

Ondansetron in Pregnancy and the Risk of Congenital Malformations: A Systematic Review

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Abstract

Objective: Ondansetron, not approved for use in pregnancy, is increasingly being prescribed for nausea and vomiting in pregnancy and hyperemesis gravidarum. A number of recent lawsuits have highlighted the possibility that ondansetron may cause congenital malformations. The aim of this study was to systematically review epidemiological evidence on the potential association of prenatal exposure to ondansetron and congenital malformations.

Methods: Systematic searches in Medline and Embase were performed in June 2017 using controlled vocabulary and key words, and references of search results were reviewed. Full papers (RCTs, cohort, and case-control studies) were eligible for inclusion if they reported fetal outcomes of prenatal ondansetron exposure in humans. Excluded were: case reports, studies involving pre-medication with ondansetron prior to CS, animal studies, and foreign languages studies.

Results: Ten epidemiologic studies were included: five large retrospective cohort studies, two prospective observational studies, two population-based case-controls, and a retrospective case series. Sample sizes ranged from 17 to 1 501 434 infants exposed to ondansetron. A case-control study identified an association between prenatal exposure to ondansetron and cleft palate, and one cohort study found an increased risk of cardiovascular defects. These findings were not reproduced in the other studies.

Conclusion: While further investigation of the literature is needed, our results highlight the paucity of evidence linking prenatal exposure to ondansetron to an increased risk of congenital malformations. There is a need for additional epidemiologic studies to confirm whether ondansetron represents a safe

and effective alternative treatment for nausea and vomiting in pregnancy and hyperemesis gravidarum.

Résumé

Objectif : L'ondansétron n'a pas été approuvé chez les femmes enceintes; or il est de plus en plus prescrit pour traiter la nausée, les vomissements et l'hyperémèse associés à la grossesse. Un certain nombre de poursuites en justice a souligné récemment la possibilité que ce médicament soit à l'origine de malformations congénitales. Cette étude visait à faire un examen systématique des données épidémiologiques sur l'association potentielle entre l'exposition prénatale à l'ondansétron et les malformations congénitales.

Méthodologie : En juin 2017, nous avons mené des recherches systématiques dans Medline et Embase à l'aide d'une terminologie et de mots-clés contrôlés, et avons examiné les références des résultats obtenus. Les articles en texte intégral (ECR, études de cohorte, études cas-témoin) étaient admissibles s'ils faisaient état des résultats de l'exposition prénatale à l'ondansétron chez l'humain. Les déclarations de cas, les études portant l'administration du médicament en vue d'une césarienne, les études sur des animaux et les études de langue étrangère ont été exclues.

Résultats : Dix études épidémiologiques ont été retenues : cinq grandes études de cohorte rétrospectives, deux études observationnelles prospectives, deux études cas-témoin basées sur des populations et une étude de série de cas rétrospective. La taille des échantillons allait de 17 à 1 501 434 bébés. Une étude cas-témoin a montré une association entre l'exposition prénatale à l'ondansétron et la fente palatine, et une étude de cohorte a mis en évidence un risque accru de malformations cardiovasculaires. Ces résultats n'ont pas été observés dans les autres études.

Conclusion : Même si un examen plus poussé de la littérature serait nécessaire, nos résultats indiquent un manque de données associant l'exposition prénatale à l'ondansétron et le risque accru de malformations congénitales. D'autres études épidémiologiques devront être menées pour déterminer si l'ondansétron constitue un traitement efficace et sécuritaire de la nausée, des vomissements et de l'hyperémèse associés à la grossesse.

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Key Words: Nausea and vomiting in pregnancy, ondansetron, congenital malformation, systematic review of the literature

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INTRODUCTION

Nausea and vomiting in pregnancy (NVP) is the most common complication of pregnancy, affecting over 60% of women in the first trimester.^{1,2} Over the years, several pharmacological agents have been shown to be safe and effective in treating NVP.^{3,4} Hyperemesis gravidarum (HG) is a continuum of NVP and involves intractable vomiting associated with weight loss, dehydration, electrolyte imbalances, ketosis, and the need for admission to hospital.⁵ If left untreated, HG can result in permanent neurological disability and death from Wernicke encephalopathy.^{5–8} Some badly affected women elect to terminate their pregnancy as a means to relieve their symptoms.⁷ While the safety and efficacy of usual medications used to treat NVP—such as pyridoxine/doxylamine and dimenhydrinate—have been widely researched, they usually offer little relief to women afflicted with HG.^{3,4,7,9} Over the past several years, ondansetron, a serotonin receptor antagonist and pregnancy class B medication, has been shown to be effective when no other treatments work.^{4,9–12} Even though there are no adequate and well-controlled studies in pregnant women, ondansetron is commonly being used as a last resort. Physicians remain cautious in prescribing ondansetron, recalling the thalidomide tragedy and taking note of class-action lawsuits in Canada and the United States in which women claim that ondansetron caused congenital malformations in their children.

Given the paucity of evidence regarding the safety of ondansetron administered for NVP and HG, a systematic review of the evidence was carried out in 2016.¹³ Carstairs concluded that the overall risk of birth defects associated with ondansetron was low but that there may be a small increase in the incidence of cardiac abnormalities in neonates exposed to ondansetron compared with those not exposed. That review conducted by a single reviewer did not identify the most recent literature but did include an abstract that has never been published as a full paper, which can be misleading because differences can occur between an abstract and the peer-reviewed publication.^{14,15} Given the limitations of Carstairs' review, we decided to undertake an updated systematic review in which the search was conducted by a senior medical librarian and all papers were independently reviewed by two reviewers.

The goal of our systematic review of the literature was to describe the potential association of ondansetron and congenital malformations to provide evidence to support clinical decision-making for women suffering from HG.

METHODS

Database searches were performed by a medical librarian (S.C.) in June 2017 using subject headings and text words

to retrieve articles related to the following concepts: “ondansetron” and “birth defects or early labour” and not “post operative vomiting and nausea.” Studies that included only adults or only animals were removed from major databases. All databases were searched from the inception to June 2017. No language restrictions were applied. Databases searched included: Ovid Medline, Ovid Embase, OVID EBMALL, Proquest Dissertations & Theses Global, CINAHL (EBSCO), and Scopus. Search strategies were adjusted appropriately for each database. Clinicaltrials.gov, Prospero, and Google Scholar were also searched. Google Scholar was date restricted to 2011–2017 and searched using two strategies. Studies were selected from the first 10 pages of each search. Search strategies are listed in (Figure 1).

Studies were included for review if they were written in English, reported human data, presented outcomes relating to birth defects following antenatal exposure to ondansetron and described results from original research. Case reports, abstracts without corresponding manuscripts, and studies evaluating pre-medication with ondansetron prior to Caesarean delivery were excluded.

Data were abstracted from each included study using a standard data collection form which included the following details: study design, data sources, number of pregnancies exposed to ondansetron, details of ondansetron exposure (dose, duration of exposure, trimester at start, indication), and outcomes (risk of congenital malformation and any other reported secondary outcomes). Data were tabulated: for individual papers, ondansetron use was described and risk (if any) of congenital malformations. No attempt was made to combine the results studies because of the heterogeneity of design and reporting.

RESULTS

Our search in June 2017 retrieved 690 studies (Figure 1). Following independent appraisal of all studies by two reviewers (ML, SR), 10 studies met inclusion criteria (Table 1).

The earliest study evaluating the safety of ondansetron in pregnancy was conducted by Einarson et al.¹⁰ Over a two-year period, this prospective comparative study extracted patient self-reported data from programs set up to provide advice on safety/risk of drugs in pregnancy in Canada and Australia. The study aim was to determine if there was an increased aggregated risk of any major malformations associated with ondansetron use in the first trimester compared with other antiemetics or non-teratogenic drugs. No significant differences were found in outcomes including risk of any major malformation for women taking ondansetron (3.6% vs. 1.9% for the combined control groups, $P = 0.52$).

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