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REVIEW

The Safety of Histamine 2 (H2) Blockers in Pregnancy: A Meta-analysis

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Abstract Heartburn and acid reflux increase the severity of nausea and vomiting of pregnancy, and may lead to more serious medical conditions. The fetal safety of histamine 2 (H2) blockers, the most common antireflux medication, during pregnancy needs to be determined. The aim herein is to determine the fetal safety of H2 blockers during pregnancy through systematic review. All original research assessing the safety of H2 blockers in pregnancy was sought. Data included congenital malformations, spontaneous abortions, preterm delivery, and small for gestational age. A random-effects model combined results. With data from 2,398 exposed and 119,892 nonexposed to H2 blockers, overall odds ratio was 1.14 [0.89, 1.45]. Further analysis revealed no increased risks for spontaneous abortions, preterm delivery, and small for gestational age with odds ratios and 95% confidence intervals (CIs) of 0.62 [0.36–1.05], 1.17 [0.94, 1.147], and 0.28 [0.06, 1.22], respectively. H2 blockers can be used safely in pregnancy.

Keywords H2 blockers · Acid reflux · GERD · Pregnancy · Malformations

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Introduction

Heartburn and/or acid reflux (HB/RF) are common medical disorders; various studies have estimated that incidence of gastroesophageal reflux disorders (GERD) in pregnancy ranges between 40% and 85% [1–5]. The onset of HB/RF can occur any time during pregnancy: in one study of 88 pregnant women, more than half (52%) of symptoms began in the first trimester and almost all (40%) by the second trimester, with only 8% of symptoms beginning in the third trimester [6]. Other studies, however, report increased severity and frequency of symptoms as gestational age increases [7, 8]. Regardless of time of onset, anecdotal and clinical evidence suggests that presence of pre-existing gastrointestinal (GI) conditions and/or symptoms as well as HB/RF during pregnancy result in increased stomach upset including symptoms ranging from acidity, constipation, diarrhea, indigestion, flatulence, bloating, epigastric pain, nausea, and vomiting [2, 3]. Heartburn in pregnancy is also associated with increased risk for GERD during pregnancy [9]. Furthermore, a more recent study has demonstrated that heartburn during pregnancy may also result in increased prevalence of GERD postpartum as well even after adjustment for confounders including weight change and body mass index [10].

Treatment of HB/RF in pregnancy is important for management of symptoms, as well to reduce nausea and vomiting of pregnancy (NVP). In a recent study, we have demonstrated that pregnant women suffering from HB/RF ($n = 194$) experience increased severity of NVP compared with pregnant women who do not experience HB/RF ($n = 188$) as measured by the validated Pregnancy Unique Quantification of Emesis (PUQE) scale and the Well-Being (WB) scale [11]. Therefore, by managing HB/RF, there can be a significant improvement in the quality of life of a

pregnant woman. Treatment of HB/RF initially entails minor lifestyle and diet modifications such as sleeping elevated and avoiding acid-containing foods. Pharmacological therapy consists of calcium and magnesium antacids; however, as symptoms worsen, alternate medications may be required including histamine 2 (H2) blockers or proton pump inhibitors (PPIs). Importantly, though, pharmacotherapy during fetal development must be based on medications that will not adversely affect fetal well-being.

Several small studies have been conducted to determine the safety of H2 blockers in pregnancy; however, their limited sample sizes preclude definitive demonstration on the fetal safety of this class of medication. The aim of the present study was to systematically review studies evaluating the safety of H2 blockers to determine overall fetal safety of H2 blockers in pregnancy.

Methods

A literature search was conducted to identify all published articles examining the safety of H2 blockers in pregnancy. The inclusion criteria consisted of all original research articles written in any language involving at least the first trimester of pregnancy exposure of an H2 blocker with the presence of a comparison group unexposed to H2 blockers, and description of outcome in terms of congenital malformations.

Searches were conducted using the following electronic databases: MEDLINE, Embase, International Pharmaceutical Abstracts, all EBM Reviews, and Cumulative Index to Nursing and Allied Health Literature. Each of these databases was searched from inception to January 2008 using the following search terms: H2 blockers, H2 antagonists, H2, birth defect, fetal abnormality, teratogenicity, malformation, Zantac (ranitidine), Pepcid (famotidine), Tagamet (cimetidine), Axid (nizatidine). In addition, references from retrieved studies and reviews were searched for further papers not captured by our search strategy.

Two independent reviewers performed article selection, and disagreements were resolved through consensus. Based on the inclusion and exclusion criteria, studies were selected that specifically examined the rate of congenital malformations after maternal exposure to H2 blockers.

Data extracted from selected articles included rate of congenital malformations, spontaneous abortions, premature delivery, and birth-weight.

Individual quality scores of accepted articles were determined by the validated Downs–Black scale [12]. This scale allows for quality scoring of randomized control trials and observational studies by assessing study quality of reporting, external and internal validities, bias, confounders, and power with a possible total score of 32.

Outcomes from included articles were pooled and weighted, and combined using a random-effects model. Data were analyzed using Cochrane's Review Manager version 4.1.1. Odds ratios and 95% confidence intervals were calculated. Publication bias was assessed with the use of a funnel plot. Heterogeneity of effects was assessed using the Q statistic.

Results

We retrieved 906 articles for potential analysis. After reviewing the titles and abstracts and excluding studies that did not include information regarding the safety of H2 blockers in pregnancy, 13 were selected for closer assessment. Four were excluded because they did not contain usable, extractable or relevant data, and an additional four were excluded because the study did not contain control groups. One article was excluded also because a portion of exposed women and controls were obtained from a site that had published a study already included in our analysis. Therefore, four articles were included in our analysis [13–16].

Of the studies selected, two were prospective cohorts and two were retrospective cohorts (Table. 1).

The average quality score was 70 ± 0.04%, which is considered to be on the border of "fair" and "good" quality. The funnel plot (data not shown) was symmetrical, indicating the absence of publication bias. The Q-statistic for heterogeneity of effects was nonsignificant ($\chi^2 = 3.44$, $p = 0.33$), rendering the data combinable.

Data from a total of 2,398 exposed and 119,892 unexposed controls were included in the meta-analysis. Using a random-effects model, odds ratio and 95% CI for incidence of congenital malformations after in utero exposure to H2 blockers was 1.14 [0.89, 1.45] (Fig. 1). Based on 738

Table 1 Characteristics of included studies

Study (year)	Study type	Number of subjects		Included data
		Exposed	Not exposed	
Garbis (2005)	Prospective cohort	553	1,390	BW, SA, Pre
Matok (2008)	Retrospective cohort	1,148	116,812	Pre
Magee (1996)	Prospective cohort	142	143	BW, SGA, SA, Pre
Ruigomez (1999)	Retrospective cohort	555	1,547	SGA, SA, Pre

BW birth-weight, *SGA* small for gestational age (<3rd centile), *SA* spontaneous abortions, *Pre* premature delivery (<36 weeks gestation)

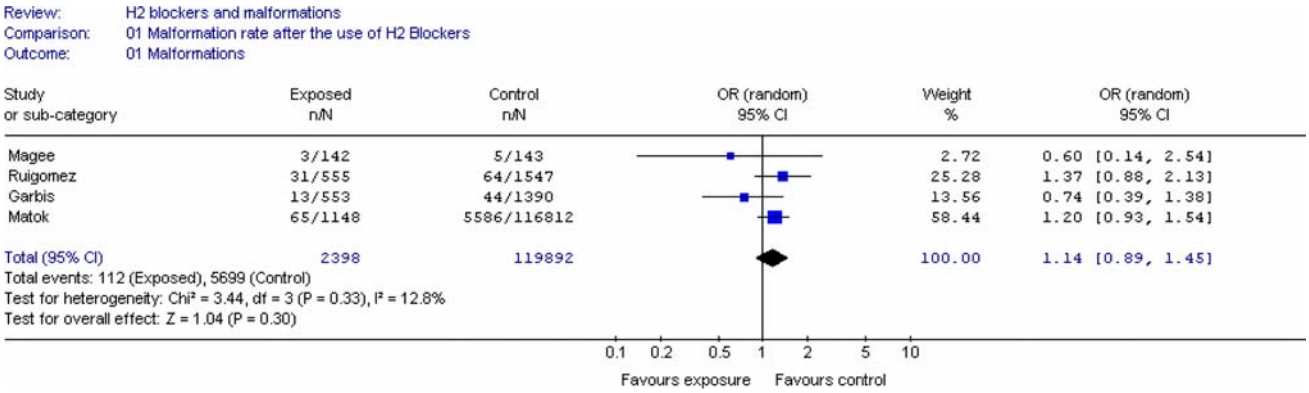

Fig. 1 Overall effect of the incidence of congenital malformations after in utero exposure to H2 blockers

exposures and 1,575 unexposed controls from two studies, the odds ratio for the incidence of spontaneous abortions after in utero exposure to H2 blockers was 0.62 [0.36, 1.05]. Odds ratio for incidence of preterm delivery from 2,421 exposures and 119,072 unexposed controls from four studies was 1.17 [0.94, 1.47], and for the incidence of small for gestational age from 611 exposures and 794 unexposed controls from two studies was 0.28 [0.06, 1.22].

Discussion

This meta-analysis based on 2,398 H2-blocker-exposed and 119,892 unexposed controls demonstrated that use of H2 blockers is not associated with an increased risk for congenital malformations. The 95% confidence intervals were very tight, suggesting that it is unlikely that a beta error may contribute to the lack of a significant effect. Furthermore, secondary analysis revealed no apparent increased risks for spontaneous abortions, preterm delivery, and small for gestational age. In fact, based on our findings, H2 blockers appear to have a trend towards a protective effect with respect to spontaneous abortions and small for gestational age.

Although only four studies were included in this meta-analysis, including one large study, the funnel plot did not reveal concerns related to publication bias, and the included studies were homogeneous, making the data from the four studies combinable. Furthermore, based on the overall acceptable quality of the studies included in this meta-analysis as assessed by using the validated Downs–Black scale, the results obtained are reassuring with respect to the safety of the use of H2 blockers in pregnancy, especially considering the large sample size. Additionally, our results are consistent with previous findings that suggest that H2 blockers are not associated with an increased risk for malformations [17–21].

Our data suggest that H2 blockers can be considered safe in managing heartburn and acid reflux in pregnancy, especially to prevent increased severity of NVP and the potential for GERD.

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References

1. Baron T, Ramirez B, Richter J. Gastrointestinal motility disorders in pregnancy. *Ann Intern Med*. 1993;118(5):366–375.
2. Ali R, Egan L. Gastroesophageal reflux disease in pregnancy. *Best Pract Res Clin Gastroenterol*. 2007;21(5):793–806. doi:10.1016/j.bpg.2007.05.006.
3. Broussard C, Richter J. Treating gastro-oesophageal reflux during pregnancy and lactation: what are the safest therapy options? *Drug Saf*. 1998;19(4):325–337. doi:10.2165/00002018-199819040-00007.
4. Mahadevan U. Gastrointestinal medications in pregnancy. *Best Pract Res Clin Gastroenterol*. 2007;21(5):849–877. doi:10.1016/j.bpg.2007.06.002.
5. Richter J. Review article: The management of heartburn in pregnancy. *Aliment Pharmacol Ther*. 2005;22:749–757. doi:10.1111/j.1365-2036.2005.02654.x.
6. Castro L. Reflux esophagitis as the cause of heartburn in pregnancy. *Am J Obstet Gynecol*. 1967;98:1–10.
7. Marrero J, Goggin P, de Caestecker J, Pearce J, Maxwell J. Determinants of pregnancy heartburn. *Br J Obstet Gynaecol*. 1992;99:731–734.
8. Everson G. Gastrointestinal motility in pregnancy. *Gastroenterol Clin North Am*. 1992;21(4):751–756.
9. Rey E, Rodriguez-Artalejo F, Herraiz M, et al. Gastroesophageal reflux symptoms during and after pregnancy: a longitudinal study. *Am J Gastroenterol*. 2007;102:2395–2400. doi:10.1111/j.1572-0241.2007.01452.x.
10. Bor S, Kitapcioglu G, Dettmar P, Baxter T. Association of heartburn during pregnancy with the risk of gastroesophageal reflux disease. *Clin Gastroenterol Hepatol*. 2007;5(9):1035–1039. doi:10.1016/j.cgh.2007.05.003.
11. Gill SK, Maltepe C, Koren G. The effect of heartburn and acid refux on the severity of nausea and vomiting of pregnancy. *Can J Gastroenterol* (accepted).
12. Downs S, Black N. The feasibility of creating a checklist for the assessment of methodological quality of both randomized and

non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52:377–384.
13. Garbis H, Elefabt E, Diav-Citran O, et al. Mathieu-Nolf M: Pregnancy outcome after exposure to ranitidine and other H-2 blockers: a collaborative study of the European Network of Teratology Information Services. *Reprod Toxicol*. 2005;19:453–458. doi:10.1016/j.reprotox.2004.09.002.
14. Magee L, Inocencion G, Kamboj L, Rossetti F, Koren G. Safety of first trimester exposure to H2 blockers: a prospective cohort study. *Dig Dis Sci*. 1996;41(6):1145–1149. doi:10.1007/BF02088230.
15. Ruigomez A, Rogriguez L, Cattaruzzi C, et al. Use of cimetidine, omeprazole and ranitidine in pregnant women and pregnancy outcomes. *Am J Epidemiol*. 1999;150(5):476–481.
16. Matok I, Gorodischer R, Koren G, Levy A. The safety of intrauterine exposure to H2-blockers: a study by linking computerized databases. Proceedings of the 11th Congress of the European Society for Developmental Pharmacology. Rotterdam, The Netherlands, June 2008, Abstract 45.
17. Colin Jones DG, Langman MJ, Lawson DH, Vessey MP. Post-marketing surveillance of the safety of cimetidine: twelve-month morbidly report. *Q J Med*. 1985;54:253–268.
18. Kallen B. Delivery outcome after the use of acid-suppressing drugs in early pregnancy with special reference to omeprazole. *Br J Obstet Gynaecol*. 1998;105(8):877–881.
19. Lalkin A, Loebstein R, Addis A, et al. The safety of omeprazole during pregnancy: a multicenter prospective controlled study. *Am J Obstet Gynecol*. 1998;179(3):727–730. doi:10.1016/S0002-9378(98)70072-9.
20. Koren G, Zemlickis D. Outcome of pregnancy after 1st trimester exposure to H2 receptor antagonists. *Am J Perinatol*. 1991;8:37–38.
21. Larson J, Patatanian E, Miner P, Rayburn W, Robinson M. Double-blind, placebo controlled study of ranitidine for gastro-esophageal reflux symptoms during pregnancy. *Obstet Gynecol*. 1997;90(1):83–87. doi:10.1016/S0029-7844(97)00126-9.