

**Greenland S et al.** Clomiphene citrate and neural tube defects: a pooled analysis of controlled epidemiologic studies and recommendations for future studies. *Fertil Steril* 64, 936-41, 1995

Type of study	<p>Pooled analysis of controlled epidemiologic studies            Studies: 11 identified, 10 included (2 cohort, 8 case-control)            10 included:</p> <ul style="list-style-type: none"> <li>- Kurachi K, Aono T, Minagawa J et al. <i>Fertil Steril</i> 1983, 40, 187-9</li> <li>- Milunsky A, Derby LE, Jick H. <i>Teratology</i> 1990, 42, 467</li> <li>- Cornel MC, ten Kate LP, Dukes MNG et al. <i>Lancet</i> 1989, 1, 1386</li> <li>- Czeizel A. <i>Lancet</i> 1989, 1, 167</li> <li>- Czeizel A, Racz J. <i>Teratology</i> 1990, 42, 505-12</li> <li>- Cuckle H, Wald N. <i>Lancet</i> 1989, 2, 1281</li> <li>- Cuckle H, Wald NJ. <i>Br J Obstet Gynaecol</i> 1982, 89, 547-9</li> <li>- Mills JL, Simpson JL, Rhoads GG et al. <i>Lancet</i> 1990, 336, 103-4</li> <li>- Mills JL. <i>Lancet</i> 1991, 337, 853</li> <li>- Mili F, Khoury MJ, Lu X. <i>Teratology</i> *</li> <li>- Werler MM, Louik C, Shapiro S et al. <i>Lancet</i> 1994, 344, 445-6</li> <li>- Shaw GM, Lammer EJ, Velie EM. <i>Reprod Toxicol</i> 1995, 9, 399-400</li> <li>- Shaw GM, Schaffer D, Velie EM et al. <i>Epidemiology</i> 1995, 6, 219-26</li> <li>- Lammer EJ. <i>Reprod Toxicol</i> 1995, 9, 491-3</li> <li>- Lammer EJ, Cordero JF. <i>JAMA</i> 1986, 255, 3128-32</li> </ul> <p>1 excluded:            - Karabacak RO, Korur C, Celiloglu M. <i>Lancet</i> 1989, 2, 1391-2</p> <p>Not included:            - unpublished studies; studies of ovulation induction that did not report results specific to CC; animal studies</p>
Where	Canada, England, Hungary, Netherlands, Japan, USA
When	1982-1995 (publication of studies) 1994-1995 (literature search)
Characteristics of the recruited patients	<p>Cohort studies: neonates exposed to studied drug with and without neural tube defects (NTD); neonates not exposed to studied drug with and without NTD            Case-control studies: anencephaly, spina bifida, other, not specified (case), considerable differences among the studies in details of case definition and ascertainment; unaffected and other malformations (controls)</p>
Exposure definition	- Timing: 12, 6, 3, 1 months preconception for oral clomiphene citrate (CC) use to count as exposure; periconceptional not further specified; not indicated
Ascertainment of drug exposure	<p>- Considerable differences among the studies in details of exposure timing and ascertainment            - Data source: records (3 studies), interviews (7 studies)</p>
Size of the studies included for pooled-analysis	<p>All studies: 85,797 (1,565 exposed, 84,232 non-exposed):            - Case-control: 3800 cases, 28,274 controls            - Cohort: 1,373 exposed, 52,350 non-exposed</p>
Malformations definition	Anencephaly, spina bifida, other, not specified
Malformations ascertainment	<p>- Data source: records (3 studies), interviews (7 studies)**            - Case source: cohort (2 studies), hospital records (1 study), registry or surveillance program (6 studies), mixed sources (1 study)</p>
Prevalence of malformations among offspring	<p>% NTD in the control groups (2 cohort studies) :            Kurachi et al: 0.27%            Milunsky et al: 0.21%</p>
Prevalence of exposure	(case-control studies)

among controls	<ul style="list-style-type: none"> <li>- Cornel MC et al: 0.8%</li> <li>- Czeizel A et al: 0.06%</li> <li>- Cuckle H et al: 2.3%</li> <li>- Mills JL et al: 1.6%</li> <li>- Mili F et al: 0.6%</li> <li>- Werler MM et al: 2.3%</li> <li>- Shaw GM et al: 0.7%</li> <li>- Lammer EJ et al: 1.2%</li> </ul> <p>Overall : 1.2%</p>
Analysis	<ul style="list-style-type: none"> <li>- Summary and for each study prevalence ratio and 95% CI were estimated (and for cohort vs case-control studies, for studies obtaining CC data from records vs interviews, for Europe vs United States and Japan), (contingency table statistics and logistic regression)</li> <li>- Homogeneity among studies was tested: the heterogeneity test was not significant P=0.16</li> </ul>
Strengths	<ul style="list-style-type: none"> <li>- Ability of the pooled analysis to increase the sample size and the statistical power</li> <li>- Relating to ovulation induction, positive and negative results were of equal interest to researchers and editors (reduced risk of publication bias)</li> <li>- Evaluation of the pooled estimate considering also 3 very small unpublished studies</li> </ul>
Weaknesses	<ul style="list-style-type: none"> <li>- Combination of well-designed studies with poorly designed ones</li> <li>- None of the studies had enough power or precision to discriminate between no effect and small effects</li> <li>- No detailed information about type of controls</li> <li>- Seven studies relied on interviews or questionnaire information to detect exposure (risk of recall bias)</li> <li>- Only two studies reported estimates adjusted for potentially confounding variables</li> <li>- Only one study attempted direct control of subfertility/infertility history</li> <li>- Not controlled for other fertility drugs, no detailed information on exposure timing and dosage, other reproductive end points, no information and control for folic acid use</li> <li>- Not indicated if the interviewers were aware of the case and control status</li> <li>- Czeizel: differential response rates (80% cases vs 67% controls)</li> <li>- Cornel: no concurrent control group</li> <li>- Mills: matched on prenatal alfafetoprotein screening status, but no matched analysis of CC and NTD</li> <li>- Werler and Lammer: malformed controls; several malformations excluded (risk of selection bias if any of the remaining control malformations associated with CC use)</li> </ul>
Main outcomes	<p>The estimated ratio of NTD prevalence among CC exposed versus unexposed pregnancies ranged from 0.55 to 5.73 among the studies, but the variation was compatible with random fluctuation. The estimated summary prevalence ratio was 1.08 (95% CI 0.8-1.5)</p>

