ONLINE SUPPLEMENT

Table DS1 Characteristics of excluded studies				
Study	Description	Results	Reason for exclusion	
Chambers et al ²⁷	225 pregnant women taking fluoxetine were compared with unexposed pregnant women	Incidence of three or more minor anomalies was significantly higher in infants exposed to fluoxetine, although there was no increased risk of major fetal anomalies	Data for paroxetine from this data-set included in Einarson <i>et al</i> ¹⁶	
Cole et al ²⁸	Data used from United Healthcare, originally collected for bupropion	Significantly increased occurrence of congenital malformation following first-trimester exposure to paroxetine as compared with other antidepressants	No unexposed control group available	
Diav-Citrin et al ²⁹	Data from Teratogen Information Services in Israel and Italy	Cardiac malformations are more frequent with paroxetine	Data for paroxetine from this data-set included in Diav-Citrin et al^{15}	
Einarson et al ³⁰	1243 women from prospectively collected data exposed to antidepressant were compared with matched controls (1243)	As a group or individual, no antidepressants are associated with an increased risk for major malformations	No separate data available for paroxetine Possibility of repletion of data from Einarson <i>et al</i> ¹⁶	
Einarson et al ³¹	Outcome of pregnancy of 150 women exposed to venlafaxine was compared with that of pregnant women who received SSRIs (150) and who received non-teratogenic drugs (150)	Use of venlafaxine during pregnancy does not increase the rate of major malformations above the baseline rate of 1–3%	Data for paroxetine from this data-set included in Einarson <i>et al</i> ¹⁶	
Ericson et al ³²	969 women from Swedish Medical Birth Register with reported use of antidepressants in early pregnancy	No increase in congenital abnormalities observable in perinatal period	Data for paroxetine and other SSRIs from this data-set included in Kallen $\&\ Ollauson^7$	
Goldstein <i>et al³³</i>	Outcome of 796 pregnancies with first-trimester exposure to fluoxetine, registered in Eli Lilly database was compared with historic reports	Maternal fluoxetine use in first trimester is unlikely to increase the risk of fetal malformations	No data for paroxetine and other antidepressants available No controls	
Hendrick et al ³⁴	Birth outcomes of 138 women who were treated with SSRIs during pregnancy	Incidence of congenital anomalies was 1.4%, comparable to general population rates	No control group No data for first trimester use of SSRIs No separate data for paroxetine	
Kallen & Olausson ⁷	6555 infants exposed to SSRIs were compared with general population	Paroxetine was found to be significantly associated with cardiovascular defects	Data for paroxetine from this data-set included in Reis & Kallen $^{\rm 17}$	
Kulin et al ³⁵	Outcome of 267 women exposed to SSRIs during first trimester was compared with that of unexposed controls	Exposure to SSRI is not associated with increased risk for major malformations, miscarriage, stillbirth or prematurity	Data for paroxetine form this data-set has been included in Einarson <i>et al</i> ¹⁶	
GlaxoSmithKline ³⁶	Women who were dispensed bupropion during their first trimester were compared with women who were dispensed other antidepressants	Prevalence of cardiovascular malformations following paroxetine exposure is 2% No risks with other antidepressants	No unexposed control group available	
Lennestal & Kallen ³⁷	Data from Swedish Medical Birth Register. Outcome of 732 women on recently introduced antidepressants (SNRI/NRI) in early pregnancy, compared with that of all deliveries in the population	No increased risk for stillbirths or congenital malformations	Data for paroxetine from this data-set included in Kallen & Ollauson ⁷	
Merlob et al ³⁸	All newborns with cardiac murmurs screened by echocardiography	Newborns exposed <i>in utero</i> to SSRIs have a twofold higher risk of mild non-syndromal heart defects than unexposed controls	All cardiac defects were mild and not of clear clinical significance Different methodology	
Ramos et al ³⁹	A case–control study including women who used antidepressants during pregnancy Cases defined as major congenital malformations in offspring	No association between duration of antidepressant use in first trimester and increased risk of major congenital malformations	Data from this data-set included in Berard <i>et al</i> ⁸	
Simon et al ⁴⁰	Infants exposed to tricyclic antidepressants and SSRIs prenatally were compared with unexposed matched controls (USA)	Neither tricyclic antidepressant nor SSRI exposure was significantly associated with congenital malformations	No separate data available for paroxetine and other SSRIs	

Table DS1 Characteristics of excluded studies (continued)				
Study	Description	Results	Reason for exclusion	
Sivojelezova et al ⁴¹	Outcome of 132 pregnant women from Teratology Information Centre (Canada) with citalopram use was compared with that of a matched disease-control group	Citalopram use in first trimester is not associated with major teratogenic risk	Data for paroxetine from this data-set included in Einarson <i>et al</i> ¹⁶	
Schleomp et al ⁴²	Data from Teratology Information Services (Germany) for 119 women on paroxetine during pregnancy were compared with that of 645 women who did not use antidepressants during pregnancy	Three congenital anomalies among infants born to women with paroxetine; none of them were cardiovascular anomalies	Data for paroxetine from the same data-set included in Einarson et al^{16}	
Wilton <i>et al</i> ⁴³	In GP setting (UK) outcome of 2511 pregnancies was reported, where newly marketed drug had been taken during the pregnancy	The proportion of infants with congenital abnormality born to mothers exposed to newly marketed drugs in the first trimester is similar to the national statistic	No cardiovascular malformation in women exposed to antidepressants	

GP, general practice; NRI, noradrenaline reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitors; SSRI, selective serotonin reuptake inhibitor.

Additional references

- 27 Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. N Engl J Med 1996; 335: 1010–5.
- 28 Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the first trimester and the prevalence of congenital malformation. *Pharmacoepidemiol Drug Saf* 2007; 16: 1075–85.
- 29 Diav-Citrin O, Shechtman S, Weinbaum D, Arnon J, Di Gianantonio E, Clementi M, et al. Paroxetine and fluoxetine in pregnancy: controlled study (abstract). *Reprod Toxicol* 2005; 20: 459.
- **30** Einarson A, Choi J, Einarson TR, Koren G. Incidence of major malformations in infants following antidepressant exposure in pregnancy: results of a large prospective cohort study. *Can J Psychiatry* 2009; **54**: 242–6.
- **31** Einarson A, Fatoye B, Sarkar M, Lavigne SV, Brochu J, Chambers C, et al. Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001; **158**: 1728–30.
- **32** Ericson A, Kallen B, Wiholm BE. Delivery outcome after the use of antidepressants in early pregnancy. *Eur J Clin Pharmacol* 1999; **55**: 503–8.
- **33** Goldstein DJ, Corbin LA, Sundell KL. Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997; **89**: 713–8.
- 34 Hendrick V, Smith LM, Suri R, Hwang S, Haynes D, Altshuler L. Birth outcomes after prenatal exposure to antidepressant medication. Am J Obstet Gynecol 2003; 188: 812–5.
- **35** Kulin NA, Pastuszak A, Sage SA, Schick-Boschetto B, Spivey G, Feldkamp M, et al. Pregnancy outcome following maternal use of the

new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998; **279**: 609–10.

- **36** GlaxoSmithKline. Epidemiology Study: Final Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations. Final Report (Study No: EPIP083). GlaxoSmithKline, 2008.
- 27 Lennestal R, Kallen B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. J Clin Psychopharmacol 2007; 27: 607–13.
- 38 Merlob P, Birk E, Sirota L, Linder N, Berant M, Stahl B, et al. Are selective serotonin reuptake inhibitors cardiac teratogens? Echocardiographic screening of newborns with persistent heart murmur. Birth Defects Res A Clin Mil Teratol 2009; 85: 837–41.
- **39** Ramos E, St-André M, Rey E, Oraichi D, Bérard A. Duration of antidepressant use during pregnancy and risk of major congenital malformations. *Br J Psychiatry* 2008; **192**: 344–50.
- 40 Simon GE, Cunningham ML, Davis RL. Outcomes of prenatal antidepressant exposure. *Am J Psychiatry* 2002; **159**: 2055–61.
- **41** Sivojelezova A, Shuhaiber S, Sarkissian L, Einarson A, Koren G. Citalopram use in pregnancy: prospective comparative evaluation of pregnancy and fetal outcome. *Am J Obstet Gynaecol* 2005; **193**: 2004–9.
- **42** Schloemp S, Paulus WE, Sterzik K, Stoz F. Congenital malformations after antidepressant medication with paroxetine in early pregnancy? *Hum Reprod* 2006; **21** (suppl 1): 112.
- **43** Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol* 1998; **105**: 882–9.