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

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Abstract

Rationale Knowledge transfer and translation (KT) has become an important component in health care systems worldwide. Antidepressant use in pregnancy has become a controversial subject for a number of reasons, including differing interpretations of study results.
Methods Selected key articles were indentified and retrieved from the literature. Relevant information was extracted and synthesized into themes, addressing each of the stated objectives.
Objectives (1) To determine how knowledge regarding 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 this information is currently disseminated.
Results All of the methods used for examining the safety of antidepressants in pregnancy have some deficiencies in study design and analysis, thus reinforcing the need for accurate interpretations when discussing results. In addition, dissemination in both the scientific and lay press has been selective and therefore potentially biased.
Conclusion It is critical, starting with the creators of knowledge, through to the recipients that discrepancies are resolved, as lack of clarity may impede the transfer of unambiguous evidence-based information from health care providers to patients, thus impacting decision making. For example, by implementing improved (KT) strategies, a pregnant, depressed woman, will be empowered to make a rational evidence-based decision regarding whether or not she should take an antidepressant during pregnancy.

Introduction

Traditional dissemination strategies have followed a mostly passive exercise of sharing knowledge, most often carried out through peer-reviewed journals and at scientific conferences. However, it was primarily directed at the creators of the knowledge, and little trickled down to the clinician and the patient who required the information that evolved from research findings. 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.

Currently, knowledge transfer (KT) has become a very important component of health care management. A widely used definition is that of the Canadian Institutes for Health Research and is described 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]. This 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 sound information.

Antidepressant use in pregnancy has become a controversial subject, largely because of inconsistent results from studies and

subsequent dissemination of conflicting information in both the scientific and lay press. Individuals requiring this information, 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 guidelines. In addition, as mental illness continues to be surrounded by controversy and stigma, the lay press also uses this information, as this has become a 'hot topic'.

The objectives of this evaluation of KT, specifically focusing on antidepressant use in pregnancy, were threefold: (1) to determine how knowledge regarding 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 be able to critically evaluate the results; and (3) to identify how this information is currently disseminated.

The creation of knowledge

Studying the safety of drugs used in pregnancy, especially psychotropics, is a complicated process with no 'gold standard' for conducting studies. Because of the ethical issues surrounding pregnancy, 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, retrospective bias, inability to know exactly if the women took their medication in pregnancy and other missing data, such as concurrent medications, medical and psychiatric co-morbidity, baseline rates of fetal anomalies/malformations (which depend on the population and/or environment), and duration of follow-up. Currently, there is no specific organization that has been directed to take on the responsibility of conducting these studies, and it appears that if the researchers have an interest in this field and have the data, a study will be conducted. The one exception is that in the United States, drug companies are now required to conduct and maintain a post-marketing pregnancy registry, following a new product release on the market [2].

Other data sources typically come from patient charts, insurance claims pharmacy records, doctor practices, health databases, hospital records and teratogen information services.

The following are current models 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 study of teratology as well as of the notion of drug safety began following Dr. W McBride's case report in the Lancet in 1961, stating that he had seen several cases of exposure to 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 be associated with a highly significant increased risk for major malformations, in infants exposed during pregnancy, which is isotretinoin (Accutane®, Roche Pharmaceuticals, Mississauga, Ontario, Canada). However, because of the heightened awareness caused by the thalidomide tragedy, it was known to be a teratogen in a much shorter time than thalidomide because of 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, by a single service or in collaboration from around the world. These services 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 with 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 with 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.

Other data sources used to conduct studies

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 practising 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 statistics and evaluating published studies are critical, 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 because of the controversy and subjectivity surrounding this field. In addition, exposure measurements are not always exact and 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 increased 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 events 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 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 birthweights (30 gm difference between groups) and stated they had found an increased risk for low birthweight [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 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 analysed [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 the 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 a Serotonin Re-uptake Inhibitors (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 birthweight, 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 with an increased risk of preterm delivery, the sample size was too small to make this conclusion ($n = 85$). In addition, decreasing the overall sample size further, hydroxyzine, a first-generation antihistamine of the diphenylmethane and piperazine class was listed as a psychotropic drug, when it is not generally used for psychiatric conditions ($n = 107$), 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. In addition, observational studies can only identify associations, but cannot be used to establish causality. 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 RCTs, so this reinforces the need to improve the rigor of the available study methods.

Of note, 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

Since the thalidomide tragedy, there have been efforts made to disseminate information regarding the safety/risk of drug use in pregnancy. The Food and Drug Administration (FDA) implemented labelling 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 describing results of studies. After many years of discussion, this will finally be implemented in June 2015. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm(accessed 7 January 2015).

Government health warnings, especially when they are regarding adverse effects of medications in pregnancy, are often 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 (September 2014), a Google search using the keywords 'antidepressants pregnancy' revealed 4 940 000 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, as well as their health care providers.

Implications for clinical practice

In a recent survey 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%) [24].

In the first of two surveys conducted with pharmacists, who are frequently the first health care provider a pregnant woman consults, we found that few community pharmacists provided evidence-based information regarding the safety of drugs in pregnancy, most notably, antidepressants. In Canada, The Netherlands and Iceland, only 14% of the participants 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 doctor, without providing any information [25]. In the second survey using the same questionnaire conducted in Argentina, the results proved to be strikingly similar [26].

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 that pharmacists are not comfortable giving advice on this subject. However, it is simply not sufficient to advise the woman to 'go ask your doctor' 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 doctors, which results in conflicting information, often because of the use of different sources of information [27].

Conclusions

It is unlikely that in the near future, pregnant women will be included in RCTs, 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 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 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 would be important to evaluate if and how the investigators have undertaken this task. In addition, it would be useful to examine the health care professional teaching programmes in universities to determine if this model has been incorporated in the curriculum, in both a didactic and experiential level. It appears that all health care 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.

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