MOTHERISK ROUNDS

Exposure to Nitrofurantoin During Early Pregnancy and Congenital Malformations: A Systematic Review and Meta-Analysis

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Abstract

Objective: Because of an increased resistance of urinary pathogens to penicillin derivatives, nitrofurantoin is commonly used as an alternative in treating urinary tract infection because a wide range of both Gram negative and positive organisms are sensitive to it. The safety of the fetus after exposure to nitrofurantoin remains controversial.

Methods: We conducted a systematic review and meta-analysis to evaluate the fetal safety of nitrofurantoin. We searched Medline, EMBASE, references from published reports, and meeting abstracts for relevant studies. Articles were included in the review if they were human studies, reported pregnancy outcomes, reported the use of nitrofurantoin in the first trimester of pregnancy, and included a comparator group of unexposed pregnancies. The primary outcome was the rate of major malformations; secondary outcomes were rates of craniosynostosis, cleft lip or palate defects, cardiovascular defects, and hypoplastic left heart syndrome.

Results: Eight studies reporting on 91 115 exposed cases and 1 578 745 unexposed controls were included in the primary meta-analysis examining the risk of major malformation. Five cohort studies reported on 9275 exposed and 1 491 933 unexposed infants, resulting in an overall RR of 1.01 (95% CI 0.81 to 1.26); however, three case–control studies with a total of 39 268 cases of major malformations and 129 394 controls gave an overall OR of 1.22 (95% CI 1.02 to 1.45). No increased risk for cardiovascular malformations, oral cleft, or craniosynostosis was identified. For assessing risk of hypoplastic left heart syndrome, only three articles were eligible; these demonstrated an OR of 3.07 (95% CI 1.59 to 5.93).

Conclusion: While no association was found between fetal exposure to nitrofurantoin and major malformation in cohort studies, there was a slight but significant teratogenic risk in case–control studies, which are more sensitive to adverse effects.

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Competing Interests: None declared.

Résumé

Objectif : Compte tenu de la résistance accrue des pathogènes urinaires aux dérivés de la pénicilline, la nitrofurantoïne est couramment utilisée à titre de solution de rechange pour la prise en charge de l'infection des voies urinaires, et ce, en raison de la vaste gamme des organismes tant Gram négatifs que Gram positifs qui y sont sensibles. L'innocuité de l'exposition du fœtus à la nitrofurantoïne demeure controversée.

Méthodes : Nous avons mené une analyse systématique et une méta-analyse afin d'évaluer l'innocuité fœtale de la nitrofurantoïne. Nous avons mené des recherches dans Medline, EMBASE, les références de rapports publiés et des résumés de réunion en vue d'en tirer les études pertinentes. Les articles ont été inclus dans l'analyse s'il s'agissait d'études menées chez l'homme, s'ils faisaient état des issues de grossesse, s'ils traitaient de l'utilisation de nitrofurantoïne au cours du premier trimestre de grossesse et s'ils comprenaient un groupe témoin de grossesses non exposées. Le taux de malformations majeures constituait le critère d'évaluation principal; les taux de craniosynostose, de fente labiale ou palatine, d'anomalies cardiovasculaires et d'hypoplasie du cœur gauche constituaient les critères d'évaluation secondaires.

Résultats : Huit études couvrant un total de 91 115 cas exposés et de 1 578 745 témoins non exposés ont été incluses dans la méta-analyse primaire examinant le risque de malformation majeure. Cinq études de cohorte se sont penchées sur 9 275 nouveau-nés exposés et sur 1 491 933 nouveau-nés non exposés, le tout donnant lieu à un RR global de 1,01 (IC à 95 %, 0,81 - 1,26); toutefois, trois études cas-témoins s'étant penchées sur un total de 39 268 cas de malformations majeures et de 129 394 cas témoins ont donné lieu à un RC global de 1,22 (IC à 95 %, 1,02 - 1,45). Aucune hausse du risque de malformations cardiovasculaires, de fente orale ou de craniosynostose n'a été identifiée. Pour ce qui est de l'évaluation du risque d'hypoplasie du cœur gauche, seuls trois articles étaient admissibles; ces articles ont donné lieu à un RC de 3,07 (IC à 95 %, 1,59 - 5,93).

Conclusion : Bien qu'aucune association n'ait été constatée entre l'exposition du fœtus à la nitrofurantoïne et la manifestation de malformations majeures dans le cadre d'études de cohorte, un risque léger mais significatif de tératogénicité a été constaté dans le cadre d'études cas-témoins (lesquelles sont plus sensibles aux effets indésirables).

INTRODUCTION

Antibacterial agents are the drugs most commonly prescribed in pregnancy, and urinary tract infection (UTI) is one of the most common medical conditions occurring during gestation, with *E. coli* responsible for 90% of cases.[1–3] Untreated UTI in pregnancy may result in significant morbidity for the pregnant woman and her fetus.[4] Because of the increasing resistance of urinary pathogens to penicillin derivatives, nitrofurantoin is a commonly used therapeutic alternative, with a wide range of both Gram negative and positive organisms sensitive to it.[5–7] Nitrofurantoin crosses the placenta very rapidly but in low concentration, and disappears readily from the fetal circulation.[8]

As a consequence of its broad spectrum of antibacterial activity and the high prevalence of UTI in pregnancy, large numbers of women worldwide receive nitrofurantoin during pregnancy. Nitrofurantoin is less appropriate for use during labour and among women with glucose-6-phosphate dehydrogenase deficiency, in whom concerns regarding the potential risk of drug-induced hemolytic anemia have been raised.[9–13]

Over the last three decades, several studies have suggested that nitrofurantoin is not associated with increased teratogenic risk in humans.[9,14–18] However, more recently, several publications have suggested an increased risk of exophthalmia, cardiovascular malformations, and oral cleft and skull anomalies.[19–22]

The objective of this systematic review therefore was to examine whether fetal exposure to nitrofurantoin during early pregnancy is associated with increased rates of major malformations.

METHODS

Search Strategy

We searched Medline for articles published from 1946 to November 30, 2013, and EMBASE for articles published from 1947 to November 30, 2013. The reference sections from retrieved articles were inspected for additional relevant publications. Meeting abstracts and proceedings published between 1980 and November 30, 2013, were also searched for studies in progress or studies not published in the peer-reviewed literature.

Searches and terminology were customized for each database, but in general we used the key words "pregnancy," "birth defects," "teratogen," "embryonic and fetal development," "congenital malformation," both in isolation and combined using the "OR" operator. The intersection of this search with articles retrieved by using the key word "nitrofurantoin" and its different commercial names comprised the final set of articles retrieved for evaluation.

Two investigators familiar with clinical study design acted as reviewers, selecting studies for inclusion in the analysis based on our inclusion criteria and following a standardized checklist.

Inclusion Criteria

Studies were included if they were cohort, case–control, or randomized trials that presented data on women exposed and not exposed to nitrofurantoin during the first trimester of pregnancy, as well as data on the total number of major congenital malformations and/or specific malformations. Exposure to nitrofurantoin was defined as exposure to the drug at any dose for any length of time during the first trimester of pregnancy, and the outcomes in exposed women were compared with the outcomes in a control group of women who were not exposed to nitrofurantoin. No restrictions on language, publication date, or publication status were imposed.

Exclusion Criteria

We excluded reviews, letters or commentaries, studies not conducted in humans, studies that did not report pregnancy outcomes, studies that did not report information on malformation rates in a way that could allow data extraction, studies without a control group, and studies that did not report specific exposure to nitrofurantoin during early pregnancy. Initially, the retrieved studies were screened by one investigator for eligibility based on their title or abstract. After identifying the articles for inclusion, the two reviewers independently extracted the relevant data from the text and tables, and entered these into two-by-two tables. Separate tables were created for all major congenital malformations and for specific major malformations, including cardiac malformations, atrial and ventricular septal defects, musculoskeletal malformations, anomalies of the eye, congenital anomalies of the skull and face bones or craniosynostosis, cleft lip or palate anomalies, and others. In cases of disagreement between the two reviewers about inclusion or data extraction, the differences were settled by discussion and consensus.

Relevant outcome data were tabulated in two-by-two tables. Statistical analysis of the extracted data was carried out using RevMan 5.1 (Cochrane IKMD, Copenhagen, Denmark).

Study data were summarized, and individual and pooled odds ratios and 95% confidence intervals were calculated