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GSK Medicine: Paroxetine
Study No.: EPI40404 (follow-up to EPIP083)
Title: EPIDEMIOLOGY STUDY: Paroxetine in the First Trimester and the Prevalence of Congenital Malformations (Follow-up to Epidemiology Study: Final Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations)
Rationale: This study was an additional cohort analysis using data from the study (EPIP083) "Preliminary Report on Bupropion in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations" and subsequently "Updated Preliminary Report on Bupropion and Other Antidepressants, including Paroxetine, in Pregnancy and the Occurrence of Cardiovascular and Major Congenital Malformations". The Bupropion study was originally undertaken because of a possible signal for cardiovascular defects, in particular those involving ventricular outflow tracts, observed in the GSK Bupropion Pregnancy Registry of uncontrolled spontaneous reports from health-care providers. The original secondary analysis, which was carried out at the request of the FDA following presentation of the Bupropion study data, was conducted to investigate the risk of major congenital malformations for other antidepressants, including paroxetine. The updated analysis expanded the calendar time period of the original study. This expanded analysis focuses specifically on paroxetine in comparison to the other anti-depressants, examining possible residual confounding by maternal characteristics and ensuring appropriate control groups.
Objectives: The objectives of this study were to further characterize women exposed to paroxetine during their first trimester of pregnancy, including an assessment of possible risk factors for congenital malformations that could be associated with paroxetine, and to calculate the prevalence and odds ratios for all congenital malformations and cardiovascular malformations among infants born to women exposed to paroxetine in the first trimester of pregnancy.
Indication: Major depressive disorder/Obsessive-compulsive disorder/Panic disorder/Social anxiety disorder/Generalized anxiety disorder/Post-traumatic stress disorder/Premenstrual dysphoric disorder
Study Investigators/Centers: Research conducted by i3 Drug Safety (formerly Ingenix), A UnitedHealth Group Company.
Research Methods:
Data Source: This study was carried out within the Ingenix Research Data Mart (RDM). The RDM is derived from comprehensive administrative databases of UnitedHealthcare, one of the largest health insurers in the United States. People have UnitedHealthcare coverage either as a direct employment benefit or as a spouse or dependent of the employed subscriber. The RDM contains medical and pharmacy claims data from 27 UnitedHealthcare affiliated health plans, located in the Northeast, South/Southeast, Midwest, and Western United States.
Study Design: The analysis was a retrospective cohort study of major congenital malformations, with a focus on cardiovascular defects, among infants born to women dispensed paroxetine in their first trimester of pregnancy. Infants born to women dispensed paroxetine during the estimated first trimester were classified into the following two cohorts: 1) infants born to women who were dispensed paroxetine as the only antidepressant during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester (i.e., the paroxetine monotherapy exposure cohort), or 2) infants born to women who were dispensed paroxetine as the only antidepressant or in addition to another antidepressant during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester (i.e. the paroxetine monotherapy or polytherapy exposure cohort). Infants born to the following two groups of women served as comparators: 1) infants born to women who received only one type of an antidepressant other than paroxetine during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester, i.e., the other antidepressant monotherapy exposure cohort; and 2) infants born to women who received only one or more than one type of an antidepressant other than paroxetine during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester (i.e. the other antidepressant mono- or polytherapy exposure cohort).

Additional analyses were conducted that stratified the study groups according to the presence of dispensings of drugs thought or suspected to be teratogenic among mothers up to one year before delivery through the end of the first trimester. Analyses of cardiovascular malformations were stratified according to the presence of dispensings of the subset of drugs thought or suspected to be teratogenic in cardiovascular defects. Teratogens were identified a priori and consisted of the following: aminoglycoside antibiotics, ACE inhibitors, androgens, anticholinergic drugs, busulfan*, carbamazepine*, cyclophosphamide*, danazol, diethylstilbestrol, etretinate*, fluconazole, indomethacin, isotretinoin*, lithium, methimazole, methotrexate*, misoprostol, oral corticosteroids, paramethadione*, penicillamine, phenytoin*, propylthiouracil, tetracycline, thalidomide*, trimethadoin*, valproic acid* and warfarin (*cardiovascular teratogens)

Throughout the study, the comparisons consisted of: 1) paroxetine monotherapy cohort vs. other antidepressant monotherapy cohort; and 2) paroxetine mono- or polytherapy cohort vs. other antidepressant mono- or polytherapy cohort.

Study Population: The cohorts developed for the Bupropion in Pregnancy study consisted of all infants born to women exposed to bupropion during the estimated first trimester, and a random sample of infants born to women exposed to other antidepressants during the first trimester. Paroxetine exposed pregnancies were identified using the other antidepressant cohort which was frequency-matched to the bupropion cohort by year of birth and selected irrespective of exposure to specific antidepressants.

These cohorts were originally created to perform the bupropion analysis as follows: all women dispensed bupropion or other antidepressants and who had a live born delivery in the RDM between January 1995 and September 2004 were identified. The subset of women aged 12-49 years as of their delivery date was selected. Cohort membership in the RDM database was further restricted to members within health plans where medical record abstraction could be conducted. In the event that a woman was identified more than once during the study period due to subsequent pregnancies, all other deliveries were assessed for exposure to the study drugs. Deliveries were excluded if the mother did not have continuous health plan enrollment for one year before the delivery date.

Study Treatment Exposures, Outcomes:

For each infant delivery, sequences of diagnoses and procedures in the medical claims data were examined to estimate a window of time when conception probably occurred. The first trimester was defined as occurring from the earliest possible conception date through 12 weeks following the latest possible conception date.

All deliveries with a dispensing of paroxetine during the first trimester (or any dispensing prior to the start of the first trimester where the number of days dispensed extended into the first trimester) were classified into one of the two paroxetine exposed cohorts: 1) the paroxetine monotherapy exposure cohort, or 2) the paroxetine mono- or polytherapy exposed cohort.

Deliveries with a dispensing of at least one antidepressant other than paroxetine during the first trimester (or any dispensing prior to the start of the first trimester where the number of days dispensed extended into the first trimester) were classified into one of the two comparison cohorts consisting of: 1) Infants born to women who received only one type of an antidepressant other than paroxetine during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester, the "other antidepressant monotherapy" exposure cohort; and 2) infants born to women who received only one or more than one type of an antidepressant other than paroxetine during the estimated first trimester window, or before the first trimester with the days supplied extending into the first trimester, i.e., the other antidepressant mono- or polytherapy exposure cohort.

The primary outcome under study was the prevalence of congenital malformations among live born infants, with a focus on cardiovascular defects. Congenital malformations were classified according to organ system and diagnosis. To verify congenital malformations, medical records were abstracted for infants with claims evidence of a congenital malformation. Medical and prescription claims data were used to characterize the mothers according to comorbid conditions, measures of health care utilization, and other concomitant prescription dispensings.

Data Analysis Methods: The prevalence of infants with congenital malformations was calculated for each of the four study cohorts groups as the number of infants with a congenital malformation confirmed through medical record abstraction divided by the total number of live-born infants. Crude odds ratios were calculated as well as odds ratios which adjusted for relevant covariates through multivariate logistic regression. Confidence intervals (CI) were calculated using exact binomial methods. No attempt was made to adjust the CI for multiple estimates and no significance testing

was performed.

Additionally, an analysis was conducted that stratified the study groups according to dispensing of drugs known or suspected to be teratogens, or known or suspected to be cardiovascular teratogens, among mothers up to one year before delivery through the end of the first trimester.

Throughout the study, the comparisons consisted of: 1) Paroxetine monotherapy vs. other antidepressant monotherapy; and 2) Paroxetine mono- or polytherapy vs. other antidepressant mono- or polytherapy.

Study Results:

In the monotherapy cohorts, the adjusted estimates for the relative prevalence of congenital/cardiovascular malformations among the offspring of paroxetine recipients during the first trimester compared with the offspring of recipients of other antidepressants during the first trimester were 1.89 (95% CI 1.20 – 2.98) for congenital malformations overall, and 1.46 (95% CI 0.74 -2.88) for cardiovascular malformations alone. In the mono- or polytherapy cohorts, the adjusted estimates for the relative prevalence of congenital/cardiovascular malformations among the offspring of paroxetine recipients during the first trimester compared with the offspring of recipients of other antidepressants during the first trimester were 1.76 (95% CI 0.1.18 – 2.64) for congenital malformations overall, and 1.68 (95% CI 0.95 -2.97) for cardiovascular malformations alone.

Results that excluded infants with maternal dispensing of drugs known or suspected to be teratogenic were consistent with results from the non-stratified analysis. In the monotherapy cohorts, the adjusted odds ratios for paroxetine compared to other antidepressant exposures was 2.03 (95% CI 1.26-3.25) for congenital malformations and 1.47 (95% CI 0.74-2.89) for cardiovascular malformations. In the mono- or polytherapy cohorts, the adjusted odds ratios for paroxetine compared to other antidepressant exposures was 1.79 (95% CI 1.17-2.73) for congenital malformations and 1.60 (95% CI 0.89 -2.89) for cardiovascular malformations. In the paroxetine monotherapy cohort, the prevalence of congenital/cardiovascular malformations following first trimester paroxetine exposure and no concurrent first trimester use of teratogens was approximately 4% (37.7 per 1000) for congenital malformations as a whole and 2% (14.7 per 1000) for cardiovascular malformations. Of the cardiovascular malformations reported in infants whose mothers were dispensed paroxetine in the first trimester, the majority were ventricular septal defects.

Demographics/Baseline Characteristics using RDM (January 1995 through September 2004)

	Paroxetine Monotherapy First Trimester	Other Antidepressant Monotherapy First Trimester		
Total infants, N	815	4198		
Maternal age at delivery				
Mean (standard deviation [SD])	30.5 (5.5)	31.1 (5.2)		
12-19 years, n (%)	21 (2.6)	60 (1.4)		
20-24 years, n (%)	94 (11.5)	376 (9.0)		
25-29 years, n (%)	238 (29.2)	1174 (28.0)		
30-34 years, n (%)	270 (33.1)	1491 (35.5)		
35-39 years, n (%)	150 (18.4)	887 (21.1)		
40-49 years, n (%)	42 (5.2)	210 (5.0)		
Infant sex				
Female, n (%)	381 (46.8)	2030 (48.4)		
Male, n (%)	434 (53.3)	2168 (51.6)		
	Paroxetine Mono- or Polytherapy First Trimester	Other Antidepressant Mono- or Polytherapy First Trimester		
Total infants, N	1020	4936		
Maternal age at delivery				
Mean (SD)	30.6 (5.4)	31.2 (5.2)		
12-19 years, n (%)	26 (2.6)	71 (1.4)		
20-24 years, n (%)	111 (10.9)	427 (8.7)		
25-29 years, n (%)	289 (28.3)	1361 (27.6)		
30-34 years, n (%)	352 (34.5)	1763 (35.7)		
35-39 years, n (%)	192 (18.8)	1042 (21.1)		
40-49 years, n (%)	50 (4.9)	272 (5.5)		
Infant sex				
Female, n (%)	469 (46.0)	2385 (48.3)		
Male, n (%)	551 (54.0)	2551 (51.7)		
Primary Outcomes				
Study Results using RDM (January 1995 through September 2004)				
Prevalence and OR of all congenital malformations, paroxetine and other antidepressant monotherapy cohorts				
	Paroxetine Monotherapy	Other Antidepressant Monotherapy		
Cases	29	83		
Total No. of Infants	815	4198		
Prevalence per 1000	35.6	19.8		
Crude OR (95% CI)	1.83 (1.19, 2.81)			
Adjusted OR (95% CI) ^a	1.89 (1.20, 2.98)			
Prevalence of congenital malformations by organ system category, paroxetine and other antidepressant monotherapy cohorts				
	Paroxetine Monotherapy First Trimester		Other Antidepressant Monotherapy First Trimester	
Total infants, N	815		4198	
Category of malformation	n	Prev per 1000 (95% CI)	n	Prev per 1000 (95% CI)
Total ^b	29	35.6 (24.9, 50.6)	83	19.8 (16.0, 24.4)
Cardiovascular	12	14.7 (8.4, 25.6)	40	9.5 (7.0, 12.9)
Central Nervous System	3	3.7 (0.8, 10.7)	3	0.7 (0.1, 2.1)
Eye	0		1	0.2 (0.0, 1.3)
Gastrointestinal	5	6.1 (2.6, 14.3)	7	1.7 (0.8, 3.4)
Genitourinary	6	7.4 (3.4, 16.0)	26	6.2 (4.2, 9.1)
Musculoskeletal	3	3.7 (0.8, 10.7)	5	1.2 (0.5, 2.8)
Orofacial	3	3.7 (0.8, 10.7)	5	1.2 (0.5, 2.8)
Respiratory	0		1	0.2 (0.0, 1.3)

^bInfants may be counted in multiple malformation categories

Prevalence and OR of cardiovascular malformations, paroxetine and other antidepressant monotherapy cohorts		
	Paroxetine Monotherapy	Other Antidepressant Monotherapy
Cases	12	40
Total No. of Infants	815	4198
Prevalence per 1000	14.7	9.5
Crude OR (95% CI)	1.55 (0.81, 2.97)	
Adjusted OR (95% CI) ^a	1.46 (0.74, 2.88)	
Distribution of congenital malformations by specific diagnosis, paroxetine and other antidepressant monotherapy cohorts		
Diagnosis	Paroxetine Monotherapy Count	Other Antidepressant Monotherapy Count
Cardiovascular	12	40
Aortic stenosis, pulmonary stenosis, tricuspid insufficiency, mitral insufficiency	0	1
Atrial septal defect	0	2
Atrial septal defect, aneurysm of the fossa ovalis, bicuspid aortic valve, ventricle enlargement	0	1
Atrial septal defect, aortic stenosis	0	1
Atrial septal defect, left pelviectasis ^c	0	1
Atrial septal defect, pulmonary stenosis	1	0
Coarctation of the aorta	0	1
Coarctation of the aorta, bicuspid aortic valve with stenosis, mitral insufficiency	0	1
Coarctation of the aorta, congenital diaphragmatic hernia ^c	0	1
Hypoplastic heart syndrome	0	1
Hypoplastic heart, coarctation of the aorta, cleft lip ^c	0	1
Patent ductus arteriosus	0	2
Patent ductus arteriosus, patent foramen ovale	1	1
Pulmonary artery sling	0	1
Pulmonary stenosis	0	1
Pulmonary valve stenosis	0	1
Tetralogy of Fallot	0	2
Transposition of the great arteries, pulmonary stenosis	1	0
Tricuspid insufficiency, hypospadias ^c	0	1
Ventricular septal defect	6	17
Ventricular septal defect, atrial septal defect	1	1
Ventricular septal defect, atrial septal defect, pulmonary stenosis	1	0
Ventricular septal defect, coarctation of the aorta	0	1
Ventricular septal defect, hypoplastic lung ^c	0	1
Ventricular septal defect, hypospadias ^c	1	0
Non-Cardiovascular	17	43
CNS		
Agenesis of corpus callosum with cerebellum hypoplasia	1	0
Congenital microcephaly	1	1
Dandy-Walker malformation with hydrocephalus		
Lipomyelomeningocele	1	1
Migrational brain disorder, brain dysgenesis	0	1
Eye		
Congenital cataracts	0	1
Gastrointestinal		
Esophageal atresia and tracheoesophageal fistula	0	1

Omphalocele	0	1
Pyloric stenosis	3	5
Imperforate anus and posterior forchette fistula	1	0
Genitourinary		
Duplicated left collecting system	0	1
Hydronephrosis	2	4
Hydronephrosis, hydroureter	0	1
Hydronephrotic kidney secondary to obstruction, meatal stenosis, preputial glandular adhesions	0	1
Hypospadias	1	13
Inguinal hernia	0	1
Malrotated ectopic kidney	0	1
Pole caliceal dilatation	0	1
Pyelectasis	0	1
Renal pelviectasis	0	0
Musculoskeletal		
Acetabular dysplasia	0	0
Arthrogryposis multiplex congenita	1	0
Congenital hip dislocation	1	3
Hip dysplasia	1	0
Orofacial		
Ankyloglossia mandubularis	0	0
Cleft lip	1	1
Cleft lip and palate	1	2
Cleft palate	0	1
Trigonocephaly secondary to premature metopic suture synostosis	0	1
Multiple		
Cleft palate, hypospadias ^c	1	0
Imperforate anus with perineal fistula, renal agenesis, hydronephrosis ^c	1	0
Total All Congenital Malformations	29	83

Prevalence and OR of all congenital malformations, paroxetine and other antidepressant mono- or polytherapy cohorts

	Paroxetine Mono- or Polytherapy	Other Antidepressant Mono- or Polytherapy
Cases	36	102
Total No. of Infants	1020	4936
Prevalence per 1000	35.3	20.7
Crude OR (95% CI)	1.74 (1.18, 2.55)	
Adjusted OR (95% CI) ^a	1.76 (1.18, 2.64)	

Prevalence of congenital malformations by organ system category, paroxetine and other antidepressant mono- or polytherapy cohorts

	Paroxetine Mono- or Polytherapy First Trimester		Other Antidepressant Mono- or Polytherapy First Trimester	
Total infants, N	1020		4936	
Category of malformation	n	Prev per 1000 (95% CI)	n	Prev per 1000 (95% CI)
Total ^b	36	35.3 (25.6, 48.5)	102	20.7 (17.1, 25.0)
Cardiovascular	17	16.7 (10.4, 26.5)	47	9.5 (7.2, 12.6)
Central Nervous System	3	2.9 (0.6, 8.6)	5	1.0 (0.4, 2.4)
Eye	0		1	0.2 (0.0, 1.1)
Gastrointestinal	5	4.9 (2.1, 11.4)	10	2.0 (1.1, 3.7)
Genitourinary	7	6.9 (3.3, 14.1)	30	6.1 (4.3, 8.7)

Musculoskeletal	4	3.9 (1.1, 10.0)	6	1.2 (0.6, 2.7)
Orofacial	3	2.9 (0.6, 8.6)	7	1.4 (0.7, 2.9)
Respiratory	0		1	0.2 (0.0, 1.1)

^bInfants may be counted in multiple malformation categories

Prevalence and OR of cardiovascular malformations, paroxetine and other antidepressant mono- or polytherapy cohorts

	Paroxetine Mono- or Polytherapy	Other Antidepressant Mono- or Polytherapy
Cases	17	47
Total No. of Infants	1020	4936
Prevalence per 1000	16.7	9.5
Crude OR (95% CI)	1.76 (1.01, 3.08)	
Adjusted OR (95% CI) ^a	1.68 (0.95, 2.97)	

^aOR adjusted for maternal age category, infant sex, geographic region, number of physician visits within 10 to 12 months before delivery, the following diagnoses within one year before delivery: gestational diabetes, bipolar disorder, cancer, hemorrhage in early pregnancy (ICD-9 640), fetal abnormalities affecting the mother (ICD-9 655), general symptoms (ICD-9 780), respiratory system or other chest symptoms (ICD-9 786), special examinations (ICD-9 V72), and dispensing of the following drugs within a year before delivery through the end of the first trimester: carbamazepine, phenytoin, hydrocodone/acetaminophen, norgestimate-ethinyl estradiol, levothyroxine, and sertraline.

Distribution of congenital malformations by specific diagnosis, paroxetine and other antidepressant polytherapy cohorts

Diagnosis	Paroxetine Polytherapy Count ^d	Other Antidepressant Polytherapy Count ^d
Cardiovascular	5	7
Aortic stenosis	1	0
Aortic stenosis, pulmonary stenosis, tricuspid insufficiency, mitral insufficiency	0	0
Atrial septal defect	0	1
Atrial septal defect, aortic stenosis	0	0
Atrial septal defect, aneurysm of the fossa ovalis, bicuspid aortic valve, ventricle enlargement	0	0
Atrial septal defect, left pelviectasis ^c	0	0
Atrial septal defect, pulmonary stenosis	0	1
Coarctation of the aorta	1	0
Coarctation of the aorta, bicuspid aortic valve with stenosis, mitral insufficiency	0	0
Coarctation of the aorta, congenital diaphragmatic hernia ^c	0	0
Hypoplastic heart syndrome	0	0
Hypoplastic heart, coarctation of the aorta, cleft lip ^c	0	0
Patent ductus arteriosus	0	0
Patent ductus arteriosus, patent foramen ovale	0	0
Pulmonary artery sling	0	0
Pulmonary stenosis	1	1
Pulmonary valve stenosis	0	0
Tetralogy of Fallot	0	0
Transposition of the great arteries, pulmonary stenosis	0	0
Tricuspid insufficiency, hypospadias ^c	0	0
Ventricular septal defect	2	4
Ventricular septal defect, atrial septal defect	0	0
Ventricular septal defect, atrial septal defect, pulmonary stenosis	0	0
Ventricular septal defect, coarctation of the aorta	0	0
Ventricular septal defect, hypoplastic lung ^c	0	0
Ventricular septal defect, hypospadias ^c	0	0

Non-Cardiovascular		2	12	
CNS				
Agenesis of corpus callosum with cerebellum hypoplasia		0	0	
Congenital microcephaly		0	0	
Dandy-Walker malformation with hydrocephalus		0	1	
Lipomyelomeningocele		0	1	
Migrational brain disorder, brain dysgenesis		0	0	
Eye				
Congenital cataracts		0	0	
Gastrointestinal				
Esophageal atresia and tracheoesophageal fistula		0	0	
Omphalocele		1	0	
Pyloric stenosis		0	3	
Imperforate anus and posterior forchette fistula		0	0	
Genitourinary				
Duplicated left collecting system		0	0	
Hip dysplasia		0	0	
Hydronephrosis		0	1	
Hydronephrosis, hydroureter		0	0	
Hydronephrotic kidney secondary to obstruction, meatal stenosis, preputial glandular adhesions		0	0	
Hypospadias		0	3	
Inguinal hernia		0	0	
Malrotated ectopic kidney		0	0	
Pole caliceal dilatation		0	0	
Pyelectasis		0	0	
Renal pelviectasis		1	0	
Musculoskeletal				
Acetabular dysplasia		0	1	
Arthrogryposis multiplex congenita		0	0	
Congenital hip dislocation		0	0	
Hip dysplasia		0	0	
Orofacial				
Ankyloglossia mandibularis		0	1	
Cleft lip		0	0	
Cleft lip and palate		0	0	
Cleft palate		0	1	
Trigonocephaly secondary to premature metopic suture synostosis		0	0	
Multiple				
Cleft palate, hypospadias ^c		0	0	
Imperforate anus with perineal fistula, renal agenesis, hydronephrosis ^c		0	0	
Total All Congenital Malformations		7	19	
^c Infants counted in multiple organ system categories of malformations				
^d Sum of malformations in the monotherapy and polytherapy groups equal the total number of malformations in the 'mono-or polytherapy' group.				
Prevalence and OR of all congenital malformations stratified by maternal teratogenic drug dispensing, paroxetine and other antidepressant monotherapy cohorts				
	No Teratogen Dispensing^e		Teratogen Dispensing^e	
	Paroxetine Monotherapy	Other Antidepressant Monotherapy	Paroxetine Monotherapy	Other Antidepressant Monotherapy
	27	70	2	13
Total No. of Infants	717	3602	98	596

Prevalence per 1000	37.7	19.4	20.4	21.8
Crude OR (95% CI)	1.98 (1.26, 3.11)		0.91 (0.20, 4.12)	
Adjusted OR (95% CI) ^f	2.03 (1.26, 3.25)		Not available	
Prevalence and OR of all congenital malformations stratified by maternal teratogenic drug dispensing, paroxetine and other antidepressant mono- or polytherapy cohorts				
	No Teratogen Dispensing^e		Teratogen Dispensing^e	
	Paroxetine Mono- or Polytherapy	Other Antidepressant Mono- or Polytherapy	Paroxetine Mono- or Polytherapy	Other Antidepressant Mono- or Polytherapy
	32	88	4	14
Total No. of Infants	880	4212	140	724
Prevalence per 1000	36.4	20.9	28.6	19.3
Crude OR (95% CI)	1.77 (1.18, 2.67)		1.47 (0.48, 4.53)	
Adjusted OR (95% CI) ^f	1.79 (1.17, 2.73)		Not available	
^e Maternal teratogenic drug dispensing within a year before delivery through the end of the estimated first trimester.				
^f OR adjusted for maternal age category, infant sex, geographic region, number of physician visits within 10 to 12 months before delivery, the following diagnoses within one year before delivery: gestational diabetes, bipolar disorder, cancer, hemorrhage in early pregnancy (ICD-9 640), fetal abnormalities affecting the mother (ICD-9 655), general symptoms (ICD-9 780), respiratory system or other chest symptoms (ICD-9 786), special examinations (ICD-9 V72), and dispensing of the following drugs within a year before delivery through the end of the first trimester: hydrocodone/acetaminophen, norgestimate-ethinyl estradiol, levothyroxine, and sertraline.				
Prevalence and OR of cardiovascular malformations stratified by maternal cardiovascular teratogenic drug dispensing, paroxetine and other antidepressant monotherapy cohorts				
	No Teratogen Dispensing^g		Teratogen Dispensing^g	
	Paroxetine Monotherapy	Other Antidepressant Monotherapy	Paroxetine Monotherapy	Other Antidepressant Monotherapy
Cases	12	38	0	2
Total No. of Infants	814	4165	1	33
Prevalence per 1000	14.7	9.1	0	60.6
Crude OR (95% CI)	1.63 (0.85, 3.12)		Not available	
Adjusted OR (95% CI) ^h	1.47 (0.74, 2.89)		Not available	
Prevalence and OR of cardiovascular malformations stratified by maternal cardiovascular teratogenic drug dispensing, paroxetine and other antidepressant mono- or polytherapy cohorts				
	No Teratogen Dispensing^g		Teratogen Dispensing^g	
	Paroxetine Mono-or Polytherapy	Other Antidepressant Mono- or Polytherapy	Paroxetine Mono- or Polytherapy	Other Antidepressant Mono- or Polytherapy
Cases	16	45	1	2
Total No. of Infants	1014	4894	6	42
Prevalence per 1000	15.8	9.2	166.7	47.6
Crude OR (95% CI)	1.73 (0.97, 3.07)		3.99 (0.30, 52.4)	
Adjusted OR (95% CI) ^h	1.60 (0.89, 2.89)		Not available	
^g Maternal dispensing of a teratogenic drug thought or suspected to affect the cardiovascular system within a year before delivery through the end of the estimated first trimester.				
^h OR adjusted for maternal age category, infant sex, geographic region, number of physician visits within 10 to 12 months before delivery, the following diagnoses within one year before delivery: gestational diabetes, bipolar disorder, cancer, hemorrhage in early pregnancy (ICD-9 640), fetal abnormalities affecting the mother (ICD-9 655), general symptoms (ICD-9 780), respiratory system or other chest symptoms (ICD-9 786), special examinations (ICD-9 V72), and dispensing of the following drugs within a year before delivery through the end of the first trimester: hydrocodone/acetaminophen, norgestimate-ethinyl estradiol, levothyroxine, and sertraline.				

Limitations: Limitations of this study include:

- There were no comparison cohorts of non-recipients of any antidepressant during the first trimester or of non-depressed women
- There are uncertainties associated with both exposure and outcome measure
- There may still be potential differences in clinical characteristics across cohorts which may have resulted in residual confounding.

See publication below for further details

Conclusion: See publication below

Publications: Cole JA, Ephross SA, Cosmatos IS, Walker AM. Paroxetine in the First Trimester of Pregnancy and the Prevalence of Congenital Malformations. *Pharmacoepidemiology and Drug Safety* 2007; 16 (10):1075-1085

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