DO FINDINGS DIFFER ACROSS RESEARCH DESIGN? THE CASE OF ANTIDEPRESSANT USE IN PREGNANCY AND MALFORMATIONS

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ABSTRACT

Background
Many studies examining the teratogenic potential of antidepressants have been published. A variety of observational designs have been used with apparent conflicting results, although odds ratios were rarely >2.

Objectives
To examine whether these apparent differences were associated with research methods such as model, comparison groups, data source, data collection procedures, definition of malformations, outcome ascertainment or management of confounders.

Methods
Medline and Embase were searched using terms: pregnancy, antidepressants, serotonin uptake inhibitors OR SSRI, AND embryonic structures OR congenital malformations OR fetal development for observational studies with original data. Data were analyzed using a structured approach and narrative review. Designs that were compared, included prospective cohort, retrospective cohort, and case-control studies. Rates of major malformations and cardiac malformations were combined by study type using random effects meta-analytic models**.**

Results
We identified 150 papers; 127 were rejected, 23 were analyzed: 9 prospective cohort, 8 retrospective cohort, and 6 case-control studies. Sample sizes were large (1,818 exposed in case-control and 16,824 in cohort studies), providing relatively robust findings. Overall Odds Ratio's for major malformations ranged from 1.03-1.24 and 0.81-1.32 for cardiac malformations. No discrepancies among research designs were identified.

Conclusions
Diverse observational models with differing strengths and weaknesses produced remarkably similar non-significant results. Perceived conflicting results may be due to subsequent dissemination of results with attention given to small statistically differences with negligible clinical importance. Improved methods of knowledge transfer and translation are required to provide sound evidence-based information to assist in decision-making surrounding the use of antidepressants in pregnancy.

Key Words: *Antidepressants, pregnancy, malformations, research design*

Prior to 2005, research using observational designs conducted on the use of SSRIs in pregnancy reported no association between SSRI use and congenital malformations.[1] However, in 2005, GlaxoSmithKline conducted a study of outcomes from 815 exposed infants and reported a

2% incidence of cardiovascular malformations (where 1% is expected in the general population), unspecified in terms of severity and unpublished in the peer reviewed literature.[2] That study motivated both the Food and Drug Administration (FDA) and Health Canada, to warn about the use of paroxetine in the first trimester of pregnancy. Since these warnings were issued seven years ago, there has been a sizable increase in the number of studies published on this topic, with some finding evidence of harm and others not. However, despite all of this new information, to date these warnings have not been updated and currently, the information is unchanged from December 2005-Dec 2011.[3,4]

Due to the ethical restrictions of randomized controlled trials (RCTs) in pregnant women, studying the gestational safety of drugs is a complex process. Consequently, observational study designs (i.e., case reports, case series, cohort studies, case-control and nested case-control studies and administrative database studies) are currently used, which obviously have many limitations.[5] Recent years have seen a increase in the number of computerized databases, which were not designed for scientific studies. However, researchers have used these databases to conduct complex analyses of data, resulting in a substantial increase in such studies. This issue was recently raised by the research group of the Organization of Teratogen Information Services (TISs) who issued a call for more complete information from database studies.[6] Together with other observational studies using different data and study designs, conflicting results have been published regarding the safety of antidepressant use in pregnancy. Understandably, this mixed information has caused anxiety for health care providers and their pregnant patients, who may require pharmacological treatment for depression.

To our knowledge, in this field of researching the safety/risk of drugs used during pregnancy, differences in study designs, including data collection, data analysis, managing confounders, and limitations inherent in observational studies have not been closely examined. Therefore, as an example we conducted a systematic review of all studies reporting on antidepressant use in early pregnancy and congenital malformations, with a special focus on cardiovascular malformations, as this has been the most conflicting outcome, in an attempt to answer this question: "Do different research designs produce different estimates of risk for antidepressant exposure in pregnancy?"

METHODS

For studies to be included in this review, articles had to report on the use of antidepressants during the first trimester of pregnancy. Included were SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and drugs from other classes of antidepressants, such as bupropion, mirtazapine, nefazodone, trazodone, and venlafaxine. The outcomes of interest were major malformations and we examined cardiac malformations separately. Studies were not considered if their focus was on later trimesters or if they investigated other outcomes such as pulmonary hypertension of the newborn (PPHN), low birth weight, or premature delivery.

Since randomized controlled trials of antidepressants are not permitted using pregnant women, we examined only observational studies. We included all types, such as cohort studies, case-control studies, and database studies, providing they had a comparison group that was not exposed to antidepressants. For cohort studies, we accepted those with either prospective or retrospective data collection, but were analyzed separately. For that purpose, data extraction sheets were developed and used to collect and compile data on each of the articles included in the review. Primary data points collected included type of study, location(s), inclusion and exclusion criteria, sample size, drugs reported on, duration of exposure, study outcomes, confounders, limitations, statistical analysis performed and conclusions.

There were no restrictions placed on year or language of publication. Databases searched included MEDLINE, and Embase on the OVID platform from inception to June 2011. Both database specific subject headings and text words were searched using the terms "congenital malformations" OR "prenatal development" OR "embryonic structures" OR "Prenatal Exposure Delayed Effects" AND "Serotonin Uptake Inhibitors" OR "Serotonin Reuptake Inhibitors" OR "SSRI" AND "case-control studies" OR "cohort" OR "registries.

Review articles were retrieved and hand searched to identify additional relevant primary research articles. Screening of articles was performed by three individuals, and discrepancies in agreement regarding inclusion were resolved by consensus.

For the purposes of analysis, studies were divided into prospective cohort studies, retrospective cohort studies, database studies, and case-control studies. Since some designs overlap, we further combined them into cohort studies, regardless of data collection method. Data were combined across studies using a random effects meta-analytic model. For cohort studies, risk ratios with 95% confidence intervals were calculated and for case-control studies, odds ratios were calculated, with 95% confidence intervals. To examine heterogeneity of effects, we calculated χ^2 and I^2. Other data were summarized descriptively and with a narrative review.

Aspects of research design that were examined were the definition of first trimester, comparison groups used, criteria for identifying congenital malformations, time of follow-up, how confounders were managed, losses to follow-up, and sample size calculations (especially *a priori*).

RESULTS

The search yielded 150 original articles, of which 23 fit our inclusion criteria (Figure 1).[7-29] To evaluate overall rates of malformations, we used 17 cohort studies, including 7 prospective cohort studies[7-13] and 7 retrospective cohort studies[14-20] as well as 3 case-control studies.[21-23] The study characteristics are summarized in Table 1. Sample sizes were quite large, with a combined total of more than 20,000 first trimester exposures to antidepressants. We also analyzed 18 studies that specifically reported on the rates of cardiovascular malformations.[19-28]

Results are summarized in the Table 2. A single prospective cohort study (7%) reported a significant association between SSRIs and congenital malformations; two cohort studies (14%; one prospective, one retrospective) reported a positive association between antidepressants and cardiovascular malformations. None of the case-control studies identified a significant relationship.

Definition of first trimester

Some studies incorporated the whole of the preconception period, (especially prescription data base studies). Others considered the first trimester from week 4 to 14 (i.e., mostly studies from TISs), while other studies provided no definition for first trimester (e.g., administrative data bases).

Comparison groups

The comparison group was dependent on the data source for the study, for example, studies from the TISs used 2 comparison groups of women: 1) those exposed to a different antidepressant medication and 2) women exposed to drugs known not to be teratogenic. There were equal numbers of exposed and non-exposed. Population-based registries and/or administrative databases most often used a single comparison group of women who were not exposed to SSRIs.

Criteria to identify congenital malformations*:*

Eight out of 23(35%) did not identify the criterion used to define a congenital malformation, while other studies specified the International Classification of Disease (ICD) codes in their analyses. The most notable difference was in the reporting of cardiovascular malformations as major malformations, as most studies included all heart malformations, including ventricular septal defects (VSDs) and atrial septal defects (ASDs), even if they closed spontaneously. When studies in which cardiovascular malformations that resolved spontaneously were excluded, there was no increased risk.[25] In addition, confirmation of the timing of diagnosis was not standardized and appeared to vary from one month to 3 years of age across all studies. Consequently, some heart malformations would not have been detected immediately after birth in the early interviews and conversely, some would have resolved spontaneously by the time the children reached 3 years of age in the later examinations.

Time of follow-up

Fourteen out of 23 (61%) studies collected data on congenital malformations at birth or in the neonatal period, while the remainder did not state when follow-up was performed.

Confounders
Most of the database studies incorporated multiple linear regressions and calculated adjusted odds ratios to eliminate the effects of potential confounders on their results. For example, in their meta-analysis, Wurst et al. developed a list of key confounders relevant to studying medications and each study in the review was evaluated according to this list.[30] Maternal age and smoking were the most common confounders adjusted for in the analysis. Many of the retrospective registry and database studies were limited by their inability to identify aspects of a women's pregnancy or medical history and most did not adjust for multiple testing.

Loss to follow-up
Loss to follow-up information was not reported in any of the studies from TISs.

Lack of a priori sample size calculation
Only 2/23 (8%) studies incorporated an *a priori* power calculation, although several studies, did discuss *post hoc* the power of their sample size.

DISCUSSION

To our knowledge, this is the first systematic review to specifically examine differences in study design among observational studies that were conducted to assess the safety/risk of antidepressant use in pregnancy. Each type of study had its own limitations, which was not always stated clearly by the authors. The prospective detailed history taking method employed at the TIS is considered a strength as it is possible to clearly ascertain that the medication was actually taken, when and for how long, while population-based studies do not always have this information. In addition, TIS studies for the most part corroborate the outcome by following up with the infant's physician. However, the two main weaknesses in using this data source are the inability to compile a large enough sample size to make a definitive conclusion, and the selection bias due to the nature of the women choosing to call a TIS.[5]

In database studies, the major strength is the much larger sample sizes which provide a better representation of the population. The limitations include for example, no knowledge of confounders for alcohol and cigarette smoking, which are known to affect pregnancy outcome.[31] In addition, as Andrews and Tennis identified in their commentary on the pitfalls of administrative databases, there is often a poor degree of correlation between actual medical diagnosis and the outcomes coded for the infant in the database.[31] In our review, in the studies that used information from a database, only half tried to overcome this limitation by incorporating a review of the medical chart into their data collection protocol. In addition, it is not known if the women in prescription databases actually took the drug, only that a prescription was redeemed. A recent study of pregnant women compared information recorded in a database with data obtained from actual patient interviews. The authors reported that in women who filled prescriptions 1 to 3 months before their last menstrual period (a commonly used time frame), as many as 43% did not use the drugs in the first trimester.[32] What strengthens this particular finding is, in our experience at Motherisk during many years of conducting these studies, a large number of women discontinued their chronic medications (especially antidepressants) prior to pregnancy, as they had been informed that pregnant women should not take any medication.[33]

This research has highlighted the inconsistencies in the methods used in this area of research, which may affect study results. However, the answer to the research question (Do results differ across research designs and methods?) appears to be "no", with the exception of reported rates of cardiac malformations. On the other hand, those results can mostly be explained by differences in time of diagnosis following birth and inclusion/exclusion of minor malformations which resolved spontaneously. For example, in a study specifically examining whether there was an association between cardiovascular malformations and SSRIs, every infant born at a center during an 8 year period was examined on the first day of life for a cardiac murmur.[25] Infants with a persistent murmur on the second or third day of life were examined by a pediatric cardiologist and referred for electrocardiography and echocardiography. The authors reported that 8/235 newborns (3.4%) were found to have had cardiovascular malformations following first-trimester exposure

to SSRIs. Four of the infants had been exposed to paroxetine, two to fluoxetine, one to citalopram and one to sertraline, and all were identified as having ventricular septal defects (VSDs), the most frequent cardiac malformation. If minor malformations which resolved spontaneously were removed from both groups, the absolute risk in both groups would be less than 1%, which is the rate expected in the general population. Moreover, there is disagreement regarding the safety of paroxetine among researchers and experts. For example, in 2010, a meta-analysis was conducted in an attempt to resolve the issue of whether paroxetine does in fact increase the risk for cardiovascular malformations.[30] The authors had concluded that there was an increased prevalence of combined cardiac defects with first trimester exposure to paroxetine. They calculated their summary estimate as a prevalence odds ratio [POR]. For combined cardiac defects, the POR was 1.46 ($CI_{95\%}$:1.17-1.82), for aggregated congenital defects, the POR was 1.24 ($CI_{95\%}$:1.08-1.43). Two commentaries were published along with that analysis presenting opposing opinions. Scialli concluded that "the scientific evidence does not support the conclusion that paroxetine causes cardiovascular defects "[34], while Bérard stated that "evidence-based literature shows consistent epidemiologic evidence that paroxetine use during pregnancy increases the risk of cardiac malformations in newborns".[35] From these statements, one is prompted to question how it could be that two experts in the same field have offered such opposing conclusions based on their evaluation of the same data.

Another important question concerns how these results are disseminated to the scientific community and the public. When individual studies are published, much is made of very small increased ORs, which have often been <2 and explained in a way that that it appears much more important than it really is. Small but statistically significant risks are important at the population level, but may be less so when considering an individual, such as a woman who is planning pregnancy or who is currently pregnant and taking a medication such as an antidepressant.[36] Conversely, studies that did not find any adverse effects are frequently ignored by the media. Subsequently, results of these studies can have a far reaching impact on events such as precedent setting lawsuits, as in the case of GlaxoSmithKline, resulting in the company ordered to pay $1.5 million to a couple whose baby was born with a heart defect following exposure to Paxil® in pregnancy. The jurors reached this conclusion following examination of only selected studies that reported an increased risk, therefore creating a huge potential bias.[37] In addition, widely disseminated results in the media of studies reporting even a marginally increased risk also can cause women to stop taking a needed antidepressant during pregnancy, sometimes with adverse consequences.[39,40] It is extremely important that such decisions be informed with balanced evidence based information.

CONCLUSIONS

We found that different research designs do not produce conflicting results *per se* and apparent differences appear to have been probably due to the way selected results were disseminated. We did note some design deficiencies among the studies examined and these findings reinforce the need to improve the rigor of study methods, which is in the most part achievable. This includes standardizing definitions for evaluation criteria for major malformations and the associated follow up period. In addition, a need exists for universally accepted definition of first trimester, with key confounders to include in regression analysis, adjusted odd ratios or relative risk calculations and very importantly, caution when performing multiple testing. Finally and of great importance, improved knowledge transfer and translation will ensure that pregnant women and their health care providers receive the most accurate evidence-based information, for decision-making regarding the use of antidepressants during pregnancy.

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TABLE 1 Studies examining pregnancy outcomes after exposure to antidepressants

CONGENITAL MALFORMATIONS EXAMINED USING PROSPECTIVE COHORT STUDIES WITH EXPOSURE DURING FIRST TRIMESTER

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Chambers[6] 1996	fluoxetine	163	women with NTEs	254	Teratology Information Service Questionnaire completed by mother Questionnaire on birth outcomes Medical records review Infant's MD completed a form Physical exam	Neonatal period	Defined as a structural defect occurring in less < 4 % of the general population that has cosmetic or functional importance.	Determination of the effects of fluoxetine during the first trimester on the frequency of major and minor structural anomalies in infants and the effects of treatment during the third trimester on birth size, gestational age, and neonatal adaptation.
Diav-Citrin[7] 2008	paroxetine fluoxetine	463 346	women with NTEs	1,467	Teratology Information Service Interview at time of inquiry f/u questionnaire to woman or physician or one month post delivery date	To 6 years but mostly 2 years	Major anomalies were defined as structural abnormalities in the offspring that have serious medical, surgical or cosmetic consequences. Ventricular septal defects (VSDs) are structural anomalies of the heart. Significant neurodevelop-mental or functional problems also considered major anomalies	The primary was to evaluate prospectively the rate of major congenital anomalies after pregnancy exposure to paroxetine compared with fluoxetine.
Einarson[8] 2009	bupropion citalopram escitalopram fluoxetine fluvoxmine mirtazapine nefazodone paroxetine	928	women who were not exposed to antidepressants	928	Teratology Information Service Interview at time of inquiry Follow-up questionnaire to woman after delivery date Confirmation with infant's MD	Not specified	Not specified	Determine whether antidepressant as a group representative an increase risk for major malformations

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First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
	sertraline trazodone venlafaxine							
Klieger-Grossmann[9] 2012	escitalopram	213	mothers with exposure to (1) other antidepressants (SSRIs, venlafaxine, bupropion, trazodone/ nefazodone, and mirtazapine) or (2) NTEs	212 212	The Motherisk Program in Toronto Swiss Teratogen Information Service The Florence Teratogen Information Service	Within 3 months of estimated delivery date	Not specified	Determine whether the use of escitalopram during pregnancy is associated with an increased risk for major malformations above the baseline of 1% to 3%.
Kulin[10] 1998	fluvoxamine paroxetine sertraline	267	Random selection of women with NTEs.	267	Teratology Information Service Interview with mother f/u questionnaire to woman after delivery date corroboration with medical records	6 – 9 months after delivery	Presence of any anomaly that has an adverse effect on either the function or the social acceptability of the individual	To assess fetal safety and risk of fluvoxamine, paroxetine, and sertraline
Nordeng[11] 2012	citalopram escitalopram sertraline paroxetine fluoxetine fluvoxamine TCAs	699	no reported use of any antidepressants in the 6 months prior to or during pregnancy	65,751	Meciical Birth Registry of Norway Two questionnaires during pregnancy	Not stated	Malformations were defined as any birth defect, Malformations according to the International Clearinghouse for Birth Defects definition. ICD-10 code Q20-28	The primary aim was to investigate whether exposure to antidepressants, and specifically SSRIs, during the first trimester was associated with the occurrence of congenital malformations above the baseline risk.
Pastuszak[12] 1993	fluoxetine	128	2 groups: women exposed to TCAs during first trimester and women with NTEs	128 128	Teratology Information Service Interview – prenatal Interview - post natal Infant's physician completed a form	8-12 months	Not defined	To compare pregnancy outcome following first-trimester fluoxetine exposure with pregnancy outcome in two matched control groups.

Congenital malformations examined using a retrospective cohort study design (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Cole[13] 2007	Bupropion	1,213	2 groups bupropion within 18 months of delivery or after 1st trimester and other antidepressants during 1st trimester	1,049 4,743	Ingenix Research Data Mart containing medical and pharmacy claims data	Not specified	a structural abnormality with surgical, medical, or cosmetic significance	To determine whether first trimester bupropion exposure maybe associated with cardiovascular or congenital malformations
Davis[14] 2007	SSRIs	1,047 exposed to SSRIs	mothers of infants not prescribed antidepressants during pregnancy, but who may have had other medications prescribed	49,663	HMO Research Network's with data from: Group Health Cooperative Harvard Pilgrim Health Care Henry Ford Health System Kaiser Permanente Colorado Kaiser Permanente Northwest	1 year	ICD 9, codes not specified	Evaluate the risk for congenital anomalies and adverse perinatal events among infants exposed to antidepressants during pregnancy
Malm[15] 2005	citalopram, fluoxetine fluvoxamine paroxetine sertraline	1,782	women with no drug purchases from 1 month prior to and during pregnancy	1,782	4 registries from Finland: Medical Birth Register, National Register of Congenital Malformations, Hospital Discharge Register, Cause-of-Death Register	Up to 1 year of age	ICD-9 for major congenital malformations	Determine whether exposure to SSRIs during early pregnancy is associated with an increased risk of major malformations.
Oberlander[16] 2008	citalopram fluoxetine fluvoxamine paroxetine sertraline venlafaxine	SSRIs: 2,625 BZ: 968 SRI+BZ: 359	women with no exposure to SSRIs	107,320	BC Linked Health Database hospital separation records; PharmaCare registry of subsidized prescriptions; the Medical Services Plan physician billing records; the registry of Medical Services Plan subscribers	Not specified	ICD-9 codes for major anomalies + VSD and ASD	To study whether the risk for major congenital malformations and congenital heart defects differs between first trimester SRI+ BZ exposure and no exposure at all.
Pedersen[17] 2009	citalopram fluoxetine paroxetine sertraline bupropion	1,370	mothers of infants not exposed to SSRIs	493,113	4 Danish registries: Medical birth registry, National register of medicinal product statistics, Fertility database National hospital register	2 years	Eurocat categorization	To investigate any association between selective serotonin reuptake inhibitors (SSRIs) taken during pregnancy and congenital major malformations

Simon[18] 2002	fluoxetine, fluvoxamine, paroxetine sertraline TCAs	185	women with no exposure to SSRIs	185	Group Health Cooperative database	Up to 2 years	Not defined	To evaluate the effects of prenatal antidepressant exposure on perinatal outcomes, congenital malformations, and early growth and development.
Wen[19] 2006	SSRIs	972	women who did not receive SSRIs	3,878	The Saskatchewan Health databases	Up to 1 year of age	ICD-9, codes not specified	The objective of the current study was to make a comprehensive assessment of the safety of prescription SSRIs in pregnancy (including periconception period), with the use of a large population database.

Congenital malformations examined using case-control studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Alwan[20] 2007	paroxetine sertraline, fluoxetine	9,622	random selection of mothers of infants born with no major birth defects	4,092	Infant cases identified from National Birth defects Prevention study Pregnancy information via structured interview of the mother	Not specified	Not specified	To determine the relationship between SSRI exposure and major malformations
Louik[21] 2007	paroxetine sertraline fluoxetine citalopram	9,849	women not exposed to anti-depressants 56 days prior to LMP to end of pregnancy	5,860	Infants identified from Slone Epidemiology Center Birth Defects Study Questionnaire completed by mother via in person interview or over the telephone.	Not specified	ICD 9, codes not specified	Evaluate whether there is an increased risk of omphalocele, craniosynostosis and congenital heart defects and also considered other specific birth defects in relation to first-trimester use of specific SSRIs.
Ramos[22] 2008	citalopram fluoxetine fluvoxamine paroxetine sertraline escitalopram bupropion mirtazapine	189	mothers of infants born with no major birth defects	2,140	Medication and pregnancy Registry data Self-administered questionnaire	12 months after birth	ICD-9 codes, codes not specified	To determine whether duration of antidepressant use during the first trimester increases the risk of major congenital malformations in offspring of women diagnosed with psychiatric disorders

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
	moclobemide nefazodone trazodone venlafaxine TCAs							

Cardiovascular malformations examined using prospective cohort studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Einarson[23] 2008	paroxetine	1,174	women exposed to drugs considered safe in pregnancy	1,174	Teratology Information Service Interview at time of inquiry f/u questionnaire to woman or physician or one month post delivery date	Not specified	Not specified	Determine whether paroxetine was associated with an increased risk of cardiovascular defects in infants of women exposed to the drug during the first trimester of pregnancy.
Merlob[24] 2009	paroxetine fluoxetine citalopram escitalopram sertraline fluvoxamine venlafaxine	235	women with no SSRI exposure	67,871	Standardized pregnancy questionnaire following discharge: medical chart review for medication and cardiovascular malformations	Second or third day of life	Not specified	The aim of the present prospective study was to compare the rate of congenital heart malformations in SSRI-exposed versus non-exposed newborns.

Cardiovascular malformations examined using retrospective cohort studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Wichman[25] 2009	fluoxetine, paroxetine sertraline citalopram escitalopram venlafaxine	808	women with no exposure to SSRIs	24,406	Mayo Clinic Division of Obstetrics delivery database Review of medical record	At birth	Congenital heart disease: abnormality in cardio circulatory structure or function that is present at birth; includes VSD even if closed prior to discharge	To determine the risk of congenital cardiac malformations with the use of SSRIs during pregnancy.

Cardiovascular malformations examined using case-control studies (exposure during first trimester)

First author and year	Medications investigated	n Exposed	Comparison group	n	Information Source	Follow-up period	Criteria used	Primary outcome
Alwan[26] 2010	bupropion	6,853	liveborn with no major birth defects, randomly selected from the same geographical populations using either birth hospital or vital records.	5,869	National Birth Defects Prevention Study Standardized telephone interviews of mothers of either case or control infants regarding demographics and pregnancy exposures.	Interviews were conducted 6 weeks to 2 years after the estimated date of delivery	Classification system developed for NBDP, incorporating three dimensions of cardiac phenotype, cardiac complexity, and extra cardiac anomalies	Association between bupropion exposure and congenital cardiac defects
Bakker[27]	paroxetine	678	children with	1,293	Eurocat Northern Netherlands	Not specified	ICD-9 and 10,	Association between use of

2010			chromosomal or single gene disorders		database, from voluntary reports review of medical charts		codes not specified	paroxetine in early pregnancy and the occurrence of specific heart defects.
Bérard[28] 2007	paroxetine Other SSRIs	Major malformations = 101 Major cardiac malformations=24	women exposed to other antidepressants, not SSRIs	1,302	3 administrative databases from Quebec: La Regie de l'Assurance Maladie du Quebec (RAMQ), Med-Echo, Le fichier des evenements demographiques du Quebec (birth and death registries) of l'Institut de la Statistique du Quebec (ISQ) Databases	12 months	ICD-9, codes not specified	Quantification of the association between exclusive first trimester exposure to paroxetine and occurrence of any major congenital malformations, and more specifically, major cardiac malformations, as compared with exclusive first trimester exposure to other selective serotonin reuptake inhibitors (SSRIs) or other antidepressants.

Abbreviations: BZ: benzodiazepines; ICD: International Classification of Diseases; NTE: nonteratogenic exposures; SSRI: Selective Serotonin Uptake Inhibitor; TCA: Tricyclic antidepressants

TABLE 2 Summary statistics (N=23 studies)*

Malformation	Model	Studies	N	Exposed	RR/OR	LL	UL	$\chi^2_{homogeneity}$	P	I^2
All	All cohort studies	14	737,929	18,824	1.10	0.97	1.18	15.73	0.264	17.3%
	Prospective cohort	7	67,729	2,982	1.24	0.95	1.62	6.00	0.423	0
	Retrospective cohort	7	670,200	13,842	1.03	0.93	1.15	5.77	0.449	0
	Case-control studies	3	30,362	1,818	1.09	0.95	1.25	0.49	0.782	0
Cardiac	All cohort studies	14	823,752	15,872	1.11	0.76	1.62	34.13	<0.001	61.9%
	Prospective cohort	8	135,962	3,389	1.32	0.71	2.46	12.14	0.096	42.3%
	Retrospective cohort	6	687,792	12,484	0.96	0.59	1.57	19.97	0.001	75.0%
	Case-control studies	4	26,177	390	0.81	0.36	1.82	26.06	<0.001	88.5%

*Data were obtained from 23 individual studies, including 9 prospective cohort, 8 retrospective cohort, and 6 case-control studies.
Where more than one control group was reported, non-teratogenic or non-exposed groups were used in these analyses.

FIG. 1 SEARCH STRATEGY AND DISPOSITION OF ARTICLES