August 9th, 2004 on neonatal withdrawal syndrome. The guideline focuses on the fact that the most serious result of an untreated depression in pregnancy is the increased potential for post-partum depression, without providing further evidence to support the claim that SSRIs do in fact prevent post-partum depression. Similarly, the guideline does not explicitly state the benefits of antidepressant use during pregnancy for the developing fetus.

The other two Health Canada Advisories on potential cardiac birth defects from 2005 and PPHN from 2006 are not mentioned on the Motherisk portal. In addition, there is no information on the Motherisk website which would inform its readers that the use of SSRIs and venlafaxine during pregnancy is off-label. Alternative treatments such as psychotherapy (cognitive behavioural therapy and interpersonal therapy) are not mentioned as treatment options for mild to moderate depression for pregnant women.

"UpToDate" Clinicians Web Portal: UpToDate is a USA-based, point-of-care online clinical information tool for healthcare professionals, available on a subscription basis (individual or institution subscription). It does not accept commercial sponsorship and is commonly used by health professionals in Canada. It is estimated that approximately 80 per cent of Canadian teaching institutions as well as approximately 50 per cent of Canadian community institutions (such as hospitals) subscribe to the UpToDate clinical portal. In addition, there are approximately 40,000 subscriptions to UpToDate from individual Canadian physicians.[27] This is around three fifths of Canadian physicians, as in 2008 there were 65,440 practising physicians in Canada. [28]

In the "Fluoxetine – drug information" drug UpToDate review, UpToDate authors are consistent with the FDA and Health Canada warnings regarding the use of SSRIs during pregnancy (Pregnancy Implication section). Both adverse reactions (neonatal withdrawal syndrome and PPHN) were stated in the Pregnancy Implication section, as well as the unknown risks of fluoxetine in utero exposure in the later child development.

A search on the UpToDate website on pregnancy and depression revealed several guidelines, one of which is the "Management of depression in pregnant women", by Misri *et al*. The guideline recommends that for mild to moderate depression, pregnant women should consider psychotherapy as a first line of treatment because it proved effective in establishing a non-symptomatic state.

Canadian Psychiatric Association (CPA) Guidelines on Depression in Pregnancy: The Canadian Psychiatric Association's "Clinical practice guidelines for the treatment of depressive disorders" from 2001 is the only guideline publically available on the CPA website regarding depression disorders. Part VI of the guideline, "Special populations", discusses the implications and treatments of depression in pregnant women. This guideline has not been updated since 2001 and therefore does not reflect the safety information from Health Canada Advisories in 2004, 2005 and 2006 on neonatal withdrawal syndrome, cardiac birth defects and PPHN, respectively.[29] In addition, the guideline does not contain the information that use of SSRIs during pregnancy is off-label.

Without specifying the degree of depression, the guideline recommends fluoxetine as the first line of treatment, followed by sertraline, fluvoxamine, paroxetine and citalopram. As a third line of treatment, interpersonal therapy is listed, along with tricyclic antidepressants and electroconvulsive therapy.

These guidelines were developed jointly by the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Canadian Psychiatric Association. CANMAT has produced an updated version of the guidelines, published in 2009.[30] The guidelines do not mention any of the Health Canada advisories, but do mention the potential for paroxetine to have a higher risk of malformations and state that there are "subtle adverse effects" from use of antidepressants in late pregnancy. They recommend fluoxetine and other SSRIs for first-line use, and do not include any recommendations on use of non-drug treatments. No information was provided on conflicts of interest in the 2001 CANMAT/CPA guideline; in the 2009 CANMAT guideline, the five authors jointly declared 40 financial links with individual drug companies. These include being members of speakers bureaus, advisory boards, and research funding.

Health Professional Communication: One of the regulatory tools that Health Canada has as its disposal is to require a manufacturer to send a letter to all health professionals about a new safety concern. This is often produced as a joint Health Canada/company letter, but Health Canada can also send such a letter out directly. These are called *Dear Health Care Professional Letters,* [31] These used to be called 'Dear Doctor' letters and have expanded to encompass all health professions. Health Professionals encompass a wide spectrum of occupations, including physicians, dentists, naturopaths, pharmacists, nurses, midwives, hospitals, registered dieticians, and other medical and support personnel involved in the delivery of healthcare.[32]

We searched for 'Dear Health Care Professional' letters related to three Health Canada Advisories: neonatal withdrawal syndrome, cardiac birth defects and PPHN. We performed this search for six innovator SSRIs [Celexa (citalopram), Cipralex (escitalopram), Prozac (fluoxetine), Paxil (paroxetine), Zoloft (sertraline) and Luvox (fluvoxamine)] and for Effexor (venlafaxine) on both Health Canada and manufacturers' websites.

Health Canada and GlaxoSmithKline sent out a joint Dear Health Care Professional Letter on the Paxil cardiac birth defects advisory, dated December 16th, 2005.[33] This is posted on both the Health Canada and the GSK websites. We found no other 'Dear Health Care Professional' letters related to the other Health Canada safety advisories on neonatal withdrawal syndrome or PPHN.

2. INTERVIEWS WITH KEY OPINION LEADERS

In light of findings from the systematic review of SSRI use in pregnancy, the federal government warnings, and lack of absence of benefit for the mother and infant, questions remain as to why there is continued and increased prescribing of SSRIs in pregnancy. A survey of practising primary care physicians was proposed as one avenue for shedding light on this discordance.

Forty-two key experts or opinion leaders were initially selected as potential participants in the survey. Six respondents disqualified themselves by saying that they had no specific expertise in the topic area. Among the final list of thirty-six respondents, fifteen completed the survey, a 42 per cent return rate. A telephone survey based on a structured questionnaire was selected as the methodology in order to reduce errors, maintain a consistent level of response and probe open-ended questions. Respondents were located in six provinces; most were from Ontario. They were academics and researchers, directors of medical or research institutions or specialist physicians. Respondents were affiliated with universities and medical schools, hospitals, professional associations and specialized health organizations. Almost half (7/15) of the respondents reported multiple affiliations. Over half of the respondents were involved in the development of guidelines or consensus statements related to the treatment of depression in pregnancy. Almost 70 per cent provided treatment directly to women with depression in pregnancy; 80 per cent attended CME events that discuss treatment options. Almost 70 per cent of the respondents were involved in multiple activities.

The majority of respondents described a current consensus around the treatment of depression in pregnancy. This involved the use of SSRI antidepressants as a predominant treatment method or as beneficial for specific levels of depression.

Almost three-quarters of the respondents also recommended non-pharmacological approaches for lower levels of depression; however, there was no consensus on what this level was. Some respondents felt that non-pharmacological approaches should be reserved for only mild depression, others stated that non-pharmacological approaches were appropriate for mild and moderate depression.

Most respondents said treatment guidelines had changed in the past decade. The two most frequently identified changes were somewhat contradictory: (1) that there was more acceptance and comfort involved in prescribing SSRIs in pregnancy, and (2) that a more cautious approach was being taken in view of the potential risks of SSRIs to the fetus.

The two most important objectives of treating depression in pregnancy were identified as the prevention of suicide of the mother and the prevention of harm to the fetus arising from a mother's untreated depression.

Respondents identified information from Motherisk as the most frequent source of information consulted by physicians when they are considering the treatment of depression during pregnancy. Resources such as the CPS or other major texts, (general) web-based resources, disease awareness organizations and the Therapeutics Initiative appear to be infrequently consulted. Only 40per cent of the respondents stated that physicians regularly consulted research in major medical journals or systematic reviews such as the Cochrane Library.

There was a general consensus that current information sources were inadequate or only marginally adequate in terms of addressing most issues related to the treatment of depression in pregnancy or treatment with SSRIs. The two areas identified has having the most serious limitations were information about safe methods for withdrawing from SSRIs and community-based support services for pregnant women who are experiencing depression.

Almost three-quarters of the respondents said that additional resources and information would be helpful to physicians when considering treatment decisions. Recommendations included published guidelines and an increase in expert resources available to women.

All respondents said that the most frequent concern expressed by patients when considering treatment with SSRIs is whether these drugs are safe for the baby. Other concerns (e.g. effectiveness in treating depression, effects on labour and delivery) were also identified.

Almost ninety percent of the respondents said that they recommended other information sources to patients when treatment of depression was being considered. In the majority of cases the recommended information source was Motherisk.

Limitations of Study

Although the sample size was insufficient to reflect the views of physicians or specialists as a whole, respondents both addressed questions in terms of general physician response, as well as including their own experiences in the answers they provided.

3. CITATION ANALYSIS: ANTIDEPRESSANT USE IN PREGNANCY: CONFLICTING MESSAGES TO CARE PROVIDERS AND THE PROPOGATION OF "UNFOUNDED BELIEFS" WITHIN MEDICAL LITERATURE.

During a period of growing evidence linking SSRI use during pregnancy to adverse outcomes for newborns and despite growing evidence of limited benefit of SSRI use for the majority of depression cases, prescribing of SSRIs remains widespread. This phase of the study stemmed from a need to better understand conflicting messages physicians and other care providers may receive about SSRI prescribing in pregnancy among articles accessed in medical databases. The purpose was to determine how both benefits and risks are presented in medical literature accessed by care providers through a systematic review of both review and commentary articles.

This phase of the study analyzed information sources accessed by physicians in order to identify conflicting messages on best practice as well as messages that differ from current evidence. This citation analysis summarizes the messages to care providers regarding risks versus benefits of SSRI use in pregnancy, highlights conflicting messages, and provides an analysis of beliefs propagated in the field which differ from the best available medical evidence. A systematic review was conducted of both review and commentary articles from medical databases to compare how the benefits versus the risks of SSRI use in pregnancy are presented to providers within the medical literature.

Assumptions about SSRI efficacy and the propagation of "unfounded beliefs":

Greenberg has highlighted how "unfounded beliefs" become conventional wisdom in medicine through the selective propagation of references to certain viewpoints to the exclusion of others.[34] Although he was describing a different health condition, many of his observations could also be applied to discussions of "untreated" depression and antidepressant use in pregnancy. Many authors refer to harm from "untreated" depression as a rationale for initiating or continuing antidepressant use in pregnancy. There is evidence that a depression diagnosis is associated with specific infant health outcomes that on average are worse than infant health if mothers are not depressed, when controlling for socioeconomic status confounders[35] . However, much of the evidence on harm associated with depression fails to distinguish between effects of poverty and poor health that can lead both to depression and to worse infant health, where poverty and poor health rather than depression diagnosis are the causal link to poor infant health outcomes. Additionally, reference to harm from "untreated" depression as a rationale for SSRI use assumes that treatment with SSRIs is effective for preventing harms associated with depression. In fact, as noted above, studies showing worse outcomes with depression fail to show that SSRI use during pregnancy prevents harm. By listing harms related to depression in pregnancy[36] and calling them "untreated," such articles may misinform physicians and add to their fears that not intervening is harmful. It is unclear to what extent beliefs regarding harms of "untreated" depression have been cited in medical literature. In addition to assumptions about efficacy of SSRIs, questions remain about whether non-drug alternatives are mentioned as appropriate first-line treatments in some circumstances.

The manner in which authors present a critique of study methodology or "limits to the evidence" affects the readers' risk-benefit assessment of SSRI use among pregnant women. Although any research evidence may be subject to critique, in this case the body of pharmaco-epidemiological evidence indicating harm from SSRI exposure in pregnancy appears to be more extensive and methodologically rigorous than evidence of harm linked to "untreated" depression or antidepressant discontinuation. In our study, we attempted to compare the types of SSRI studies where limitations to the evidence are often cited.

Methods:

Medline and Embase were searched on February 9th, 2010 for MESH headings pregnancy and SSRI from 2008 to 2010. Systematic review, reviews and commentaries were included that addressed pregnancy, antidepressants for the treatment of depression and specifically SSRI antidepressants, and made reference to one or more health outcomes. Studies that consisted of primary data collection rather than syntheses or commentaries were excluded. Specifically, cohort studies, case-control studies, RCTs, case reports, cross-sectional surveys, drug utilization studies, and pharmacokinetics studies were excluded. Studies were further excluded if they discussed pharmacokinetics only, discussed animal studies only, did not address SSRI antidepressants specifically in the body of the article, or did not address pregnancy specifically in the body of the article. Articles where the publication was categorized as a letter were excluded. The justification for excluding letters was that they were often short and difficult to interpret without the context of the dialogue that occurred between correspondences.

Analysis of citations, and biases:

Characteristics of articles were described with regard to 1) assumed benefits of SSRI use during pregnancy, measured by use of specific reference to harms of "untreated depression", 2) references to non-drug alternative therapies, 3) reference to risks associated with SSRI use during pregnancy, 4) reference to harms associated with SSRI discontinuation and specifically to the Cohen et al[37] study on relapse into depression upon discontinuation, to determine how often this specific study is cited. When reference was made to assumed benefits, non-drug alternatives, risks, and discontinuation, we noted whether or not the researchers made references to limitations of the studies.

Discussion:

Messages to care providers in medical literature very often included discussion of risks associated with SSRI use (general malformations, cardiac defects, neonatal symptoms and/or PPHN), but often also included messages regarding harms associated with lack of treatment or discontinuation of SSRIs. There is a conflict for providers in assessing the harms associated with SSRIs use against the harms associated with lack of treatment or treatment discontinuation. Nearly half of review and commentary articles from 2008-2009 made reference to specific harms associated with "untreated" depression, invoking an unfounded assumption that treatment prevents the harms.

Only one article criticized study designs on harms related to untreated depression, despite the fact that there are many methodological limitations to such studies. Additionally, among all 73 articles mentioning SSRI use in pregnancy, only 11 per cent mentioned limits to the evidence on SSRI efficacy, despite literature reporting limited benefit of SSRIs among mild, moderate and severely depressed patients [38]. Statements regarding harms of "untreated" depression represent an unfounded belief which appears to have gained authority in medical knowledge and practice on SSRI use in pregnancy.

Our study demonstrated that literature on SSRI use in pregnancy has been more likely to mention study limitations on risks, rather than limitations of studies on SSRI efficacy and risk of relapse into depression with SSRI discontinuation, despite the fact that many limitations exist in the later studies.

While all studies may have methodological limitations, in the case of discontinuation of SSRI use in pregnancy, one study[39] has been extensively cited with no reference to criticism of study design or conclusions. This may give the false impression that there is a consensus regarding the risk of relapse upon discontinuation. Overall, the biased presentation of study limitations on SSRI risks versus benefits in pregnancy has the potential to influence physicians' assessment of the risk-benefit decision of prescribing SSRIs in pregnancy in favour of prescribing SSRIs. In particular, nearly half of studies that reported risks associated with untreated depression, mentioned the risk of suicide as a possible risk of untreated depression. These citations may give physicians the mistaken impression that SSRIs are shown to prevent suicide risk among pregnant patient, when in fact there is no empirical evidence to support this, and some evidence suggesting increased rates of suicidal ideation and suicidality with SSRI use [40]. Overall, physicians and the women they care for would be better served if they were provided with more balanced information on the risks versus benefits of SSRI use in pregnancy.

Limitations and further study:

This study involved a limited time period (2008 to 2009), and therefore cannot adequately answer the question of how the literature evolved over time. A future study using a more limited inclusion criteria over a longer period of time would be better suited to answering questions about how knowledge regarding SSRI use in pregnancy has evolved over the twenty-year time period since SSRIs have been used. A further limitation of this study is that it involved reading and coding of statements made in literature of various lengths and formats. It is possible that several interpretations of recommendations can be made. We have attempted to overcome these limitations by including reference to specific terms (e.g. specific reference to "untreated depression" and specific outcomes associated with them).

Conclusion:

Pregnant women need comprehensive, accurate and unbiased information about the pros and cons of the range of options available for the treatment of depression in pregnancy, including information on the range of severity of depression and how this might affect treatment decisions, including in some cases a 'watch and wait' approach. They also need to know what type of scientific evidence supports different treatment options, and specifically whether or not antidepressants have been shown to be beneficial in pregnancy. Given the evidence indicating harm to the fetus, and the lack of scientific

evidence of benefit, the frequent advice in the medical literature and among authorities in Canada recommending use in pregnancy appears unfounded.

We found that information provided to the public and professionals was often conflicting and that the warnings in Health Canada safety advisories were not being communicated well.

This report reveals that information available to women on depression in pregnancy is conflicting and unclear, sometimes lacking any reference to important national health warnings. A systemic review of the medical literature revealed no significant benefit to the mother or infant in the use of SSRI antidepressants in pregnancy for treatment of depression when compared with placebo, non-drug treatments or no-treatment. This lack of evidence raises questions about the messages physicians are receiving, and especially the extent to which they are being informed about the current uncertainties about benefit, and the evidence of a potential for harm. A survey of physicians in influential positions in their communities (guideline developers, reproductive psychiatrists, teratology information centre) reveals a consensus that SSRI antidepressants are beneficial in pregnancy. Similarly, an analysis of review articles and editorials found that most authors were more likely to critique the methods of studies that indicate harm than of studies supporting a benefit.

This report is motivated by a concern with a dissonance between the evidence supporting and the practice of prescribing SSRI antidepressants in pregnancy. A precautionary approach to drug use in pregnancy would suggest avoiding use of products with a potential for harm unless clear evidence exists that benefits will outweigh harm.

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