

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684-92.

Supplementary Table 1. Associations between Maternal Use of Any SSRI and Birth Defects Stratified by Prepregnancy Obesity.*

Birth Defect	No SSRI			SSRI				P-value mult. interaction
	Not obese [†]		Obese Crude OR (95% CI)	Not obese		Obese		
	No.	No.		No.	Crude OR (95% CI)	No.	Crude OR (95% CI)	
No major defects (control infants)	3241	559		70		13		
Anencephaly	161	29	1.0 (0.7-1.6)	7	2.0 (0.8-4.5)	2		‡
Spina bifida	310	110	2.1 (1.6-2.6)	1		5	4.0 (1.1-12.1)	‡
Conotruncal heart defects	712	157	1.3 (1.0-1.6)	15	1.0 (0.5-1.7)	10	3.5 (1.4-8.7)	0.05
Septal heart defects	1423	317	1.3 (1.1-1.5)	27	0.9 (0.5-1.4)	16	2.8 (1.3-6.4)	0.04
Right ventricular outflow tract obstruction	480	120	1.4 (1.2-1.8)	12	1.2 (0.6-2.2)	4	2.1 (0.5-6.7)	0.75
Left ventricular outflow tract obstruction	513	115	1.3 (1.0-1.6)	10	1.0 (0.4-1.8)	4	1.9 (0.4-6.3)	0.45
Cleft lip with or without palate	882	157	1.0 (0.8-1.3)	13	0.7 (0.3-1.2)	8	2.3 (0.8-5.9)	0.03
Cleft Palate alone	476	100	1.2 (0.9-1.5)	9	0.9 (0.4-1.8)	2	1.0 (0.1-4.6)	0.98
Esophageal atresia	232	40	1.0 (0.7-1.4)	7	1.4 (0.5-3.1)	2	2.1 (0.2-9.6)	0.62
Anorectal atresia	298	74	1.4 (1.1-1.9)	8	1.2 (0.5-2.6)	0		‡
Hypospadias, 2 nd or 3 rd degree	661	114	1.1 (0.9-1.4)	7	0.5 (0.2-1.1)	7	2.2 (0.7-6.9)	0.04
Transverse limb deficiencies	263	53	1.2 (0.8-1.6)	6	1.1 (0.4-2.4)	2		‡
Craniosynostosis	338	59	1.0 (0.7-1.3)	15	2.0 (1.1-3.7)	8	5.9 (2.4-14.3)	0.06
Omphalocele	132	28	1.2 (0.8-1.9)	6	2.1 (0.9-4.9)	4	7.5 (2.4-23.4)	0.15
Diaphragmatic hernia	219	53	1.4 (1.0-1.9)	9	1.9 (0.8-3.9)	1		‡
Gastroschisis	378	12	0.2 (0.1-0.3)	10	1.2 (0.6-2.4)	1		‡

* SSRI use is reported for the period from 1 month before to 3 months after conception. Data are taken from the National Birth Defects Prevention Study for the period 1997 through 2002. Obesity defined as weight (kg) divided by height (m) squared, 30 or greater. SSRI denotes selective serotonin reuptake inhibitor, mult. multiplicative, OR odds ratio, and CI confidence interval. Infants whose mothers had prepregnancy diabetes mellitus type 1 or 2 are excluded.

† Reference category.

‡ Multiplicative interaction not calculated due to sparse cells (≤ 2 exposed cases)

Supplementary Table 2. Associations between Maternal Use of Any SSRI and Isolated Birth Defects.*

Birth Defect	No. of infants	No. exposed	Crude Analysis	Adjusted Analysis [†]	
			OR (95% CI)	OR (95% CI)	P-value
No major defects (control infants)	4092	83			
Anencephaly	194	9	2.4 (1.1-4.7)	2.6 (1.2-5.6)	0.02
Spina bifida	410	5	0.6 (0.2-1.4)	0.5 (0.2-1.5)	0.25
Conotruncal heart defects	818	17	1.0 (0.6-1.8)	1.1 (0.6-1.8)	0.74
Septal heart defects	1563	31	1.0 (0.6-1.5)	1.0 (0.6-1.5)	0.34
Right ventricular outflow tract obstruction	610	15	1.2 (0.7-2.1)	1.3 (0.7-2.3)	0.36
Left ventricular outflow tract obstruction	610	11	0.9 (0.4-1.7)	0.8 (0.4-1.6)	0.70
Cleft lip with or without palate	994	20	1.0 (0.6-1.6)	0.8 (0.5-1.5)	0.61
Cleft palate alone	504	10	1.0 (0.5-1.9)	0.9 (0.5-1.8)	0.79
Anorectal atresia	182	4	1.1 (0.4-3.0)	0.8 (0.2-2.7)	0.77
Hypospadias, 2 nd or 3 rd degree	754	13	0.8 (0.4-1.5)	0.7 (0.4-1.4)	0.35
Transverse limb deficiencies	292	8	1.4 (0.5-2.9)	1.4 (0.7-3.1)	0.31
Craniosynostosis	387	22	2.9 (1.8-4.7)	2.5 (1.5-4.2)	<0.001
Omphalocele	100	4	2.0 (0.7-5.7)	1.6 (0.5-5.4)	0.41
Diaphragmatic hernia	236	8	1.7 (0.8-3.5)	1.5 (0.7-3.5)	0.25
Gastroschisis	379	11	1.4 (0.7-2.7)	1.4 (0.7-2.8)	0.27

* SSRI use is reported for the period from 1 month before to 3 month after conception. Data are taken from the National Birth Defects Prevention Study for the period from 1997 through 2002. SSRI denotes selective serotonin reuptake inhibitor, OR odds ratio, and CI confidence interval.

[†] Odds ratios are adjusted for maternal race or ethnic group, maternal obesity, maternal smoking and family income. Infants whose mothers had prepregnancy diabetes mellitus type 1 or 2 are excluded.

Supplementary Table 3. Associations between Maternal Use of Fluoxetine, Sertraline or Paroxetine and Birth Defects*

Birth Defect	No. of infants	Fluoxetine		Sertraline		Paroxetine	
		No.	Adjusted [†] OR (95% CI)	No.	Adjusted [†] OR (95% CI)	No.	Adjusted [†] OR (95% CI)
No major defects (control infants)	4092	29		32		18	
Anencephaly	214	0		4	3.2 (1.1-9.3)	5	5.1 (1.7-15.3)
Spina bifida	457	1		5	1.2 (0.4-3.5)	0	
Conotruncal heart defects	977	6	0.9 (0.4-2.3)	9	1.3 (0.6-2.7)	7	1.6 (0.7-4.0)
Septal heart defects	1931	17	1.3 (0.7-2.4)	10	0.7 (0.3-1.5)	15	1.7 (0.8-3.5)
Right ventricular outflow tract obstruction	669	4	0.9 (0.3-2.7)	4	0.8 (0.3-2.3)	7	2.5 (1.0-6.0)
Left ventricular outflow tract obstruction	691	6	1.3 (0.5-3.1)	2	0.4 (0.1-1.6)	5	1.3 (0.4-3.8)
Cleft lip with or without palate	1127	7	0.9 (0.4-2.1)	9	0.9 (0.4-2.0)	7	1.3 (0.5-3.1)
Cleft palate alone	620	5	1.1 (0.4-3.0)	3	0.6 (0.2-1.9)	5	1.7 (0.6-4.8)
Esophageal atresia	300	5	2.4 (0.9-6.4)	2		1	
Anorectal atresia	418	1		4	0.7 (0.2-2.8)	2	
Hypospadias, 2 nd or 3 rd degree	823	6	0.8 (0.3-2.0)	5	0.8 (0.3-2.4)	3	0.6 (0.2-2.4)
Transverse limb deficiencies	346	3	1.3 (0.4-4.4)	3	1.2 (0.4-4.0)	2	
Craniosynostosis	432	10	2.8 (1.3-6.1)	6	1.7 (0.7-4.2)	5	2.3 (0.8-6.4)
Omphalocele	181	3	1.7 (0.4-7.3)	3	1.5 (0.4-6.6)	6	8.1 (3.1-20.8)
Diaphragmatic hernia	297	2		4	1.8 (0.6-5.3)	2	
Gastroschisis	413	3	1.0 (0.3-3.5)	3	0.9 (0.3-3.3)	5	2.9 (1.0-8.4)

* Use of fluoxetine, sertraline, and paroxetine is reported for the period from 1 month before to 3 months after conception. Data are taken from the National Birth Defects Prevention Study for the period from 1997 through 2002. OR denotes odds ratio, and CI confidence interval.

† Odds ratios are adjusted for maternal race or ethnic group, maternal obesity, maternal smoking and family income. Infants whose mothers had prepregnancy diabetes mellitus type 1 or 2 are excluded.