THE USE OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN PREGNANCY

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Abstract

Objective: To provide an update of literature on the safety of using selective serotonin reuptake inhibitors (SSRIs) during pregnancy.

Methods: MEDLINE was searched for English-language papers published from 1985 to 2003 on human studies of SSRIs, using the key words "serotonin reuptake inhibitors," "citalopram," "fluoxetine," "fluvoxamine," "paroxetine," and "sertraline."

Results: The literature search yielded 12 338 publications. Previous studies on the safety of SSRIs in pregnancy were often based on small samples from medical centres, with heterogeneous design and outcome ascertainment methods, and had yielded inconsistent results. Consequently, the management of pregnant women with depression poses challenges to clinicians who are hesitant to prescribe anti-depression drugs, including SSRIs, because of concern about potential risks to the fetuses. Failure to adequately treat maternal depression can lead to progressively worsening depression that greatly compromises maternal-fetal health and can impair bonding and childcare in the postpartum period.

Conclusions: Because of the uncertainty regarding the safety of SSRI use during pregnancy, consultation with specialists experienced in treating depression may be helpful when treating pregnant women with SSRIs. Large-scale, population-based studies to comprehensively assess the safety of SSRIs in pregnancy are needed.

Résumé

Objectif : Offrir une mise à jour de la littérature au sujet de l'innocuité du recours aux inhibiteurs spécifiques du recaptage de la sérotonine (ISRS) pendant la grossesse.

Méthodes : Des recherches ont été menées dans MEDLINE en vue d'en tirer les articles de langue anglaise, publiés entre 1985 et 2003, portant sur les études chez l'homme des effets des ISRS, et ce, à l'aide des mots clés suivants : *serotonin reuptake inhibitors, citalopram, fluoxetine, fluvoxamine, paroxetine* et *sertraline*.

Résultats : La recherche documentaire a permis l'obtention de 12 338 publications. Les études précédentes sur l'innocuité du recours aux ISRS pendant la grossesse, dont la conception et les méthodes de détermination des issues étaient hétérogènes, étaient souvent fondées sur de petits échantillons provenant de centres médicaux et n'ont obtenu que des résultats inconséquents. Ainsi, la prise en charge des femmes enceintes atteintes de dépression continue d'être un défi pour les cliniciens, lesquels hésitent à prescrire des antidépresseurs (dont les ISRS) en raison de leurs préoccupations au sujet des risques potentiels de ceux-ci pour les fœtus. L'incapacité de traiter adéquatement la dépression maternelle peut mener à une aggravation progressive de celle-ci (ce qui compromettrait grandement la santé fœto-maternelle), ainsi que nuire à l'établissement de liens entre la mère et l'enfant et aux soins prodigués à ce dernier au cours de la période post-partum.

Conclusions : En raison de l'incertitude entourant l'innocuité du recours aux ISRS pendant la grossesse, la consultation de spécialistes expérimentés en matière de prise en charge de la dépression peut s'avérer utile, lorsque l'on envisage le recours à des ISRS dans le cas de femmes enceintes. Des études de grande envergure sur la population générale s'avèrent nécessaires pour évaluer de façon approfondie l'innocuité du recours aux ISRS pendant la grossesse.

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Key Words

Depression; antidepressive agents; serotonin reuptake inhibitors; pregnancy; fetus; prescriptions, drug; fetal growth retardation

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INTRODUCTION

Depression is a common disorder among women of childbearing age.[1-5] The estimated prevalence of depression among women in community samples varied from 10% to 25%, with peak prevalence between the ages of 25 and 44 years.[1-5] O'Hara *et al.* estimated that 9% of pregnant women have an illness that meets the stricter Research Diagnostic Criteria for Depression.[5] Approximately 70% of patients with depression respond to antidepressant drug therapy and may experience a complete recovery from their depression.[6] Anti-depressants are also used to treat anxiety disorders, agoraphobia, panic attacks, obsessive-compulsive neuroses, migraine headaches, and chronic pain.[7]

Selective serotonin reuptake inhibitors (SSRIs) are considered the first-line drugs for pregnant women with severe depression.[1,8] All SSRIs are classfied as "Pregnancy Category C"

medications under the Food and Drug Administration (FDA) labelling system for drug use in pregnancy.[9] A drug is classified "C" if animal studies have not been conducted or if animal studies have shown an adverse effect, and there are no adequate or well-controlled studies in pregnant women. While existing knowledge seems to indicate that the SSRIs are not associated with major teratogenicity, findings on minor malformations and neonatal complications are mixed.[10]

In this paper, we provide an update of the literature on SSRIs in pregnancy, discuss the dilemma in the clinical management of severe depression in pregnancy, and propose research strategies that could lead to better clinical management of severe depression using SSRIs in pregnant women.

METHODS

MEDLINE was searched for English-language papers published from 1985 to 2003 on the uses of SSRIs in humans, employing the key words "serotonin reuptake inhibitors," "citalopram," "fluoxetine," "fluvoxamine," "paroxetine," and "sertraline." This search strategy yielded 12 338 publications. The titles of these papers were scanned and those with abstracts suggesting relevance to our study were chosen for review. Because of the heterogeneity in the study designs, outcomes of interest, and outcome ascertainment methods used in these studies, we have not attempted to pool results from different studies by systematic review or meta-analysis. This review is therefore structured as an update.

MECHANISM OF ACTION

SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline)[11] execute their therapeutic effects by inhibiting serotonin reuptake.[12] This neurotransmitter is involved in many physiological systems that affect sleep, appetite, pain perception, mood, thermal regulation, gut function, sexual function, cognitive function, motor function, sensory interpretation, and balance.[13] The development of SSRIs represented an important advancement in the medical treatment of depression and depression-related disorders.[12] SSRIs are the treatment of choice for most depressed patients because of the drug's tolerability, safety in overdose, and good compliance.[12]

USE IN PREGNANCY

The current FDA rating of category C indicates that the risk of SSRIs to fetuses cannot be ruled out, even though several animal teratology studies with SSRIs did not find an increased risk of congenital malformation or perinatal problems.[14-17]

Studies of the safety of SSRIs in human pregnancy have yielded inconsistent results.[10,14,18-24] Four Toronto-based cohort studies demonstrated no increase in risk of major birth defects or other adverse outcomes for infants born to mothers who were exposed to SSRIs as compared to those born to mothers who were exposed to other anti-depression and non-teratogen drugs.[14,18-20] Newport and Stowe summarized the findings of 67 studies with 3050 cases of SSRI use during pregnancy and 240 cases of use during lactation, and did not find apparent association between exposure to SSRIs and adverse pregnancy outcomes.[21]

On the other hand, a study in Seattle found that compared with non-exposure in subjects matched by year of birth, maternal age, mother's lifetime use of anti-depressants, and mental health care, exposure to SSRIs during pregnancy was associated with reduced pregnancy length and low birth weight, and exposure during the third trimester was associated with a lower Apgar score.[22] Hendrick *et al.* found that use of SSRIs during pregnancy was not associated with increased risks of neonatal complications or congenital anomalies, but that maternal exposure to high doses of fluoxetine throughout pregnancy might be associated with low birth weight.[23] Casper *et al.* found that motor development and motor control in infants born to mothers exposed to SSRIs might have been subtly affected, compared with those of infants born to mothers with major depression disorders who elected not to take medication.[24] A California study compared infants born to 228 women who were exposed to fluoxetine with infants born to 254 women identified in a similar manner who were not taking fluoxetine.[10] The infants born to women exposed to fluoxetine had an increased risk of presence of 3 or more minor anomalies (defined as having no cosmetic or functional importance), preterm birth, admission to special care nursery, poor neonatal adaptation (jitteriness, hypoglycemia, poor muscle tone, respiratory distress, weak or absent crying, or desaturation on feeding), and lower mean birth weight.[10] The authors also analyzed the SSRIs-related risk by trimester, and found that only late exposure was associated with increased risks of preterm birth, admission to a special care nursery, and poor neonatal adaptation.[10] The trimester-specific analysis yielded interesting results that shed light on the potential mechanisms of SSRIs-related fetal and infant risks. Oberlander *et al.* observed that fetuses with lengthy exposure to SSRIs may develop associated reduced responses to pain and increased parasympathetic cardiac modulation in recovery following an acute neonatal noxious event.[25]

Several limitations in previous studies on the safety of SSRIs in human pregnancy could explain the inconsistency of the results in these studies. These studies were often based on small samples from medical centres, with high probability of selection bias and low study power. The study designs, outcomes of interest, and outcome ascertainment methods used in these studies were so heterogeneous that a pooling of results from different studies by systematic review is difficult.

CLINICAL MANAGEMENT OF DEPRESSION IN PREGNANT WOMEN

Management of pregnant women with depression poses challenges to clinicians. Because of concerns over the potential risks

to the fetus, clinicians are hesitant to prescribe anti-depression drugs, including SSRIs, to pregnant women.[1,8] However, failure to adequately treat depression in pregnant women can lead to a progressively worsening depression that greatly compromises maternal-fetal health, and can impair bonding and child-care in the postpartum period.[26] Depressed women who discontinue anti-depressant medication early in pregnancy show a 50% relapse rate of depression by the third trimester.[27] A recent study by researchers at the Hospital for Sick Children in Toronto found that physicians often advised women in pregnancy or in lactation to stop taking anti-depressant, anti-psychotic, or anti-anxiety drugs.[28] However, an abrupt discontinuation of these drugs, especially in pregnant women with severe depression, can cause sudden suicidal impulses and other serious psychiatric problems.[1,8,28] Among the 37 pregnant women who participated in the study, all of whom discontinued their anti-depressant, anti-psychotic, or anti-anxiety medication, 11 (30%) considered suicide, 26 (70%) reported psychological and physical withdrawal symptoms such as depression, anxiety, nausea, fainting, or diarrhea, and 4 (11%) had to be admitted to hospital.[28]

In the early 1980s, almost 5000 pregnancies were terminated in Hungary because of the supposed teratogenic effect of drugs and defensive practice by physicians.[29] Moreover, depression during pregnancy itself has been associated with low birth weight and preterm delivery, while postnatal depression may result in neglect of the child, causing emotional and behavioural problems, as well as cognitive delay.[30]

DISCUSSION

Because of the major heterogeneity in study design, outcome of interest, and outcome ascertainment methods in the studies reviewed, we have not been able to provide a pooled effect of SSRIs on fetal outcomes through such mechanisms as meta-analysis. Because of the weaknesses in study methodology and uncertainties in results reported in the original studies, no clear-cut recommendations could be made. The limitations in previous studies call for major research initiatives on the safety of SSRIs in pregnancy.

Given the uncertainty of the safety of SSRIs in pregnancy, caution should be applied in the prescription of SSRIs for women of reproductive age with severe depression. A balanced approach, weighing the need to control maternal disorders against the potential risk of fetal exposure, should be taken when dealing with the individual patient. In the meantime, large-scale, population-based cohort studies are needed for a comprehensive assessment of the safety of using SSRIs during pregnancy. A cohort study design allows assessments of the association of SSRIs and several pregnancy outcomes simultaneously, the relative safety of SSRIs in pregnancy compared with other anti-depression drugs, the sensitive time period of fetal risk to exposure, and the dose-response relationship of prescription SSRIs in pregnancy. The sensitive exposure time period could be outcome-specific. For example, the effect on major congenital anomaly of exposure to SSRIs may be most sensitive in the periconceptional period, while the effect on neonatal morbidity may be most sensitive to exposure in late gestation. The large sample size will allow detection of a moderately increased risk of SSRIs, and will be able to assess the effect of individual SSRIs instead of combining them together. The findings from large-scale cohort studies may have direct implication in the management of depression in pregnancy. For example, if a study finds an increased risk of adverse fetal and infant outcomes of in utero SSRI exposure, physicians caring for women with depression may need to consider changing to alternative pharmacological treatments.

Women requiring treatment by an SSRI should be fully informed about the potential risk of these drugs, and consultation with specialists experienced in treating depression may be needed. The comparison of risk profiles of different anti-depression drugs, as well as the most sensitive exposure time period and dosage, can help physicians in prescribing anti-depression drugs in particular clinical scenarios. For example, if a particular SSRI is safer than other SSRIs or other anti-depression drugs, physicians could consider shifting to that particular SSRI for pregnant women. If the harmful effects of SSRIs are demonstrable only in early gestation and in high dosage, physicians could consider delaying the prescription or reducing the dosage (e.g., by periodically discontinuing prescription) of SSRIs. On the other hand, if the large-scale cohort studies find no increased risk of adverse fetal and infant outcomes of in utero SSRIs exposure, then women who suffer from severe depression can receive the better medical treatment, without worrying about fetal risks.

CONCLUSIONS

The safety of SSRIs in pregnancy remains uncertain and there is a need for large-scale, population-based comprehensive studies to examine the safety of SSRIs' uses in pregnancy. A balanced approach should be taken to simultaneously consider the need to treat depression in a pregnant woman and the safety of the fetus. A consultation with a specialist experienced in treating depression may be helpful.

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