

Nikfar S et al. Use of proton pump inhibitors during pregnancy and rates of major malformations. A meta-analysis. *Digestive Diseases and Sciences* 47, 1526-29, 2002

Type of study	<p>Meta-analysis: 5 articles and 1 personal communication included (5 cohort studies: 3 prospective, 2 retrospective)</p> <ul style="list-style-type: none"> - Lalkin A, Loebstein R, Addis A et al. <i>Am J Obstet Gynecol</i> 179, 727-30, 1998 - Kallen B. <i>Br J Obstet Gynaecol</i> 105, 877-81, 1998 - Nielsen GL, Sorensen HT, Thulstrup AM et al. <i>Aliment Pharmacol Ther</i> 13, 1085-89, 1999 - Ruigomez A, Garcia Rodriguez LA, Cattaruzzi C et al. <i>Am J Epidemiol</i> 150, 476-81, 1999 - Moretti M, personal communication <p>Studies were excluded if they did not report on the rates of major malformations, did not include a comparison group of pregnant women not exposed to studied drugs, or did not report on first trimester exposure to the drugs</p>
When	From year of drug release to 2001
Characteristics of the recruited patients	Newborns exposed to the studied drugs with and without major malformations; newborns non-exposed to the studied drugs with and without major malformations
Characteristics of the treated diseases	Lalkin A et al, 1998: reflux esophagitis/heartburn (27%), peptic ulcer (26%), gastritis (19%)
Exposure definition	<ul style="list-style-type: none"> - Intake during the first trimester of pregnancy - Proton pump inhibitors (PPIs): omeprazole, lansoprazole, pantoprazole and other PPIs - Moretti M: median dose: 20mg/day (range 10-80mg/day); mean duration of therapy: 15.3 weeks (range 3days-42 weeks)
Ascertainment of drug exposure	Not indicated
Size of the studies included for meta-analysis	All PPIs: 593 exposed, 15,330 non-exposed newborns Omeprazole only: 534 exposed, 2,003 non-exposed newborns
Malformations definition	Not indicated
Malformations ascertainment	Pregnancy outcome ascertainment with either registry linkage or by direct interview with the mother
Prevalence of malformations among offspring	All PPIs: 5.0% Omeprazole only: 3.8%
Analysis	<ul style="list-style-type: none"> - All included studies pooled and weighted - Data analyzed using Cochrane's Review Manager version 4.1. RR and 95% CI calculated using the Mantel-Haenszel method - Chi-square test used to test for heterogeneity (P=0.94 and 0.89 indicate that the studies could be combined)
Strengths	<ul style="list-style-type: none"> - Ability of the meta-analysis to increase the sample size and the statistical power - Two reviewers independently reviewed the retrieved articles - Evaluation of the study's power analyses
Weaknesses	<ul style="list-style-type: none"> - Combination of well-designed studies with poorly designed ones - Negative studies more likely not published and not identified - Descriptive data on the drugs-exposed women available only from two studies - No description of observed birth defects - No information about ascertainment of drugs exposure, malformations definition, other reproductive end points - Not indicated the excluded studies
Main outcomes	With almost 600 exposed pregnancies (any PPI, most often omeprazole), the summary RR for all major malformations was

1.18 (95% CI 0.7-1.9) (P=0.7). In conclusion, PPIs do not present a major teratogenic risk when used in recommend doses