Reproductive Toxicology 52 (2015) 78–82

Contents lists available at ScienceDirect

Reproductive Toxicology

journal homepage: www.elsevier.com/locate/reprotox

Exposure to fluconazole and risk of congenital malformations in the offspring: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 20 November 2014
Received in revised form 15 January 2015
Accepted 17 February 2015
Available online 25 February 2015

Keywords:
Vulvovaginal candidiasis
Fluconazole
Infants
Pregnancy
Teratogenicity
Cardiovascular defects

ABSTRACT

Vulvovaginal candidiasis (VVC) affects up to 75% of women at least once during their lifetime, mostly during the reproductive age, and recurrence rate is about 50%. Because half of all pregnancies are unplanned and pregnant women have an increased risk of VVC recurrence, the likelihood of inadvertently being exposed to fluconazole in pregnancy is increased. Thus, we aimed to examine the risk of congenital malformations in the offspring of women exposed to fluconazole in the first trimester of pregnancy. The rate for overall malformations was 1.10 (95% CI 0.98–1.25), for heart defect was 1.29 (95% CI 1.05–1.58), for craniofacial defects was 1.25 (95% CI 0.88–1.77), and for limb/musculoskeletal defects was 0.82 (95% CI 0.59–1.13). In conclusion, the use of fluconazole in the first trimester does not appear to increase the overall risk for congennital malformations. More studies are needed to address the potential increased rate of heart defects.

WHAT IS ALREADY KNOWN ON THIS TOPIC?

- *Vulvovaginal candidiasis* (VVC) affects up to 75% of women at least once during their lifetime, mostly during the reproductive age, and recurrence rate is about 50%.
- Because half of all pregnancies are unplanned and pregnant women have an increased risk of VVC recurrence, the likelihood of inadvertently being exposed to fluconazole in pregnancy is increased.
- While several studies have addressed the safety of fluconazole at doses used for VVC, earlier reports of infants with cranifofacial and skeletal malformations after the drug was used for treatment of systemic mycosis during pregnancy have led to confusion regarding the possible drug-induced adverse fetal effects.

WHAT THIS STUDY ADDS?

- This study provides a quantitative analysis of all controlled studies and estimates the risk of congenital malformations in the offspring of women exposed to fluconazole in the first trimester of pregnancy.

1. Introduction

Vulvovaginal candidiasis (VVC) is reported to affect up to 75% of women at least once during their lifetime, mostly during the reproductive age, and recurrence rate is about 50% [1]. Physiologic changes during pregnancy may increase the vaginal colonization rates of *Candida* strains and hence, the risk for VVC [2,3]. Increased recurrence rates of VVC and decreased therapeutic responses have been reported among pregnant women [3]. Although topical azole antifungals are usually the first choice for the treatment of VVC, oral azole agents, which are often preferred by patients to avoid local side effects and messiness [4], were shown to be of same effectiveness [5].

Fluconazole is a triazole antifungal agent characterized by high oral bioavailability and a good safety profile [3,5]. Because half of all pregnancies are unplanned [6] and pregnant women have an increased risk of VVC recurrence [3], the likelihood of inadvertently

Abbreviations: CI, confidence interval; OR, odd ratio; VVC, *Vulvovaginal candidiasis*.

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http://dx.doi.org/10.1016/j.reprotox.2015.02.009
0890-6238/

being exposed to fluconazole in pregnancy is increased. While several studies have addressed the safety of fluconazole at doses used for VVC [7–13], earlier reports of infants with cranifofacial and skeletal malformations after the drug was used for treatment of systemic mycosis during pregnancy have led to confusion regarding the possible drug-induced adverse fetal effects [14–17]. Therefore, it is important to establish whether the exposure to fluconazole during pregnancy poses an increased risk for congenital malformations or not.

The aim of this systematic review and meta-analysis was to synthesize the results from all controlled studies in an attempt to provide a conclusive answer on the risks of congenital malformations associated with the exposure to fluconazole in the first trimester of pregnancy.

2. Materials and methods

2.1. Search strategy and study selection

We performed a literature search through MEDLINE, EMBASE, and Web of Science through 30 October 2014. The terms "fluconazole", "pregnancy", "congenital malformations", "malformations", and "birth defects" were used in the search with no language restrictions. Thereafter, additional relevant articles were obtained from the reference lists of these articles and from other reviews.

2.2. Inclusion and exclusion criteria

All studies were selected according to the following inclusion criteria: cohort or case–control studies that reported fetal outcome after exposure to any dose of fluconazole used in the first trimester of pregnancy and compared the outcome with that of a control group who were not exposed to fluconazole. We excluded studies reporting non-human research, case reports, reviews, studies with no control group or studies investigating the exposure to fluconazole after the first trimester of pregnancy. Thereafter, two authors independently assessed the articles to determine whether they met the inclusion criteria. In cases of disagreement, consensus was achieved by discussion between the two authors.

2.3. Statistical analyses

The meta-analysis was conducted using Review Manager 5 and Chi-squared test was used to test for heterogeneity. The data were pooled to estimate the odd ratio (OR) using a Mantel–Haenszel random effects model. The primary outcome measure was the rates of congenital malformations, limb/musculoskeletal defects, craniofacial defects, and heart defects. The articles' quality was assessed using the Newcastle-Ottawa Scale (NOS) where the quality score was reported as a percentage of the applicable items presented in the article [18]. We considered the article acceptable to be included in the meta-analysis when its quality score was above 50%. Potential publication bias was tested by sensitivity analyses.

3. Results

3.1. Meta-analysis of included studies

Using our inclusion and exclusion criteria, four studies were accepted for the analysis (Fig. 1) [7–10]. These studies are summarized in Table 1. The summary OR for included studies was 1.10 (95% CI 0.98–1.25) for overall malformations (Fig. 2), 1.29 (95% CI 1.05–1.58) for heart defect (Fig. 3), 1.25 (95% CI 0.88–1.77) for craniofacial defects (Fig. 4), and 0.82 (95% CI 0.59–1.13) for limb/musculoskeletal defects (Fig. 5). There was no heterogeneity

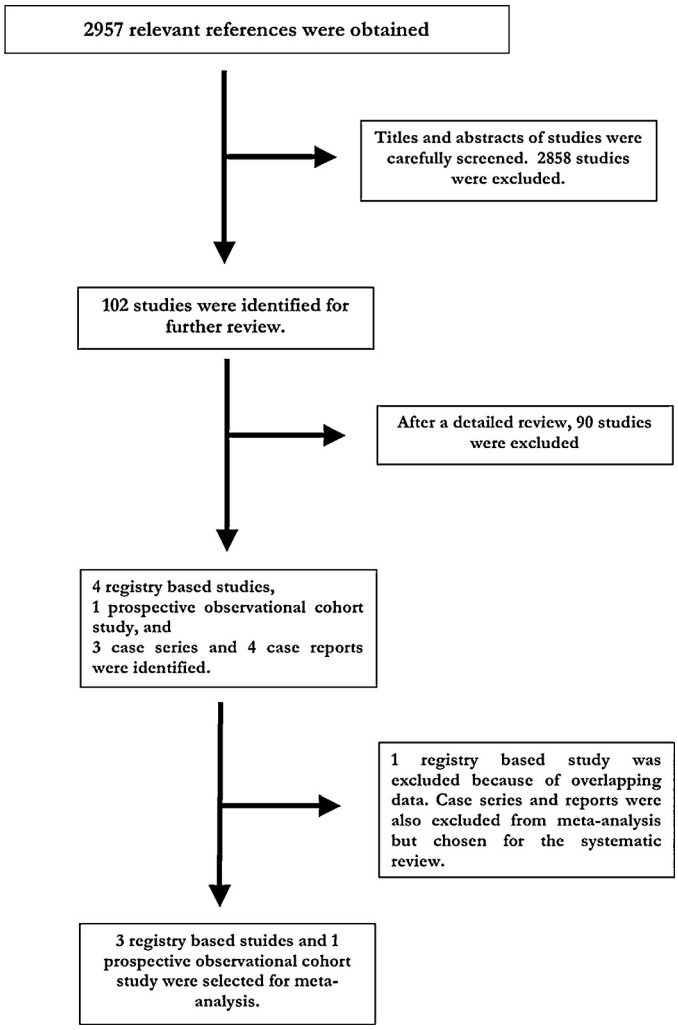

Fig. 1. Study flow diagram.

among the included studies for different end points ($p = 0.64–0.99$) suggesting that the studies were combinable. Potential publication bias was assessed and ruled out by sensitivity analyses. The studies by Molgaard et al. [9] and Norgaard et al. [10] accounted for most of the relative weight (80.2% and 16.6%, respectively). In sensitivity analyses, we excluded these two studies one by one in order to recalculate the pooled risk. The OR remained insignificant when each study was excluded in the analysis of overall congenital malformation rates. The only exception was in the rate of heart defects where the exclusion of the study by Molgaard et al. [9] resulted in insignificant OR.

3.2. Use patterns of fluconazole in the included studies

As shown in Table 2, the upper dosage limit of fluconazole for an uncomplicated VVC was 300 mg (2 times 150 mg daily). The proportion of women who were exposed to fluconazole for an uncomplicated VVC (i.e. ≤300 mg) was 92% in Jick study, 96% in Norgaard study, and 87% in Molgaard-Nielsen study. In Mastroiacavo study, we were not able to estimate the rate of women exposed to fluconazole for an uncomplicated VVC due to reporting method of this study. There was no information on the numbers of patients with systemic mycosis in any of the studies. With respect to the differentiation between low-dose and high-dose fluconazole, there was no clear cut-off. Although 300 mg may cumulatively be considered as a cut-off dose, this differentiation must also include the