

Type of study	<p>Meta-analysis:            Studies: 1,902 citations identified, 180 studies selected:            22 included (15 case-control, 6 cohort, 1 randomized control trial) (criteria for inclusion: controlled studies of human populations, prospective/retrospective studies, maternal exposure during the first trimester, full publications):</p> <ul style="list-style-type: none"> <li>- Nelson MM, Forfar JO. <i>BMJ</i> 1, 523-7, 1971</li> <li>- Richards ID. <i>Adv Exp Med Biol</i> 27, 441-55, 1972</li> <li>- Karkinen-Jaaskelainen M, Saxen L. <i>Am J Obstet Gynecol</i> 118, 815-8, 1974</li> <li>- Saxen I. <i>Int J Epidemiol</i> 4, 37-44, 1975</li> <li>- Turner G, Collins E. <i>Lancet</i> 2, 338-9, 1975</li> <li>- Slone D, Siskind V, Heinonen OP et al. <i>Lancet</i> 1, 1373-5, 1976</li> <li>- Newman NM, Correy JF, Dudgeon GI. <i>Aust NZ J Obstet Gynaecol</i> 17, 156-9, 1977</li> <li>- Gierup J, Lundkvist K. <i>Z Kinderchir</i> 28, 39-42, 1979</li> <li>- Winship KA, Cahal DA, Weber JCP et al. <i>Arch Dis Child</i> 59, 1052-60, 1984</li> <li>- Aselton P, Jick H, Milunsky A et al. <i>Obstet Gynecol</i> 65, 451-5, 1985</li> <li>- Zierler S, Rothman KJ. <i>NEJM</i> 313, 347-52, 1985</li> <li>- Werler MM, Mitchell AA, Shapiro S. <i>NEJM</i> 321, 1639-42, 1989</li> <li>- Tikkanen J, Heinonen OP. <i>Eur J Epidemiol</i> 6, 348-56, 1990</li> <li>- Correy JF, Newman NM, Collins JA et al. <i>Aust NZ J Obstet Gynaecol</i> 31, 340-4, 1991</li> <li>- Drongowski RA, Smith RK Jr, Coran AG et al. <i>Fetal Diagn Ther</i> 6, 14-27, 1991</li> <li>- Werler MM, Mitchell AA, Shapiro S. <i>Teratology</i> 45, 361-7, 1992</li> <li>- Lynberg MC, Khoury MJ, Lu X et al. <i>Am J Epidemiol</i> 140, 244-55, 1994</li> <li>- Siffel C, Czeizel AE. <i>Mutat Res</i> 334, 293-300, 1995</li> <li>- Torfs CP, Katz EA, Bateson TF et al. <i>Teratology</i> 54, 84-92, 1996</li> <li>- Martinez-Frias ML, Rodriguez-Pinilla E, Prieto L. <i>Teratology</i> 56, 241-3, 1997</li> <li>- Shaw GM, Todoroff K, Velie EM et al. <i>Teratology</i> 57, 1-7, 1998</li> <li>- Pattison NS, Chamley LW, Birdsall M et al. <i>Am J Obstet Gynecol</i> 183, 1008-12, 2000</li> </ul> <p>158 excluded (criteria for exclusion: uncontrolled studies, case reports/case series of &lt;6 patients, editorials, reviews, animal studies, studies with significant differences between exposed/control groups (ie: other drug therapies), studies with only premature closure ductus arteriosus as a primary outcome, no English language)</p>
When	<p>Medline (1966-2000), Embase (1980-2000), Toxline (1994-2000), EBM Reviews-Cochrane Database of Systematic Reviews (1991-2000).            Medline search repeated in 2001</p>
Characteristics of the recruited patients	<p>Newborns exposed to the studied drug with and without congenital malformations; newborns non-exposed to the studied drug with and without congenital malformations</p>
Characteristics of the treated diseases	<p>Not indicated</p>
Exposure definition	<p>Intake during the first trimester of pregnancy</p>
Ascertainment of drug exposure	<p>Indicated for each study</p>
Size of the studies included for meta-analysis	<p>8 studies-overall risk: 16,138 treatment*, 49,890 control            5 studies-gastroschisis: 261 treatment, 2,449 control            *refers to women exposed to studied drug in cohort studies or affected children in case-control studies*</p>
Malformations definition	<p>Not indicated</p>
Malformations ascertainment	<p>Indicated for each study</p>
Prevalence of malformations among offspring	<p>***</p>
Analysis	<ul style="list-style-type: none"> <li>- Cochrane Review Manager software (version 4.1, Update Software, Oxford) to calculate the pooled OR and 95% CI, using the Mantel-Haenszel method, assuming a random-effect model</li> <li>- Chi-square test used to test for heterogeneity:              8 studies-overall risk were heterogeneous (17.31, df=7, P=0.016);              5 studies-gastroschisis: test for heterogeneity: 4.43, df=4, P=0.35</li> </ul>
Strengths	<ul style="list-style-type: none"> <li>- Ability of the meta-analysis to increase the sample size and the statistical power</li> <li>- Two reviewers independently included the studies and extracted data</li> <li>- Information on ascertainment of drug exposure and outcome</li> <li>- Evaluation of strengths and weaknesses for included studies</li> <li>- Evaluation of the study's power analyses</li> <li>- Information about computerized/manual searches of references</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>- Combination of well-designed studies with poorly designed ones</li> <li>- Negative studies more likely not published and not identified</li> <li>- Studies were heterogeneous</li> <li>- Case-control studies: control infants with no birth defects (risk of recall)</li> </ul>

	<p>bias), possibility of confounding by indication, in one study diagnosis of gastroschisis confirmed in 58% of the cases, other drugs could have contributed to the observed association</p> <ul style="list-style-type: none"> <li>- Cohort studies: studied drug was an over the counter medication (some control subjects could have been exposed to studied drug)</li> <li>- No information about dosage, malformations definition, other reproductive end points</li> </ul>
Main outcomes	<p>In the 8 studies that reported an overall risk, the risk of congenital malformations in offspring of women exposed to aspirin was not significantly higher than that in control subjects (OR 1.33, 95% CI 0.9-1.9). However, a significantly increased risk of gastroschisis (OR 2.37, 95% CI 1.4-3.9) was found (5 case-control studies)</p>