

Addis A et al. Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. *Psychological Medicine* 30, 89-94, 2000

Type of study	<p>Meta-analysis: Studies: 31 identified (published/unpublished reports) 4 included (cohort studies: 4 prospective: 2 controlled, 2 uncontrolled) (criteria for inclusion: human exposure to any dosage of studied drug during the first trimester of pregnancy, prospective report of outcome of pregnancy) - Pastuszak A, Schick-Boschetto B, Zuber C et al. <i>JAMA</i> 269, 2246-8, 1993 - Brunel P, Vial T, Roche I et al. <i>Therapie</i> 49, 117-22, 1994 - Chambers CD, Johnson KA, Dick LM et al. <i>NEJM</i> 335, 1010-15, 1996 - McElhatton PR, Garbis HM, Elefant E et al. <i>Reproductive Toxicology</i> 10, 285-94, 1996 27 excluded (criteria for exclusion: retrospective exposure): - not original studies: -Cooper GL. <i>Br J Psychiatry</i> 3, 77-86, 1988 - Matthews DA, Manu P, Lane TJ. <i>Am J Medical Science</i> 302, 269-77, 1991 - Rand EH. <i>Am Family Physician</i> 43, 847-54, 1991 - De Cuyper G, Rombaut P, Van Moffaert M. <i>Acta Neuropsychiatrica</i> 4, 77-85, 1992 - Schwartz JT, Brotman AW. <i>Drugs</i> 44, 981-92, 1992 - Anonymous. <i>Int J Gynaecol Obstet</i> 43, 203-11, 1993 - Altshuler LL, Szuba MP. <i>Neurologic Clinics</i> 12, 613-35, 1994 - Edwards JG. <i>Prescribers' J</i> 34, 197-204, 1994 - Kacew S. <i>Int J Clinical Pharmacology Therapeutics</i> 32, 335-43, 1994 - Mortola JF. <i>Drug Safety</i> 10, 160-9, 1994 - Nightingale SL. <i>JAMA</i> 271, 1067, 1994 - Lee A, Donaldson S. <i>Pharmaceutical J</i> 254, 87-90, 1995 - Schorr SJ, Richardson D. <i>Obstet Gynecol Clinics North American</i> 22, 369-83, 1995 - Altshuler LL, Cohen L, Szuba MP et al. <i>Am J Psychiatry</i> 153, 492-606, 1996 - Miller LJ. <i>Primary Care Update Obstet Gynecol</i> 3, 79-86, 1996 - case reports: - Sichel DA, Cohen LS, Dimmock JA et al. <i>J Clinical Psychiatry</i> 54, 156-9, 1993 - Spencer MJ. <i>Pediatrics</i> 92, 721-2, 1993 - Livingston JC, Johnstone WM, Hadi HA. <i>Am J Perinatol</i> 11, 116-8, 1994 - Franko D, Hilsinger E. <i>Harvard Review Psychiatry</i> 2, 282-7, 1995 - Vendittelli F, Alain J, Nouvaille Y et al. <i>Eur J Obstet Gynecol Reprod Biol</i> 38, 85-6, 1995 - retrospective cohorts: - Edwards JG, Inman WH, Wilton L et al. <i>Br J Psychiatry</i> 164, 387-95, 1994 - Rosa F. <i>Reproductive Toxicology</i> 8, 444-5, 1994 - letters/abstracts followed by full articles: - Schick-Boschetto B, Zuber C. <i>Teratology</i> 45, 460, 1992 - Chambers CD, Johnson KA, Jones KL. <i>Teratology</i> 47, 386, 1993 - Goldstein DJ, Marvel DE. <i>JAMA</i> 270, 2177, 1993 - Nulman I, Koren G. <i>Teratology</i> 53, 304-8, 1996 - exposure during the third trimester only: - Goldstein DJ. <i>J Clinical Psychopharmacology</i> 15, 417-20, 1995</p>
When	1988-1996
Characteristics of the recruited patients	Newborns exposed to the studied drug with and without major malformations; newborns non-exposed to the studied drug with and without major malformations
Characteristics of the treated diseases	Not indicated
Exposure definition	Intake during the first trimester of pregnancy

Ascertainment of drug exposure	Not indicated
Size of the studies included for meta-analysis	367 exposed women;
Malformations definition	Major malformations: abnormalities resulting from abnormal formation of tissue leading to a compromise of function or requiring surgical correction
Malformations ascertainment	Not indicated
Prevalence of malformations among offspring	1-3% of all pregnancies (Stevenson, 1993)
Analysis	<ul style="list-style-type: none"> - Cohort studies with/without control groups pooled to calculate the meta-analytical weighted average of foetal risk for major malformations (data combined using a random effects model, modified for use with single groups) - For cohort studies with control groups a Mantel-Haenszel summary OR and 95% CI calculated - The test of homogeneity: $X^2=0.81$, $df=3$, $P=0.85$ showed that all studies detected an effect size of similar magnitude and direction
Strengths	<ul style="list-style-type: none"> - Ability of the meta-analysis to increase the sample size and the statistical power - Included only prospective studies - Evaluation of the study's power analyses - Information about computerized/manual searches of references - Description of observed birth defects
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 - No information about ascertainment of drug exposure and malformations, other reproductive end points - Possibility of confounding by indication (two studies without controls) - Small number of studies
Main outcomes	The use of fluoxetine during the first trimester of pregnancy is not associated with measurable teratogenic effects in human. Combination of controlled/uncontrolled studies shows a weighted risk of 2.6% (95% CI 1.0-4.2%). The summary OR from the two controlled studies (OR 1.33, 95% CI 0.5-3.6) was not significant