RISK ASSESSMENT OF BIRTH DEFECTS IN HUMAN PREGNANCY

by

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ABSTRACT

Major birth defects occur in 2% to 3% of liveborn infants and are the leading cause of infant mortality. The cause of most birth defects is unknown. The objectives of this thesis are to (1) assess the risk of having a birth defect in human pregnancy following maternal use of common antidepressant medications and to (2) evaluate the risk of a birth defect or subsequent adverse outcome in relation to restricted fetal growth in early pregnancy.

I used data from the National Birth Defects Prevention study, a population-based case-control study of birth defects risk factors in the US to study the rates and patterns of antidepressant medication use around pregnancy and compare the prevalence of common antidepressant medication use among mothers of cases and mothers of controls. I found that selective serotonin reuptake inhibitors (SSRIs) were the most commonly used antidepressants among pregnant women, followed by bupropion, and that the rate of maternal antidepressant use significantly increased over the period between 1998 to 2005. I found that maternal use of SSRIs in early pregnancy was associated with the occurrence of anencephaly, craniosynostosis and omphalocele in the infant, whereas early pregnancy exposure to bupropion was associated with an increased risk for left outflow tract heart defects.

I also conducted a retrospective cohort study using ultrasound examination data on singleton pregnancies in women with regular menstrual cycles who had crown-rump length (CRL) measurements at the Ultrasound Unit of British Columbia Women's Hospital. I found that a first trimester CRL in the 10^{th} centile or less was strongly

associated with subsequent spontaneous abortion, delivering through a cesarean section or having an infant with low birth weight or length.

The results presented in this thesis indicate that maternal treatment with common antidepressant medications may increase the risk for certain birth defects and that restricted growth of the embryo may adversely affect subsequent pregnancy outcomes.

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LIST OF ABBREVIATIONS

Adjusted odds ratio (AOR)

BC Perinatal Database Registry (BCPDR)

Confidence interval (CI)

Crown rump length (CRL)

Food and Drug Administration (FDA)

Intrauterine growth retardation (IUGR)

Last menstrual period (LMP)

National Birth Defects Prevention Study (NBDPS)

Odds ratio (OR)

Relative risk (RR)

Selective norepinepherine reuptake inhibitor (SNRI)

Selective serotonin reuptake inhibitor (SSRI)

Serotonin (5-HT)

Serotonin transporter (5-HTT)

Tetracyclic antidepressants (TCA)

Ultrasound (US)

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DEDICATION

To my son, Jamal,

the joy of my life

CO-AUTHORSHIP STATEMENT

In chapter 2, “Patterns of antidepressant medication use among pregnant women in a US population”, I was responsible for the study design, performing the research, data analysis and interpretation of the data presented, and I was responsible for manuscript preparation with input from all contributing authors.

In chapter 3, “Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects, I was responsible for the study design, performing the research, data analysis and interpretation of the data presented. I was also responsible for preparation of the manuscript with input from all contributing authors. Sonja A. Rasmussen and Richard S. Olney were responsible for clinical case review.

In chapter 4, “Maternal use of bupropion and risk for congenital heart defects”, I was responsible for the study design, performing the research, data analysis and interpretation of the research presented. I was responsible for preparation of the manuscript with input from all contributing authors. Lorenzo D. Botto undertook case review of cardiac defects and Sonja A. Rasmussen was responsible for clinical case review.

In chapters 2, 3 and 4, collection of data was undertaken by the National Birth Defects Prevention Study (NBDPS). The NBDPS is a large ongoing multisite case-control study of birth defects risk factors conducted by the U.S. Centers for Disease Control and Prevention (CDC), Atlanta, Georgia. The study features meticulous definitions of cases and extensive information regarding pregnancy exposures obtained by standardized

telephone interviews with the mothers of thousands of babies with and without birth defects every year at 10 participating U.S. sites: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah.

In chapter 5, “Birth outcome in relation to low fetal crown rump length on early ultrasound examination”, I was responsible for design of the research project, data collection, analysis and interpretation of the data presented and manuscript preparation with input from all contributing authors.

1 INTRODUCTION

Congenital anomalies or birth defects are diagnosed in about 1 in 20 infants within the first year after birth and account for up to 25% of all perinatal deaths.[1] Genetic factors including chromosome abnormalities and single gene conditions are causes for about 15% of all recognized congenital anomalies; environmental factors are thought to account for about 10%, while gene-environment interactions produce about 20% to 25%. The cause for 50% of all congenital anomalies remains unknown.[2] My thesis was designed to identify factors that predispose to the development of some of these idiopathic birth defects.

This thesis is composed of two main parts that assess the risk of having a birth defect in human pregnancy. In Chapters 2, 3 and 4, I describe the frequency and patterns of antidepressant use among women in the perinatal period and during pregnancy, and compare the prevalence of maternal treatment with the two most commonly used classes of antidepressants during early pregnancy among infants with birth defects and controls. The second part of my thesis, described in chapter 5, attempts to determine if low crown-rump length measurements on early ultrasound examination predict having an infant with a birth defect or other adverse pregnancy outcomes.

1.1 Teratogenicity of drugs in human pregnancy: Antidepressants

A human teratogen is an agent that alters the growth or structure of the developing embryo or fetus, causing birth defects. Treatment with several prescription drugs has been established as being teratogenic in humans; some exposures that have been

found to induce a high risk for major birth defects include thalidomide, valproic acid and isotretinoin.[3] Unfortunately, prescription drugs are not tested for safety in human pregnancy before they are approved for marketing, and the passive adverse event reporting schemes required after approval have proven to be inefficient means of identifying drug treatments that cause birth defects. As a consequence, the average time required to recognize the human teratogenic potential of a newly marketed drug is more than 7 years, and the teratogenic risk or safety associated with more than 90% of prescription drugs approved since 1980 is unknown.[4]

In 2005, the Centers for Disease Control and Prevention announced that antidepressants were the leading therapeutic class of prescribed medications, according to a comprehensive analysis of ambulatory care visits to physicians' offices and hospital emergency and outpatient departments.[5] Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressant medications in general[6] and during pregnancy[7]. Fluoxetine (Prozac®), was introduced in 1988 and soon became the most frequently prescribed medication for depression worldwide.[8] Other currently used SSRIs include sertraline (Zoloft®), paroxetine (Paxil®), citalopram (Celexa®), escitalopram (Lexapro®) and fluvoxamine (Luvox®). Bupropion, the second most commonly used antidepressant in the US[7], was first marketed as an oral antidepressant (Wellbutrin®) and was subsequently developed as a non-nictoine aid to smoking cessation (Zyban®).[9] Other less frequently used antidepressants include tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs) and serotonin modulators.

The US Food and Drug Administration (FDA) initially classified all SSRIs in Pregnancy Category C (human data lacking; animal studies positive OR not done), but in 2005 the FDA and the manufacturer agreed to change paroxetine's label to Category D (human data show risk, but benefit may outweigh), indicating that there is evidence of risk to the fetus from studies in pregnant women and that paroxetine should not be used during pregnancy unless potential benefits outweigh the potential risk to the fetus.[10] This change was issued in response to preliminary analyses of two observational studies, unpublished at the time, which showed increased risks of cardiac defects[11] or congenital malformations overall[12] in infants of mothers treated with paroxetine in the first trimester of pregnancy compared to infants of mothers unexposed to SSRIs[11] or exposed to other antidepressants.[12]

SSRIs all share a similar mechanism of action in depression, but they vary with regard to their chemical structures and pharmacokinetic properties.[13] Therefore, although many studies of pregnancy outcome treat all drugs of this class as if they were the same, different SSRIs could affect the developing fetus differently. All available studies indicate that maternal SSRI treatment during the first trimester of pregnancy does not increase the overall risk of birth defects greatly, but data on some specific birth defects or maternal treatment with some particular SSRIs suggest that there may be an increased risk in certain circumstances. A summary of the main analytical studies on the risk of major malformations with SSRI treatment during the first trimester of pregnancy is presented in Table 1.1.

Below is a review of the several types of epidemiological studies that have been undertaken to assess the risks of first trimester treatment with frequently used antidepressants. It is important to understand the major differences between these studies and highlight their strengths and weaknesses in terms of their capability of identifying the potential teratogenicity of antidepressant treatment.

1.1.1 Exposure cohort (Teratogen Information Service) studies

This type of study identifies pregnant women when they request counseling about the teratogenic potential of medications or other products and then follows the women to determine pregnancy outcome. The first three reported epidemiological studies of pregnancy outcome in women who had taken SSRIs were performed through teratogen information services and found no significant difference in the rate of major malformations among the children of women who took fluoxetine[14, 15] or other SSRIs[16] during pregnancy compared to the children of women who did not. However, the rate of minor congenital anomalies was significantly higher in exposed pregnancies in the only study in which outcome was determined by physical examination of the child rather than by verbal report of the mother.[15] Because of their relatively small size and design, these studies could only detect very strong teratogenic effects. Also, in an exposure cohort study, women who call a teratogen information service tend to be from higher socioeconomic groups who are at a lower risk of having babies with many birth defects, making it more difficult to extrapolate the study findings to the population as a whole.

Table 1.1 Studies of selective serotonin reuptake inhibitor (SSRI) use during the first trimester of pregnancy and the risk of congenital anomalies in the infant.

Study	Study design	Cases/exposure (n)	Comparison group (n)	Findings	
				All malformations OR (95% CI)	Specific malformations OR (95% CI)
Pastuszak et al.[14]	Prospective cohort (teratogen information service)	Fluoxetine (128)	TCA (74); non-teratogenic exposure (128)	No significant difference	NA
Chambers et al.[15]	Prospective cohort (teratogen information service)	Fluoxetine (228)	Unexposed to SSRIs (254)	No difference in major malformations (P value: 0.63); significant increase in minor malformations (P value: 0.03)	NA
Kulin et al.[16]	Prospective cohort (teratogen information service)	Sertraline (147) Paroxetine (97) Fluvoxamine (26) (Studied as a group)	Unexposed to SSRIs (267)	No significant difference (RR: 1.06, 95% CI: 0.43-2.62)	NA
Diav-Citrin et al.[17]	Prospective cohort (teratogen information service)	Fluoxetine (346) Paroxetine (463) (Studied separately)	Unexposed to SSRIs or known teratogenics (1467)		Increased risk for cardiovascular anomalies with fluoxetine exposure (AOR: 4.47, 95% CI: 1.31-15.27)
Cole et al.[12]	Retrospective cohort (Data from United Healthcare)	Paroxetine monotherapy (815) Paroxetine mono- or polytherapy (1020)	Exposed to other antidepressants monotherapy (4198) or mono- or polytherapy (4936)	Increased risk for any congenital malformation (AOR: 1.89, 95% CI: 1.20-2.98) for monotherapy; (AOR: 1.76, 95% CI: 1.18-2.64) for mono- or polytherapy	No significant difference for cardiac malformations (AOR: 1.46, 95% CI: 0.74-2.88) for monotherapy; (AOR: 1.68, 95% CI: 0.95-2.97) for mono- or polytherapy

Study	Study design	Cases/exposure (n)	Comparison group (n)	Findings	
				All malformations OR (95% CI)	Specific malformations OR (95% CI)
Davis et al.[18]	Retrospective cohort	SSRIs (805) Paroxetine (182) (Studied as a group and separately)	Unexposed to SSRIs (49 031)	No significant difference among all SSRIs (RR: 0.97, 95% CI: 0.81-1.16) or among paroxetine-exposed infants (RR: 1.03, 95% CI: 0.73-1.48)	No significant difference for cardiac septal defects among all SSRIs (RR: 0.93, 95% CI: 0.50-1.73) or among paroxetine-exposed infants (RR: 0.50, 95% CI: 0.07-3.54). No significant difference for other cardiac anomalies among all SSRIs or paroxetine-exposed infants.
Simon et al.[19]	Retrospective cohort (population-based)	Fluoxetine (129) Sertraline (22) Paroxetine (38) (Studied as a group)	Unexposed to SSRIs (185)	No significant difference (OR: 1.36, 95% CI: 0.56-3.30)	NA
Wogelius et al.[20]	Retrospective cohort (population-based)	All SSRIs within second or third month after conception (453)	Unexposed to SSRIs (150,908)	Increased risk for congenital malformations (AOR: 1.8, 95% CI: 1.2-2.7)	Increased risk for congenital heart malformations (AOR: 1.6, 95% CI: 1.0-2.6)
Wen et al.[21]	Retrospective cohort (Population-based)	SSRIs (972)	Unexposed to SSRIs (3878)	No significant difference (AOR: 0.98, 95% CI: 0.59-1.64)	NA
Kallen and Otterblad Olausson[22]	Prospective cohort (population-based)	All SSRIs (6481) Fluoxetine (860) Sertraline (1807) Paroxetine (908) Citalopram (2579) Fluvoxamine (36) Escitalopram (66) (Studied as a group and separately)	Unexposed to any SSRI	No significant difference for any SSRI or individual SSRIs (AOR for any SSRI: 0.89, 95% CI: 0.79-1.07)	Increased risk for cardiovascular malformations with paroxetine exposure AOR: 1.63, 95%CI: 1.05-2.53)

Study	Study design	Cases/exposure (n)	Comparison group (n)	Findings	
				All malformations OR (95% CI)	Specific malformations OR (95% CI)
Malm et al.[23]	Retrospective cohort (population-based)	Fluoxetine (129) Sertraline (22) Paroxetine (38) (Studied as a group)	Unexposed to SSRIs (185)	No significant difference (OR: 1.36, 95% CI: 0.56-3.30)	NA
Berard et al.[24]	Retrospective cohort (population-based)	All SSRIs within second or third month after conception (453)	Unexposed to SSRIs (150,908)	Increased risk for congenital malformations (AOR: 1.8, 95% CI: 1.2-2.7)	Increased risk for congenital heart malformations (AOR: 1.6, 95% CI: 1.0-2.6)
Louik et al.[25]	Retrospective case-control (population-based)	Infants with birth defects (9849) subdivided in 14 categories	Infants without birth defects (5860)	NA	Associations between sertraline use and omphalocele (AOR: 5.7, 95% CI: 1.6-20.7) and septal defects (AOR: 2.0, 95% CI: 1.2-4.0) and between paroxetine use and right ventricular outflow tract obstructive defects (AOR: 3.3, 95% CI: 1.3-8.8)
Oberlander et al.[26]	Retrospective cohort (population-based)	All SSRIs (2,625) Fluoxetine (638) Sertraline (608) Paroxetine (993) Citalopram (101) Fluvoxamine (119) (Studied as a group and separately, monotherapy and in combination with benzodiazapine)	No exposure (107,320)	Increased risk for any congenital malformation following fluoxetine and benzodiazapine polytherapy in pregnancy	Increased risk for congenital heart defects among SSRI and benzodiazapine exposed pregnancies. Increased risk for congenital heart defects following citalopram exposure in pregnancy.

Study	Study design	Cases/exposure (n)	Comparison group (n)	Findings	
				All malformations OR (95% CI)	Specific malformations OR (95% CI)
Ramos et al.[27]	Nested case-control study (population-based)	Infants with major malformations (189)	Infants with no minor or major malformation diagnosed within the first 12 months (2,140)	No significant difference between mothers of cases and controls in terms of any antidepressant use or duration of antidepressant use.	NA.
Wichman et al.[28]	Retrospective cohort	All SSRIs (808) Fluoxetine (184) Sertraline (296) Paroxetine (134) Citalopram (122) Escitalopram (8) Venlafaxine (53) (studied as a group)	No exposure (24 406)	NA	No significant difference (P=0.23)
Pedersen et al.[29]	Retrospective cohort	All SSRIs (1370) Fluoxetine (348) Sertraline (259) Paroxetine (299) Citalopram (460) More than one type of SSRI (193) (Studied as a group and separately)	No exposure (493 113)	No significant difference	Increased risk for septal heart defects with any SSRI (AOR: 1.99, 95%CI: 1.13-3.53), and specifically with citalopram (AOR: 2.52, 95%CI: 1.04-6.10), sertraline (AOR: 3.25, 95%CI: 1.21-8.75) and taking more than one SSRI (AOR: 4.70, 95%CI: 1.24-12.7) Increased risk for any cardiac malformation and taking more than one type of SSRI (AOR: 3.42, 95%CI: 1.40-8.34)
Merlob et al.[30]	Prospective cohort	All SSRIs (235) Fluoxetine (66) Sertraline (8) Paroxetine (92) Citlaopram (43) Fluvoxamine (4) Studied as a group	No exposure (67 636)	NA	Increased risk for cardiac malformations with any SSRI exposure (RR: 2.17, 95% CI: 1.07-4.39)

Study	Study design	Cases/exposure (n)	Comparison group (n)	Findings	
				All malformations OR (95% CI)	Specific malformations OR (95% CI)
Alwan et al.[31] [1]	Retrospective case-control using NBDPS data (population based)	Infants with major birth defects (9622) subdivided in 18 categories	Infants with no birth defects (4092)	NA	Association between SSRI use and occurrence of anencephaly (AOR 2.4, 95% CI 1.1-1.5), craniosynostosis (AOR 2.5, 95% CI 1.5-4.0), and omphalocele (AOR 2.8, 95% CI 1.3-5.7)

AOR: Adjusted odds ratio; **NA**: not applicable; **NBDPS**: National Birth Defects Prevention Study; **OR**: odds ratio; **RR**: relative risk; **TCA**: tricyclic antidepressants.

[1] This study is described in detail in Chapter 3

A more recent exposure cohort study performed in Israel, Italy and Germany showed an increased risk of congenital anomalies in general and of cardiovascular anomalies in particular among the infants of women treated with fluoxetine or paroxetine early in pregnancy.[17] After adjustment for potential confounders, the increased risk for cardiovascular anomalies remained significant only for fluoxetine exposure.

With regard to bupropion, a prospective cohort study was performed through teratogen information services of the Motherisk Program in Toronto[32], which reported 105 livebirths with no major malformations among 136 women exposed to bupropion in the first trimester. The rate for spontaneous abortions, however, was significantly higher in the bupropion exposed group compared to a non-teratogen exposed group.

1.1.2 Studies based on linked administrative records

These are usually performed as cohort studies and may be population-based. Data are collected for administrative purposes (e.g., as prescription records or hospital discharge summaries) at the time a medical service is provided and are electronically linked to birth outcomes on a case-by-case basis. The main advantage of linked administrative record studies is their relative cost effectiveness – they use existing databases to identify exposed pregnancies and adverse outcomes, so it is not necessary to collect such data specifically for the study. However, this is also the greatest limitation of these studies because data collected for other purposes are not ideal for identifying associations between maternal drug exposures during pregnancy and birth defects in the offspring. For example, a record indicating that a particular medication was dispensed does not always establish when or even whether the drug was actually

taken. In addition, because of the cohort design, very large sample sizes (often many thousands of exposures) are necessary to assess possible associations with specific birth defect outcomes.

A study of maternal SSRI treatment with birth outcomes performed through linkage of hospital discharge records to pharmacy records within a large US health maintenance organization found no increased risk of major malformations[19], although this study only had the power to detect large risks of birth defects.

GlaxoSmithKline, the manufacturer of paroxetine, performed a study of linked administrative records from a US managed healthcare corporation and found an increased risk of major birth defects overall, and of heart defects specifically, among 815 infants whose mothers had received prescriptions for paroxetine as compared with infants whose mothers had received prescriptions for other antidepressants during pregnancy.[12] The use of a comparison group of women exposed to other antidepressants may limit confounding by maternal underlying illness. Based on the same linked data, the authors conducted a second study to look for an association of cardiovascular defects among infants of women who had received prescriptions for bupropion during the first trimester of pregnancy when compared to infants whose mothers received prescriptions for other antidepressants or infants whose mothers received bupropion prescriptions after the first trimester of pregnancy. No significant association was found.[33]

Another study based on administrative databases in Quebec, Canada, found a dose-dependent association of fetal malformations with maternal treatment with over 25

mg/day of paroxetine early in gestation.[24] A small but statistically significant increase of cardiac defects was also noted. These comparisons were made in reference to women taking other antidepressants. Using data from the same linked databases, these investigators found no association of any antidepressant use during the first trimester with risk of major birth defects in the child when women who did not take SSRIs during pregnancy but had been diagnosed with a psychiatric disorder prior to pregnancy were used as the comparison group.[27]

A study using data from 5 large US health maintenance organizations compared 182 infants whose mothers were prescribed paroxetine during the first trimester of pregnancy to infants whose mothers were not prescribed antidepressants at any time in pregnancy.[18] An increased risk of eye or limb anomalies among paroxetine-exposed infants was observed in this study[18], but a follow-up chart review revealed that the anomalies in most cases were either unconfirmed or resolved without treatment. No increased risk of cardiovascular anomalies was found, but the study had limited statistical power to detect an increased risk of similar magnitude to the one found in the GlaxoSmithKline study.[12] The lack of assessment for potential confounders was also a limitation.

An increased rate of congenital heart defects was observed among infants of mothers given prescriptions for an SSRI in combination with a benzodiazepine compared to no exposure to either drug in a population-based record linkage study in British Columbia.[26] Although such an association was not observed with monotherapy of any SSRI, citalopram treatment alone showed an association with a congenital heart defect, while fluoxetine taken with a benzodiazepine was associated with an increased risk for any

congenital defect. The main strength of this study was the ability to control for maternal depression; however, data for several other variables that may have contributed to birth defects were unavailable, and a diagnostic bias could not be ruled out.

Finally, a recent retrospective cohort study linking four Danish nationwide registries found an increased risk for septal heart defects in the infants of mothers who took an SSRI in early pregnancy, particularly if the medication used was sertraline or citalopram or a combination of more than one type of SSRI.[29]

1.1.3 Population-based prospective cohort studies

In this type of study, exposures are recorded during pregnancy without knowledge of the outcomes, which are obtained for an entire population in a comprehensive and ongoing fashion. The main advantage of such studies is that the number of affected births accumulates over time, allowing for increased power to test associations of rare outcomes without the need for the very high costs entailed by project-specific data collection.

A Danish population-based cohort study comparing the infants of untreated women to the infants of women who had been given prescriptions for any SSRI found a significant association with congenital anomalies in general.[20] The authors found stronger associations in the defined period when organogenesis occurs than at other times during pregnancy, as would be expected if the association were causal. However, the authors do not distinguish between the effects of different SSRI medications or even report which specific SSRI was most commonly prescribed to the women included. The study may also be subject to surveillance bias, whereby knowledge of the mother's

SSRI use during pregnancy might lead physicians to perform more thorough examinations of infants of exposed women, and to diagnostic bias, whereby infants born to SSRI-treated mothers were more likely to receive intensive neonatal care, which may increase ascertainment of malformations.

No significant increase in the overall rate of major malformations in infants of mothers with first trimester SSRI purchases was found in a Finnish cohort study, but a 3-fold increased risk of heart defects was observed among the infants of women with fluoxetine purchases during the first trimester of pregnancy.[23] This study was population based and included a large number of pregnancies in women who had purchased SSRIs.

Initial data from the Swedish Medical Birth Register showed no significant increase in the prevalence of malformations among children born to 969 women treated with SSRIs or other antidepressants during pregnancy[34, 35], but analysis of an updated cohort of 908 women who had been treated with paroxetine early in pregnancy showed a greater than expected prevalence of cardiovascular defects in the infants.[22] This population-based cohort study has a sample size that is sufficient to detect moderate increases in the risk of birth defects and the ability to account for many confounding factors. However, multiple testing is a critical limitation because many different types of malformations were studied without a prior hypothesis, and some of the associations found probably occurred by chance despite their nominal statistical significance.

In a recent prospective hospital-based cohort study in Israel[30], all infants of SSRI exposed mothers who had a persistent cardiac murmur on day 2 or 3 of life were

specifically examined by a pediatric cardiologist and by echocardiography to detect the presence or absence any cardiac abnormality. The authors found a doubling of the risk for nonsyndromic cardiac anomalies among infants of first-trimester SSRI exposed mothers compared to infants of unexposed mothers. This study, however, had a small sample size, and the analyses lacked information on and adjustments for potential confounders.

1.1.4 Retrospective case-control studies

In contrast to cohort studies, which measure the frequency of outcomes in exposed or unexposed control pregnancies, case-control studies measure the frequency of exposure in the pregnancies of mothers of babies with or (as controls) without birth defects. Exposure information in case-control studies is usually collected retrospectively through interviews or questionnaires given to mothers. These investigations are very useful for studying rare outcomes such as specific birth defects but may be limited by recall bias. They are also relatively expensive to perform because of the need to collect large amounts of data specifically for the study. Large data sets are required to obtain sufficient statistical power in case-control studies because even "common" exposures like SSRI treatment occur in no more than a small fraction of pregnancies.

In a case-control analysis performed with data from the Slone Epidemiology Center Birth Defects Study, investigators found a 3-fold greater frequency of maternal paroxetine treatment during the first trimester of pregnancy among infants with obstructive cardiac defects involving the right ventricular outflow tract in comparison to

infants without birth defects.[25] Associations were also found with first-trimester maternal sertraline treatment among infants with cardiac septal defects or omphalocele.

The first three studies outlined in this thesis use data from the National Birth Defects Prevention Study (NBDPS), an ongoing population-based multi-site case-control study of birth defect risk factors conducted in 10 US states. Using this case-control approach, I compared the frequency of maternal SSRI and bupropion use between mothers of case infants and mothers of control infants.

1.1.5 Animal studies of antidepressant exposure during pregnancy

Human clinical studies of the teratogenicity of drug treatments in pregnancy are all observational because it would not be ethical to perform experimental studies or randomized controlled trials in pregnant women to look for teratogenic effects. The use of animal models is, therefore, important, as they permit control of many potential confounding factors that may impair clinical studies. It is difficult to extrapolate results of available animal studies to humans, but available animal data do indicate the potential for SSRIs to alter morphogenesis.[36-39]

Evidence of reduced proliferation of fetal heart cells following blockade of serotonin 5-HT uptake by paroxetine has been demonstrated in rat models.[40] Delayed ossification was observed in the fetuses of rats or rabbits given 5 and 10 times the maximum human therapeutic dose of sertraline during the period of organogenesis.[41] No evidence of teratogenicity is said to have occurred in preclinical animal teratology studies with other SSRIs.[42-45]

With regard to bupropion, the frequency of malformations was not increased among the offspring of rats or rabbits treated during pregnancy with the equivalent of 19-56 or 3-19 times the maximum human therapeutic dose of bupropion[46], although it is unclear how carefully the pups were examined to determine the presence or absence of heart defects.

1.2 First trimester fetal growth and later outcome

Ultrasound imaging in the first trimester can be used to measure the crown-rump length (CRL) of the embryo. Early growth can then be estimated by comparing the actual size of the embryo or fetus with the expected size using standard growth charts based on gestational age estimated from the date of the last menstrual period (LMP). This procedure has been used frequently within the past 25 years for dating pregnancies.[47,48]

Later in pregnancy, fetal growth is measured by different ultrasound measurements – usually biparietal diameter, femur length and abdominal circumference. Because the majority of fetal weight gain occurs during the third trimester of pregnancy, studies have been conducted in which women at high risk for poor fetal growth were given dietary supplementation during the third trimester in order to reduce the risk of a baby born with low birth weight, but such treatments showed little or no effect on the infants of healthy pregnant women.[49] Instead, evidence now points towards a first trimester origin of fetal growth impairment[50] and suggests that the variability in size between embryos of identical age is greatest during the embryonic period of development prior to 8 weeks gestation.[51]

Smith[49] has summarized the evidence that fetal growth abnormalities originate from first trimester trophoblast dysfunction and that abnormal placentation in the first trimester of pregnancy is a key predictor for late pregnancy complications. Experimental studies in sheep showed that periconceptional undernutrition for the period of 60 days before and 30 days after conception resulted in accelerated fetal hypothalamic-pituitary-adrenal axis maturation, which subsequently led to an increased rate of preterm birth.[52]

Most human studies reporting a relationship between early growth and fetal outcome have used conceptions achieved through assisted reproductive techniques[51, 53] or twin-twin comparisons.[51] However, Smith et al.[50] reported a larger study of 4000 women attending prenatal care and found an association of smaller than expected CRL in the first trimester with low birth weight at term and extremely premature birth. Several studies were subsequently published showing that poor fetal growth measured using two ultrasound examinations in the second and third trimester was associated with an increased risk of small birth size and adverse neonatal outcome.[54-56] The use of fetal growth was shown to be a significantly better predictor than fetal size of risk for poor outcomes independent of absolute birth weight.[57]

The relationship of small size of the embryo early in gestation has also been investigated for some particular birth defects, and the data show a shortening of the CRL in aneuploidies with high postnatal mortality, notably trisomy 18[58-62] and trisomy 13.[59-61] Using data from the Metropolitan Atlanta Congenital Defects Program, significant associations of low birth weight for gestational age at delivery were shown for gastrointestinal, cardiovascular, central nervous system, genitourinary, musculoskeletal and craniofacial malformations.[63] These results suggest the possibility that fetal growth

restriction as early as the first trimester could be associated with the occurrence of birth defects that are not of chromosomal origin.

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2. PATTERNS OF ANTIDEPRESSANT MEDICATION USE AMONG PREGNANT WOMEN IN A US POPULATION[2]

2.1 Introduction

The risk of major depression among women ranges from 10 to 25%, with peak prevalence during childbearing age.[1-3] Untreated antepartum depression is a strong predictor of adverse reproductive outcomes, such as cesarean or preterm delivery, low birth weight, and neonatal intensive care unit admission[4-6]. In a comprehensive analysis of ambulatory care visits to physicians' offices and hospital emergency and outpatient departments, the U.S. Centers for Disease Control and Prevention found antidepressants to be the leading class of medications prescribed in 2005.[7] Selective serotonin-reuptake inhibitors (SSRIs) account for the majority of antidepressant prescriptions worldwide.[8]

Recent literature indicates a possible risk to the fetus with maternal use of SSRIs in pregnancy: In case-control studies, first trimester use has been associated with an increased risk for certain birth defects [9, 10], including cardiac defects[10, 11], while a number of cohort studies have shown an association between maternal use of an SSRI early in pregnancy and congenital malformations in general[12-14] or cardiac malformations in particular[13-17]. Third trimester use is a risk factor for neonatal

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withdrawal or toxicity[18-23], prematurity[18, 20, 22-26], low birth weight[19, 20, 23, 24] and persistent pulmonary hypertension of the newborn.[27, 28]

In 2006, the prevalence of SSRI use from 3 months before conception through the end of pregnancy was briefly described, based on data from the National Birth Defects Prevention Study (NBDPS) on infants born between 1997 and 2002.[29] In the present study, we expand and update this previous report to characterize the prevalence and pattern of antidepressant use in the periconceptional period and during pregnancy among women who had infants without birth defects between 1998 and 2005.

2.2 Methods

The NBDPS is the largest ongoing population-based case-control study of environmental and genetic risk factors for more than 30 selected categories of major birth defects in North America.[30] In the analysis reported here, we used data on mothers of liveborn infants with no major birth defects (controls), randomly selected from hospital or birth-certificate records from ten U.S. states (Arkansas, California, Georgia, Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas and Utah). Data from mothers of infants born on or after January 1, 1998, who had an estimated date of delivery on or before December 31, 2005, were included. Participation during this time period was 66.2%. This study received institutional review board approval at all participating sites.

Extensive information on the mother's characteristics and exposure to antidepressant medications during the period between 3 months before conception to delivery was collected by standardized telephone interviews conducted in English or Spanish

between 6 weeks and 2 years after the estimated date of delivery. Mothers with incomplete interviews were excluded. During the interview, mothers were asked about a number of specific medications by brand name including the following antidepressants: Prozac® (fluoxetine), Zoloft® (sertraline), Paxil® (paroxetine), and Wellbutrin® (bupropion). Mothers were also asked about their use of any other medications during this period. Time of conception was calculated as estimated date of delivery minus 266 days. Women were considered unexposed if they did not report use of any antidepressant medication in the period from 3 months before conception through the end of pregnancy.

Crude and adjusted odds ratios and 95% confidence intervals were calculated using logistic regression analyses to identify maternal characteristics associated with antidepressant use. These included maternal age (continuous), maternal race (non-Hispanic white, other), maternal education (≤12 years, >12 years), maternal prepregnancy body mass index [BMI] (continuous), any maternal smoking or alcohol use from 1 month before to three months after conception, use of any dietary supplement containing folic acid from one month before to one month after conception, annual family income (<$20,000, ≥$20,000), parity (no previous live births, ≥1 live births), pregnancy intendedness, timing of recognition of pregnancy (during 1st month, later than 1st month following conception), and presence or absence of pregestational type 1 or 2 diabetes mellitus or hypertension.

The chi-square test for trend was used to evaluate changes in reported use over time for Arkansas, California, Georgia, and Iowa. These states were selected because they contributed data from the same geographic areas for all of the 9 study years.

McNemar's chi-square statistic was used to assess the significance of the difference in proportions of antidepressant use during different months of pregnancy. All statistical analyses were performed with SPSS 11.0 (SPSS, Inc., Chicago, Illinois).

2.3 Results

A total of 6,582 mothers of infants without birth defects who had an estimated date of delivery between 1998 and 2005 and who completed the interview were included in this analysis. During this study period, the reported frequency of any antidepressant use in the period from 3 months before conception through the end of pregnancy was 4.5% (N=299) (Table 2.1). SSRIs accounted for the majority of reported antidepressants used, with an overall frequency of 3.8%. The most commonly reported SSRI was sertraline (1.6%), followed by fluoxetine (1.1%). Bupropion was the most commonly used non-SSRI antidepressant (0.7%), and the remaining reports were for a variety of other antidepressants, including venlafaxine (0.2%), tricyclics and other norepinepherine-reuptake inhibitors (0.2%), and serotonin modulators (0.1%).

Mothers who reported use of an antidepressant during the period between 3 months before conception until the end of pregnancy were more likely to be non-Hispanic white, to have higher education or a higher family income, to be taking folic acid and to have had more than one previous live birth compared to mothers who did not report use of an antidepressant (Table 2.2). Periconceptional smoking or alcohol use and having prepregnancy type 1 or 2 diabetes or hypertension were also associated with antidepressant use during this period. Following adjustments for all of the other characteristics listed in Table 2.2, independent significant associations with

antidepressant use remained only for maternal non-Hispanic white race and prepregnancy type 1 or 2 diabetes.

Table 2.1 Frequency of antidepressant use among 6,582 mothers of infants without birth defects in the three months before conception through the end of their pregnancy, NBDPS 1998-2005*

Antidepressant type	Number	% of antidepressant use	% of women taking antidepressants
Any antidepressant	299	-	4.5
Selective Serotonin-Reuptake Inhibitors	248	82.9	3.8
Sertraline	105	35.1	1.6
Fluoxetine	72	24.1	1.1
Paroxetine	51	17.1	0.8
Citalopram	16	5.4	0.2
Escitalopram	16	5.4	0.2
Bupropion	43	14.4	0.7
Serotonin Norepinephrine-Reuptake Inhibitors (Venlafaxine)	10	3.3	0.2
Tricyclics and other Norepinephrine-Reuptake Inhibitors	12	4.0	0.2
Serotonin modulators	7	2.3	0.1
Use of more than one antidepressant at the same time	23	7.7	0.3

* 35 women reported taking more than one type of antidepressant drug in the period of 3 months before conception to the end of pregnancy.

Using data from Arkansas, California, Georgia and Iowa, a significantly increasing time trend of antidepressant use around pregnancy is shown in figure 2.1 ($P < 0.001$). Reported use increased from 2.5% in 1998 to 5.5% in 2000, but dropped again to 3.0% in 2001, and then increased linearly over the years to reach 8.1% by 2005. Reported

use of an SSRI also showed a significant increase from 1.7% in 1998 to 6.1% in 2005 (P = 0.001).

Table 2.2 Characteristics of mothers of infants without birth defects who reported use of antidepressant medications in the period of 3 months before conception through the end of pregnancy, NBDPS 1998-2005.

Mothers' characteristics	Reported antidepressant use		OR (95% CI)	AOR (95% CI)*
	Yes N (%)	No N (%)		
Race or ethnic group				
Non-Hispanic white	252 (84.6)	3682 (58.9)	**3.8 (2.8-5.2)**	**4.5 (2.0-10.1)**
Other	46 (15.4)	2569 (41.1)	1.0 (Ref)	1.0 (Ref)
Education				
≤ 12 yr	101 (33.8)	2626 (41.9)	1.0 (Ref)	1.0 (Ref)
> 12 yr	198 (66.2)	3643 (58.1)	**1.4 (1.1-1.8)**	1.1 (0.5-2.2)
Annual family income				
< $20,000	62 (21.8)	1832 (32.1)	1.0 (Ref)	1.0 (Ref)
≥ $20,000	222 (78.2)	3881 (67.9)	**1.7 (1.3-2.2)**	0.8 (0.4-1.7)
Prepregnancy type 1 or 2 diabetes				
No	275 (98.2)	5839 (99.4)	1.0 (Ref)	1.0 (Ref)
Yes	5 (1.8)	37 (0.6)	**2.9 (1.1-7.4)**	**7.7 (1.3-44.1)**
Prepregnancy hypertension				
No	238 (79.9)	5442 (86.8)	1.0 (Ref)	1.0 (Ref)
Yes	60 (20.1)	828 (13.2)	**1.7 (1.2-2.2)**	0.7 (0.3-2.0)
Cigarette smoking†				
None	211 (70.6)	5113 (81.5)	1.0 (Ref)	1.0 (Ref)
Yes	86 (29.4)	1162 (18.5)	**1.8 (1.4-2.4)**	1.6 (0.8-3.2)
Alcohol use†				
No	146 (48.8)	3986 (63.8)	1.0 (Ref)	1.0 (Ref)
Yes	153 (51.2)	2261 (36.2)	**1.8 (1.5-2.3)**	1.7 (0.9-3.2)
Folic acid use‡				
No	119 (39.8)	3105 (49.5)	1.0 (Ref)	1.0 (Ref)
Yes	180 (60.2)	3173 (50.5)	**1.5 (1.2-1.9)**	1.5 (0.8-3.0)
Parity				
No previous live births	103 (34.4)	2543 (40.5)	1.0 (Ref)	1.0 (Ref)
≥1 previous live births	196 (65.6)	2733 (59.5)	**1.3 (1.0-1.6)**	1.8 (0.9-3.6)

Mothers' characteristics	Reported antidepressant use		OR (95% CI)	AOR (95% CI)*
	Yes N (%)	No N (%)		
Pregnancy intendedness				
No	76 (38.0)	1579 (34.4)	1.0 (Ref)	1.0 (Ref)
Yes	124 (62.0)	3010 (65.6)	0.8 (0.6-1.1)	0.5 (0.3-1.0)
Timing of pregnancy recognition				
During 1st month following conception	162 (54.4)	3214 (51.4)	1.0 (Ref)	1.0 (Ref)
Later than1st month following conception	136 (45.6)	3045 (48.6)	1.0 (0.6-1.6)	0.8 (0.4-1.6)
Location by state§				
Arkansas	28 (16.4)	305 (12.5)	1.2 (0.7-2.1)	
California	11 (6.4)	267 (10.9)	0.5 (0.3-1.1)	
Georgia	11 (6.4)	254 (10.4)	0.5 (0.3-1.2)	
Iowa	23 (13.5)	253 (10.3)	1.2 (0.6-2.1)	
Massachusetts	23 (13.5)	294 (12.0)	1.0 (Ref)	
New York	7 (4.1)	134 (5.5)	0.7 (0.3-1.6)	
North Carolina	27 (15.8)	362 (14.8)	0.9 (0.5-1.7)	
Texas	10 (5.8)	247 (10.1)	0.5 (0.3-1.1)	
Utah	31 (18.1)	330 (13.5)	1.2 (0.7-2.1)	
	Mean (SD)	**Mean (SD)**		
Maternal age, yr	28.5 (5.8)	27.6 (6.1)	1.0 (1.0-1.0)	1.0 (1.0-1.1)
Pre-pregnancy Body Mass Index (BMI), Kg/m^2	25.4 (6.2)	24.9 (5.6)	1.0 (0.9-1.0)	1.0 (1.0-1.1)

* Chi square test or analysis of variance *P*-value.

† Reported use in the one month before to 3 months after conception

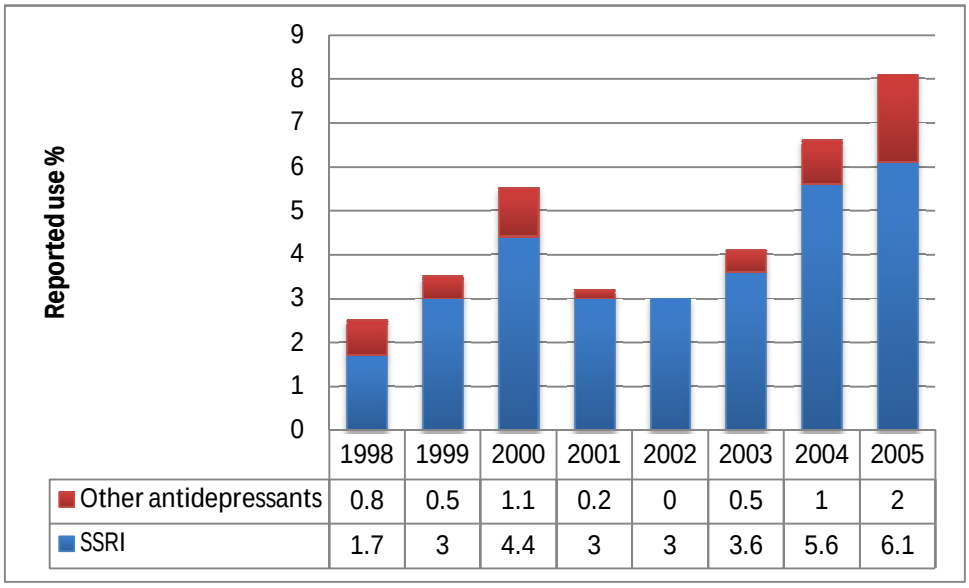
‡ Reported use in the one month before to 1 month after conception

§ Only data from 2003-2005 are used for this comparison. Chi square test was used in comparison to the state of Massachusetts.

¥ Adjusted for all other characteristics in this table except location by state using logistic regression (for categorical variables) or linear regression (for continuous variables)

SD: Standard deviation

Figure 2.1 Trend in the frequency of antidepressant medication use in the period of 3 months before through the end of pregnancy is shown over a 9-year period among women residing in Arkansas, California, Georgia or Iowa. NBDPS 1998-2005.



	1998	1999	2000	2001	2002	2003	2004	2005
Other antidepressants	0.8	0.5	1.1	0.2	0	0.5	1	2
SSRI	1.7	3	4.4	3	3	3.6	5.6	6.1

Figure 2.2 Frequency of antidepressant medication use per pregnancy month among 6,582 women of infants without birth defects. NBDPS 1998-2005.

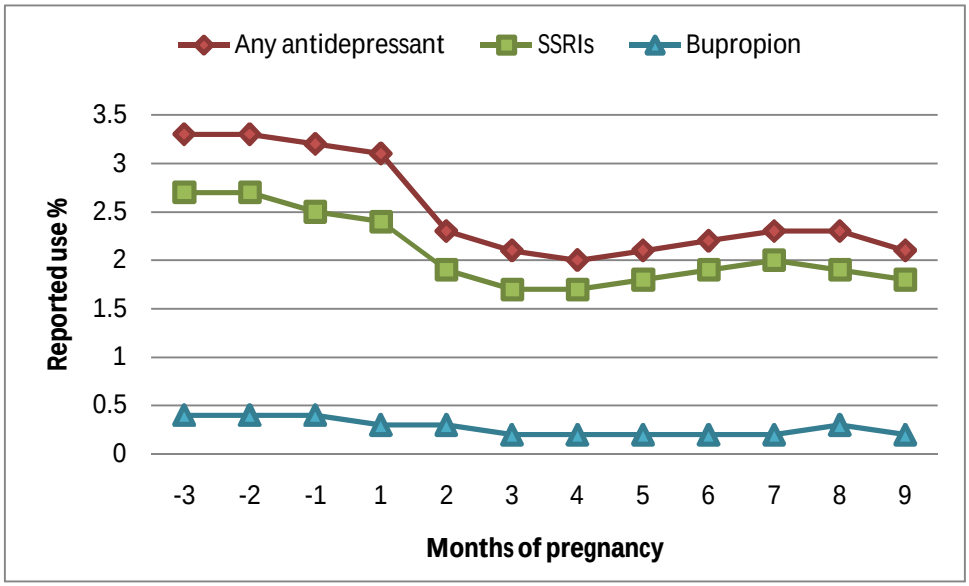


Figure 2.2 shows rates of reported antidepressant use by month of pregnancy. A sharp decrease in frequency of use is shown for the second month after conception: of the 202 women who used an antidepressant in the first month of pregnancy, 58 (28.7%) had stopped using their medication by the second month ($P<0.001$), and an additional 24 mothers (11.9%) had stopped by the third month post conception. Of the 82 women who used an antidepressant in the first month of pregnancy and discontinued treatment by the third month post conception, only 8 (10%) resumed later in pregnancy. The rate of antidepressant use after the third month following conception remained constant at 2.0-2.2%. The same patterns were observed for SSRIs and bupropion. The decrease in use is consistent with time of pregnancy recognition; of the 58 women who stopped using the antidepressant by the second month, 50 (86%) found out they were pregnant during the first or the second month after conception.

Twenty three women (8.0% of the women reporting antidepressants) reported use of more than one type of antidepressant medication simultaneously for two or more consecutive months between 3 months before and the end of pregnancy. Concomitant use of bupropion with an SSRI was common (14 women), while four women reported use of two different SSRIs simultaneously, and five used an SSRI in combination with either venlafaxine or a serotonin modulator. Twelve other women switched from one type of antidepressant medication to another at some point in pregnancy, but there was no apparent pattern for switching or time of switching.

2.4 Discussion

We describe patterns of antidepressant use around pregnancy using data from the NBDPS from mothers of liveborn infants without birth defects (controls) who had an estimated date of delivery between 1998 and 2005. A 3-fold increase in the rate of reported antidepressant use among pregnant women was noted over this 9-year period in the 4 states that contributed data from the same geographical region for the entire period, reaching a frequency of 8.1% in 2005. This was mainly attributable to an increase in SSRI use. Several recent studies in the US and the Netherlands have noted similarly increasing rates of antidepressant or SSRI use among pregnant women over time.[31-34] SSRIs have become increasingly popular in the last decade and are now also being prescribed for a variety of indications other than depression.[35] We were unable to determine the indication for which mothers were taking antidepressants because the women were not asked about this.

Nearly half of the women who reported taking an antidepressant in the month before conception stopped using it by the third month after conception, which appears to be related to the time at which pregnancy was recognized. This may indicate that many women stop taking an antidepressant upon recognition of pregnancy and/or that their healthcare providers may be reluctant to continue this treatment after pregnancy has been recognized. The decline in use was evident regardless of the type of antidepressant taken. These results are consistent with those reported in recent studies that showed decreased rates of antidepressant use or prescription after pregnancy occurred.[33, 34, 36, 37] In one population-based study using data from a prescription

database in the Netherlands[34], the authors found a gradual but significant decrease in the overall rate of SSRI use from before pregnancy and throughout the three trimesters, with a similar pattern evident over a 9-year period.

In a recent study of women with major depression, a higher rate of relapse during pregnancy was observed in women who discontinued antidepressant use after conception, compared to those who remained on medication during pregnancy.[38] If health care providers and their pregnant patients attempt to decrease the fetal risk of antidepressant use during pregnancy by discontinuing treatment, some women will be put at risk for relapse of their depression and its associated adverse pregnancy outcomes.[4, 19, 39]

Our study found associations of reported antidepressant use before and during pregnancy with higher education, smoking and non-Hispanic white race, in agreement with the results of previous reports[16, 33, 34, 36]. The association of antidepressant use observed following adjustments to other characteristics with type 1 or 2 diabetes prior to pregnancy has also been reported in a recent study[40], and clinically significant depression has been implicated to increase the risk of diabetes mellitus in other studies.[41]

Maternal sertraline treatment in early pregnancy has been investigated separately from other SSRIs in 4 studies[9, 10, 15, 17], and only two of these showed an association with birth defects (omphalocele[10] and cardiac septal defects[10, 17]) in the infant. Many more studies have reported on the safety or risk of maternal fluoxetine and paroxetine use in pregnancy. Some of the findings have been inconsistent[42], although evidence of an

association of cardiac defects with maternal paroxetine exposure has been found in four studies.[10, 11, 15, 43]

NBDPS controls are generally representative of the populations from which they are derived[44], but[30] it is important to note that our data may not fully represent the general population because they were obtained from mothers who had given birth to liveborn babies without birth defects and excluded women whose pregnancies had resulted in spontaneous or induced abortions, fetal deaths or infants with birth defects. In addition, the data were obtained from mothers residing in 10 US states and may not be representative of the US population as a whole. Another limitation of our study design is the retrospective nature of the exposure data. We cannot rule out the possibility of inaccurate recall, but this seems unlikely to account for the associations we observed with race, income, or alcohol or tobacco use. In addition, a recent study comparing prospective documentation to maternal retrospective recall of medication exposure in pregnancy concluded that retrospective data collection is unlikely to produce systematic underreporting of maternal psychotropic medication use.[45] With respect to the reporting of individual medications, however, inaccurate selective recall may have had an effect because women were asked specifically about their use of fluoxetine, sertraline, paroxetine, or bupropion using familiar brand names, but not about any other antidepressants.

Our finding of increasing rates of antidepressant use among pregnant women between 1998 and 2005 is supported by other recent studies.[31, 32 33, 34] One might expect changes in more recent years as a result of statements from the U.S. Food and Drug Administration (FDA) (e.g., FDA's warning related to a possible association of birth

defects and maternal paroxetine treatment in 2005[46] and the 2006 public health advisory related to SSRIs and persistent pulmonary hypertension of the newborn[47]). Therefore, there is a continuing need for large population-based studies with sufficient power to assess current use of antidepressants in pregnancy and to understand the effects of these medications on the developing fetus. In the meantime, healthcare providers who prescribe antidepressant medications to women of childbearing age should carefully assess and discuss the potential risks and benefits of continuing treatment during pregnancy with each patient.

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3. USE OF SELECTIVE SEROTONIN-REUPTAKE INHIBITORS IN PREGNANCY AND THE RISK OF BIRTH DEFECTS[3]

3.1 Introduction

The lifetime risk for major depression among women is 10 to 25 percent, with a peak prevalence during childbearing years.[1, 2] Selective serotonin reuptake inhibitors (SSRIs) are the most frequently used class of antidepressant medications in general[3] and during pregnancy.[4] Available data on the safety of SSRI medications in human pregnancy are limited, but recent investigations suggest that maternal SSRI treatment during pregnancy may be associated with birth defects generally,[5-7] or congenital heart defects in particular.[5, 7, 8]

We used data from the National Birth Defects Prevention Study (NBDPS) to evaluate the relationship between maternal SSRI treatment in early pregnancy and the occurrence of selected birth defects.

3.2 Methods

3.2.1 Study subjects and data collection

The NBDPS is an ongoing multi-site case-control study of environmental and genetic risk factors for more than 30 selected categories of major birth defects. Case infants

[3] A version of this chapter has been published. Alwan S, Reefhuis J, Rasmussen SA, Olney RS, Friedman JM. (2007) Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. N Engl J Med. 356: 2684-2692

were diagnosed with at least one selected birth defect and were ascertained through population-based birth defects surveillance systems at eight study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, and Texas).[9] We used data on infants born on or after October 1, 1997, who had an estimated date of delivery on or before December 31, 2002. Case infants were live births (all participating sites) or fetal deaths at ≥20 weeks' gestation (Arkansas, California, Georgia, Iowa, Massachusetts, and Texas). Pregnancies with reliably-ascertained defects that were electively terminated were also included in Arkansas, California, Georgia, Iowa, and Texas. Infants with recognized or strongly suspected chromosome abnormalities or single-gene conditions were excluded from the study.

The controls were liveborn infants with no major birth defects who were randomly selected from hospital or state birth-certificate records from the same geographic areas. Only one case or control infant was included from each multifetal pregnancy.

Birth defect categories that had at least 200 case mothers interviewed were selected for the analysis. This number was determined as that needed to obtain 80% power with an odds ratio of 2.5, given a 2.1% exposure rate to SSRIs among control mothers. Information on infants in each defect category were reviewed without knowledge of exposure status by clinical geneticists, who confirmed case eligibility and classified the cases as isolated (no additional major unrelated defect) or multiple (more than one major unrelated birth defect).[10] To reduce pathogenetic heterogeneity, cases with complex sequences (e.g., omphalocele-exstrophy-imperforate anus-spinal defects phenotype)[11] were excluded, and isolated defects were analyzed separately. A total of 709 infants who had more than one eligible birth defect were included in multiple

analyses. Each case with a heart defect was reviewed by a team of experts in pediatric cardiology and epidemiology of heart defects and assigned to a single cardiac diagnostic category.

Demographic and pregnancy exposure information was collected at 6 weeks to 2 years after the estimated date of delivery by standardized telephone interviews in English or Spanish with mothers of case and control infants.[9] Infants for whom complete maternal interviews were unavailable were excluded. The participation rates among case and control mothers were 71.1 and 68.6 percent, respectively.

The mothers were asked whether they took any of a specific list of medications identified by brand name, including Prozac (fluoxetine), Zoloft (sertraline) and Paxil (paroxetine) during and before pregnancy, and when each medication was taken. The women were also asked about their use of other medications during this period, which enabled us to analyze associations with other SSRIs. Exposure was defined as reported use of any SSRI from one month before to three months after conception (the date of conception was calculated as 266 days before the estimated date of delivery). Women were considered unexposed if they did not take a SSRI at any time during pregnancy or the three months before conception. Women who took non-SSRI antidepressants were included in the unexposed group.

3.2.2 Statistical analysis

Our hypothesis for this exploratory study was that SSRI exposure early in pregnancy is associated with one or more of the selected categories of birth defects. Crude analyses were done using Pearson's chi-square tests, and odds ratios and Fisher's exact

confidence limits were calculated with SPSS software, version 10.0, and with SABER, with the use of the same control group for every comparison.

The following potential confounders were evaluated: maternal race (non-Hispanic white vs. other), maternal age (35 years of age vs. 35 or older), maternal education (12 years or less vs. more than 12 years), prepregnancy obesity (body mass index [the weight in kilograms divided by the square of the height in meters] <30 vs.≥30), maternal smoking or alcohol use from one month before to three months after conception, maternal folic acid use from 1 month before to 1 month after conception, annual family income (less than $20,000 vs.$20,000 or more), singleton vs. multiple pregnancy, parity (no previous live births vs. one or more previous live births), and presence or absence of prepregnancy hypertension. Potential confounders were first evaluated for associations with SSRI exposure and with each of the specific defects, and were excluded from the logistic regression if their removal resulted in a change in risk estimate of less than 10 percent. All confounders retained in the model for any of the defects were included in the final models for all defects. Infants of mothers with prepregnancy type 1 or 2 diabetes were excluded from adjusted analyses because of the strong association of diabetes with birth defects.

For the defects with positive associations, we performed post-hoc analyses of SSRIs stratified by factors that were associated with both maternal SSRI use and with the outcomes. These factors were maternal race or ethnic group, age, education, presence or absence of obesity, presence or absence of smoking, presence or absence of hypertension, and singleton vs. multiple pregnancy. After identification of effect modification by obesity for craniosynostosis, as indicated by the Breslow-Day test, we

further evaluated the effect of obesity for all defects by performing analyses with a 4-level variable (obesity alone, SSRI exposure alone, both SSRI exposure and obesity, neither SSRI exposure nor obesity) by asymptotic and Fisher's exact logistic regression in LogXact software, version 4.0.[12]

We also performed crude and adjusted analyses for isolated defects only and assessed the association between four specific SSRIs (fluoxetine, sertraline, paroxetine, and citalopram [Celexa]). Analyses were done for four combined defect categories and between three specific SSRIs (fluoxetine, sertraline, and paroxetine) and 16 categories of birth defects when there were at least 3 exposed cases. Additional analyses were performed assessing the association between the use of any SSRI during two other time intervals of pregnancy and 16 categories of birth defects. No adjustment was made for the multiple comparisons performed.

3.3 Results

Eighteen birth defect categories and 8 heart defect subcategories met the criterion of at least 200 case mother interviews. Interviews were incomplete for 163 case or control mothers, and 5 mothers reported depression but did not report use of antidepressants. These subjects were excluded from the analysis, leaving 9,622 case and 4,092 control infants.

Of the 13,714 case or control mothers included, 408 (3.0%) reported using an SSRI at some point before or during pregnancy. The reported frequency of SSRI use in the period from 1 month before to 3 months after conception was 2.3%; 230 mothers of case infants (2.4%) and 86 mothers of control infants (2.1%) reported using an SSRI.

The SSRI most commonly used by control mothers was sertraline (0.8%), followed by fluoxetine (0.7%), paroxetine (0.5%) and citalopram (0.2%).

Table 3.1 gives the characteristics of case and control mothers and their reported use of SSRIs. Control mothers were significantly more likely than case mothers to be younger than 35 years of age, to have more than 12 years of education, and to have a higher family income. Mothers of infants with birth defects were more likely than mothers of control infants to smoke, have diabetes or hypertension and to be obese.

For two defects, anotia or microtia and intestinal atresia, there was only one case exposed, and therefore these defects were excluded from further analyses. Of the 16 remaining categories and 8 subcategories, three showed significant associations with SSRI use; anencephaly (214 infants, 9 exposed), craniosynostosis (432 infants, 24 exposed) and omphalocele (181 infants, 11 exposed) (Table 3.2). Confounders that met our criteria were maternal race, obesity, smoking, and family income, and these were included in the adjusted analyses.

After *post hoc* analyses assessing potential effect modification by seven variables showed significant effect modification by obesity for the association between SSRIs and craniosynostosis (P= 0.05 by the Breslow-Day test), we performed additional exploratory analyses of effect modification by obesity for all categories of defects using a four-level variable (Table 3.3). Among women who did not use SSRIs, obese women were more likely than nonobese women to have infants with conotruncal heart defects

Table 3.1 Characteristics of mothers of case and control infants. NBDPS 1997-2002

	Case mothers (N = 9,622)	Control mothers (N = 4,092)	X^2 *P* Value
Maternal race-ethnicity	**N/total N (%)**		
Non-Hispanic white	5861/9603 (61.0)	2454/4081 (60.1)	0.01
Non-Hispanic black	978/9603 (10.2)	491/4081 (12.0)	
Hispanic	2238/9603 (23.3)	931/4081 (22.8)	
Other	526/9603 (5.5)	218/4081 (5.0)	
Maternal age			
< 35 years	8057/9622 (83.7)	3508/4092 (85.7)	0.003
≥ 35 years	1565/9622 (16.3)	584/4092 (14.3)	
Maternal education			
≤ 12 years	4278/9613 (44.5)	1705/4084 (41.7)	0.003
> 12 years	5335/9613 (55.5)	2379/4084 (58.3)	
Maternal prepregnancy body mass index (BMI)			
Underweight (BMI < 18.5 kg/m^2)	565/9265 (6.1)	233/3931 (5.9)	<0.001
Normal weight (BMI 18.5-24.9 kg/m^2)	4975/9265 (53.7)	2253/3931 (57.3)	
Overweight (BMI 25-29.9 kg/m^2)	2058/9265 (22.2)	861/3931 (21.9)	
Obese (BMI ≥ 30 kg/m^2)	1667/9265 (18.0)	584/3931 (14.9)	
Maternal smoking*			
None	7488/9612 (77.9)	3294/4087 (80.6)	0.005
1-14 cigarettes per day	1721/9612 (17.9)	646/4087 (17.9)	
15-24 cigarettes per day	335/9612 (3.5)	126/4087 (3.1)	
> 25 cigarettes per day	68/9612 (0.7)	21/4087 (0.5)	
Annual family income			
< $20,000	2923/8750 (33.4)	1115/3564 (31.3)	0.05
≥ $20,000, < $50,000	2845/8750 (32.5)	1167/3564 (32.7)	
≥ $50,000	2982/8750 (34.1)	1282/3564 (36.0)	
Pregestational (Type 1 or 2) Diabetes			
No	8691/8884 (97.8)	3833/3854 (99.5)	<0.001
Yes	193/8884 (2.2)	21/3854 (0.5)	
Hypertension prior to pregnancy			
No	8093/9479 (85.4)	3558/4086 (87.1)	0.009
Yes	1386/9479 (14.6)	528/4086 (12.9)	
Maternal alcohol intake*			
No	5899/9622 (61.3)	2501/4092 (61.1)	0.84
Yes	3723/9622 (38.7)	1591/4092 (38.9)	

	Case mothers (N = 9,622)	Control mothers (N = 4,092)	X^2 *P* Value
	N/total N (%)		
Maternal folic acid intake 1 month before to one month after conception			
No	4832/9622 (50.2)	2056/4092 (50.2)	0.98
Yes	4790/9622 (49.8)	2036/4092 (49.8)	
Plurality			
Singleton pregnancy	8996/9606 (93.6)	3957/4087 (96.8)	<0.001
Multiple pregnancy	610/9606 (6.4)	130/4087 (3.2)	
Parity			
No previous live births	4171/9619 (43.4)	1635/4090 (40.0)	<0.001
≥ 1 previous live births	5448/9619 (56.6)	2455/4090 (60.0)	
Use of SSRIs*			
No†	9320/9550 (97.6)	3979/4065 (97.9)	0.30
Yes	230/9550 (2.4)	86/4065 (2.1)	
Use of non-SSRI antidepressants*			
No†	9229/9302 (99.2)	3954/3974 (99.5)	
Yes	73/9302 (0.8)	20/3974 (0.5)	0.08
Time interval of expected due date to interview date			
< 1 year	6127/9603 (63.8)	3216/4077 (78.9)	
≥ 1 year	3476/9603 (36.2)	861/4077 (21.1)	<0.001

* Exposure anytime between 1 month before and 3 months after conception.
† No exposure for the period 3 months before through the end of pregnancy.

(adjusted odds ratio, 1.3; 95% confidence interval [CI], 1.0 to 1.6) and septal heart defects (adjusted odds ratio, 1.3, 95% CI, 1.1 to 1.5). The associations were stronger among women reporting SSRI use: for conotruncal heart defects, the adjusted odds ratio was 3.5 and the 95% CI was 1.4 to 8.7; for septal heart defects, the adjusted odds ratio was 2.8 and the 95% CI was 1.3 to 6.4. Among nonobese women, SSRI use was associated with craniosynostosis (adjusted odds ratio, 2.0; 95% CI, 1.1-3.7), but the risk was greater among obese women who reported SSRI use (adjusted odds ratio, 5.9; 95% CI, 2.4 to 14.3).

Restricting the analyses to cases with isolated defects resulted in wider confidence intervals and a loss of statistical significance but only a slight reduction in the odds ratios (Table 3.5). Restricting the exposure period to the first two months of pregnancy did not change the estimates appreciably (data not shown). Since the critical period for

Table 3.2 Associations between maternal use of any SSRI and major birth defects, NBDPS 1997-2002.

Birth Defect Categories (N)	SSRI					
	Crude Analysis			Adjusted Analysis*		
	Exposed N	Odds Ratio	95% CI	Odds Ratio	95% CI	*P*-value
Controls (4,092)	83					
Anencephaly (214)	9	2.0	1.0-4.3	2.4	1.1-5.1	0.02
Spina bifida (457)	7	0.7	0.3-1.6	0.7	0.3-1.7	0.47
Anotia/microtia (253)	1					
Conotruncal heart defects (977)	25	1.3	0.8-2.1	1.3	0.8-2.1	0.19
Transposition of great arteries (309)	9	1.4	0.7-3.0	1.4	0.7-3.0	0.27
Tetralogy of Fallot (428)	10	1.2	0.6-2.3	1.2	0.6-2.5	0.47
Septal heart defects (1931)	43	1.1	0.7-1.7	1.1	0.7-1.6	0.51
Perimembraneous VSD (797)	18	1.1	0.6-1.9	1.2	0.7-1.9	0.57
ASD secundum (768)	17	1.1	0.6-1.9	1.1	0.6-1.8	0.76
ASD NOS (252)	5	1.0	0.3-2.4	1.0	0.4-2.5	0.99
Right outflow tract heart defects (669)	16	1.2	0.7-2.0	1.3	0.7-2.2	0.38
Pulmonary valve stenosis (480)	12	1.3	0.6-2.3	1.3	0.7-2.4	0.38
Left outflow tract heart defects (691)	14	1.0	0.5-1.8	0.9	0.5-1.7	0.82
Hypoplastic left heart (218)	3	0.6	0.2-2.2	0.6	0.2-2.1	0.50
Coarctation of aorta (358)	7	1.0	0.3-2.1	0.8	0.3-2.0	0.74
Cleft lip with or without palate (1127)	22	1.0	0.6-1.6	0.8	0.5-1.4	0.63
Cleft palate (620)	11	0.9	0.4-1.7	0.8	0.4-1.5	0.56

Birth Defect Categories (N)	SSRI					
	Crude Analysis			Adjusted Analysis*		
	Exposed N	Odds Ratio	95% CI	Odds Ratio	95% CI	*P*-value
Esophageal atresia (300)	9	1.5	0.7-3.0	1.3	0.6-2.7	0.48
Intestinal atresia (262)	1					
Anorectal atresia (418)	8	1.0	0.4-2.0	0.7	0.3-1.8	0.53
Hypospadias, 2nd or 3rd degree (823)	14	0.8	0.4-1.5	0.7	0.4-1.4	0.32
Transverse limb deficiencies (346)	8	1.1	0.5-2.4	1.2	0.6-2.6	0.55
Craniosynostosis (432)	24	2.8	1.7-4.5	2.5	1.5-4.0	< 0.001
Omphalocele (181)	11	3.2	1.6-6.1	2.8	1.3-5.7	0.005
Diaphragmatic hernia (297)	10	1.7	0.8-3.3	1.6	0.8-3.3	0.18
Gastroschisis (413)	11	1.3	0.7-2.5	1.3	0.6-2.6	0.42

VSD: Ventricular septal defect; ASD: Atrial septal defect; NOS: not otherwise specified.
* Adjusted for maternal race, obesity, smoking, and family income. Cases with pregestational (type 1 or 2) diabetes are excluded.

craniosynostosis development may extend beyond the first trimester, we examined SSRI use during the second or third trimesters and found a lower odds ratio (17 exposed; adjusted odds ratio, 1.9; 95% CI, 1.0 to 3.5). Sixteen of these women were also exposed to an SSRI during the first trimester.

In additional *post hoc* analyses, we evaluated the risks associated with 4 individual SSRIs by assessing associations for all 18 evaluated defects combined and of specific groups of birth defects (Table 3.4). None of the individual SSRIs was associated with significantly increased risks of all 18 birth defects combined, the four cardiac birth defects combined, or the 14 noncardiac birth defects combined. The use of paroxetine or citalopram significantly increased the risk of the pooled group of anencephaly, craniosynostosis, and omphalocele (Table 3.4).

We also assessed the association between the three most commonly used SSRIs (fluoxetine, sertraline and paroxetine) and 16 specific categories of birth defects, but these analyses were limited by the small numbers of exposed cases for each category (See Table 3.6). We found one significant association each for fluoxetine and sertraline: fluoxetine use was associated with craniosynostosis (10 exposed infants; adjusted odds ratio, 2.8; 95% CI, 1.3-6.1) and sertraline use with anencephaly (4 exposed infants; adjusted odds ratio, 2.8; 95% CI, 1.1 to 9.3). We found four significant associations for paroxetine: with anencephaly (five exposed infants; adjusted odds ratio, 5.1; 95% CI, 1.7 to 15.3), right ventricular outflow tract obstruction defects (seven exposed infants; adjusted odds ratio, 2.5; 95% CI, 1.0 to 6.0), omphalocele (six exposed infants; adjusted odds ratio, 8.1;95% CI, 3.1 to 20.8), and gastroschisis (five exposed infants; adjusted odds ratio, 2.9; 95% CI, 1.0 to 8.4). None of the mothers of case infants with defects found to be associated with SSRI use was concomitantly exposed to medications with a known teratogenic effect.

Table 3.3 Crude odds ratios with Fisher's exact confidence intervals and multiplicative interaction p-values for associations between maternal use of any SSRI and selected birth defects stratified by maternal prepregnancy obesity (BMI ≥30). NBDPS 1997-2002.

Birth Defect	No SSRI			SSRI				p-value multi-plicative interaction
	Not obese*	Obese		Not obese		Obese		
	N	N	Odds Ratio (95% CI)	N	Odds Ratio (95% CI)	N	Odds Ratio (95% CI)	
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 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 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 Outflow Tract defects	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 Outflow Tract defects	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	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, 2nd or 3rd 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 defects	263	53	1.2 (0.8-1.6)	6	1.1 (0.4-2.4)	2	1.9 (0.2-8.4)	†
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		†

Cases with pregestational (type 1 or 2) diabetes are excluded.

* Reference category.

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

Table 3.4 Adjusted odds ratios (ORs) and 95% confidence intervals for associations of maternal use of individual SSRIs and pooled birth defect categories. NBDPS 1997-2002.

	Fluoxetine		Sertraline		Paroxetine		Citalopram	
	Exposed N	Adjusted* OR (95% CI)	Exposed N	Adjusted* OR (95% CI)	Exposed N	Adjusted* OR (95% CI)	Exposed N	Adjusted* OR (95% CI)
Controls	29		32		18		7	
18 Birth Defect Categories Pooled	76	1.1 (0.7-1.7)	68	0.9 (0.6-1.4)	70	1.6 (0.9-2.7)	22	1.2 (0.5-2.8)
4 Heart Defect Categories[†‡]	33	1.2 (0.7-2.1)	22	0.7 (0.4-1.3)	32	1.7 (0.9-3.1)	11	1.5 (0.6-4.0)
14 non Heart Defect Categories[†‡]	47	1.1 (0.7-1.7)	51	1.0 (0.6-1.6)	42	1.5 (0.9-2.7)	12	1.0 (0.4-2.5)
3 Birth Defect Categories Previously Identified as Positively Associated with SSRI use[†¥]	13	1.9 (1.0-4.0)	13	2.0 (1.0-3.9)	16	4.2 (2.1-8.5)	6	4.0 (1.3-11.9)

* Adjusted for maternal race, obesity, smoking and family income. Cases with pregestational (type 1 or 2) diabetes are excluded.

[†] Cases with at least one defect from the heart defect categories and at least one defect from the non-heart defect categories have been included in both categories.

[‡] The 4 heart defect categories include conotruncal, septal, right outflow tract, and left outflow tract heart defects. The 14 non-heart defect categories include anencephaly, spina bifida, anotia/microtia, cleft lip with or without palate, cleft palate, esophageal atresia, intestinal atresia, anorectal atresia, hypospadias (2nd or 3rd degree), transverse limb deficiencies, craniosynostosis, omphalocele, diaphragmatic hernia and gastroschisis.

[¥] These include cases with craniosynostosis, omphalocele or anencephaly, defects previously identified as associated with maternal use of any SSRI.

Table 3.5: Crude and adjusted odds ratios (ORs) and 95 percent confidence intervals for associations of maternal use of any SSRI between one month before and 3 months after conception and the occurrence of selected isolated birth defects, NBDPS 1997-2002.

Birth Defect Categories (N)	SSRI					
	Crude Analysis			Adjusted Analysis*		
	Exposed N	OR	95% CI	OR	95% CI	P-value
Controls (4,092)	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 outflow tract heart defects (610)	15	1.2	0.7-2.1	1.3	0.7-2.3	0.36
Left outflow tract heart defects (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 (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, 2nd or 3rd 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

* Adjusted for maternal race, obesity, smoking and family income. Cases with pregestational (type 1 or 2) diabetes are excluded.

Table 3.6 Adjusted odds ratios (ORs) and 95 percent confidence intervals for associations of maternal use of specific SSRIs and selected birth defects, NBDPS, 1997-2002.

	Fluoxetine		Sertraline		Paroxetine	
	Exposed N	Adjusted* OR (95% CI)	Exposed N	Adjusted* OR (95% CI)	Exposed N	Adjusted* OR (95% CI)
Controls	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 outflow tract heart defects (669)	4	0.9 (0.3-2.7)	4	0.8 (0.3-2.3)	7	2.5 (1.0-6.0)
Left outflow tract heart defects (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 (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, 2nd or 3rd 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)

* Adjusted for maternal race, obesity, smoking and family income. Cases with pregestational (type 1 or 2) diabetes were excluded.

3.4 Discussion

Using data from a population-based case-control study, we found no significant increase in the risks of the majority of birth defects assessed, including congenital heart defects. However, we observed associations between SSRI use and the occurrence of

anencephaly, craniosynostosis, and omphalocele, defects that had not been previously associated with maternal SSRI use in pregnancy

Studies in laboratory animals have demonstrated delayed ossification after maternal treatment with sertraline.[13, 14] A specific role of serotonin in cardiac and craniofacial morphogenesis has been established in the rodent embryo.[15-17] Several recent reports have suggested possible associations between maternal SSRI use during pregnancy and birth defects in humans. An increased risk was seen for heart defects, specifically ventricular and atrial septal defects, among infants whose mothers took paroxetine (but not other SSRIs) in a report from the Swedish Medical Birth Register.[18] The authors did not find the associations we observed between SSRI use and craniosynostosis or abdominal wall defects (omphalocele and gastroschisis were not examined separately).

Cole et al. conducted a US study of linked administrative records from a US managed care organization[19] and found an increased risk of major birth defects in general and of cardiovascular defects in particular among infants whose mothers received prescriptions for paroxetine compared to prescriptions for other antidepressants during pregnancy. Similar results were shown in an exposure cohort study among women treated with paroxetine or fluoxetine during the first trimester as compared to women who did not take SSRIs.[20] A cohort study based on administrative data from Quebec, Canada, showed that the risk of major birth defects and of heart defects were greater among infants whose mothers were prescribed high doses of paroxetine during early pregnancy than among those whose mothers took non-SSRI antidepressants, but this association was not seen among infants whose mothers were prescribed lower doses of paroxetine.[7]

In a Finnish cohort study, the overall risk for major malformations was not significantly increased among infants born to women treated with fluoxetine during the first trimester of pregnancy, but a 3-fold increased risk of heart defects was noted.[21] A Danish cohort study found an increased risk of congenital malformations in general among women given prescriptions for any SSRI.[6] Other epidemiological studies have not found a significant association between major birth defects and maternal SSRI treatment during pregnancy.[22-26] However, all previous studies had limitations, such as insufficient power, issues with birth defect ascertainment or classification, inability to address potential confounding, or poor information on exposure.

Some, but not all, or our findings are consistent with those of another large case-control study.[27] Like our report, that study showed no significant associations between SSRI use overall and congenital heart defects. It did show significant associations of paroxetine use and right ventricular outflow tract obstruction defects (six infants; adjusted odds ratio, 3.3; 95% CI 1.3 to 8.8) and neural tube defects (four infants; adjusted odds ratio 3.3; 95% CI 1.1 to 10.4; anencephaly and spina bifida were not examined separately). However, that report found no significant association between craniosynostosis and SSRI use, and for omphalocele, it found a significant association only with sertraline.

Our study is population-based and includes a large birth sample, allowing the evaluation of the relationship between SSRI use and specific types of birth defects. The study also includes careful case definitions and review and exclusion of infants with chromosome abnormalities and single-gene disorders. Although the large size of our study overall allowed for consideration of several potential confounders and effect modifiers, the small number of exposed cases for each individual defect remains a limitation.

Because of the large number of comparisons evaluated in our analysis, it is likely that some of the observed associations reflect chance variation. We performed a total of 265 tests, with 54 positive results at the 0.05 significance level; we would have expected 14 positive results to occur by chance. Not all positive tests are reported, and it is not possible to identify which, if any, of the observed associations are due to chance alone. Analyses of other datasets are warranted to replicate our findings

The effect modification by maternal prepregnancy obesity we observed for the association between SSRI use and the occurrence of some birth defects has not, to our knowledge, been reported previously, and confirmation is needed. However, maternal obesity itself has been associated with an increased risk of neural tube defects,[28, 29] congenital heart defects[28, 30] and other defects.[28, 31] The effect modification we observed may reflect differences in the pharmacokinetics of these lipophilic drugs in individuals with varying percentages of body fat.[32]

An important limitation of this study is our inability to separate the effect of maternal SSRI use from that of the underlying depression. Only 39 case or control mothers reported having depression when asked a general question about illnesses during pregnancy. All but 5 of these women reported taking an antidepressant medication during pregnancy. Data on dosage were unavailable, preventing analysis of dose–response relationships. Mothers were prompted by brand name for the three most commonly used SSRIs, leading to potential underreporting of other SSRIs. Exposures were determined by maternal report, and there is always a potential for recall bias. Selection bias may have occurred because participation was less than 100%; however, it is unlikely that participation varied according to SSRI exposure, and therefore any selection bias was probably in favor of the null hypothesis.

Our study did not find an increased risk for most birth defects, and SSRI exposure was present in only a small number of cases with certain defects. Absolute risks associated with SSRIs appear small in comparison to the general baseline risks of birth defects that exist in every pregnancy. Maternal stress and depression during pregnancy have been associated with adverse reproductive outcomes,[33, 34] and discontinuation of antidepressant treatment in pregnant women with serious depressive illness may have adverse effects on the mother and her baby.[35] Thorough assessment of the potential risks and benefits of SSRI treatment is necessary to allow women of reproductive age to make informed decisions about such therapy.

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4. MATERNAL USE OF BUPROPION AND RISK FOR CONGENITAL HEART DEFECTS[4]

4.1 Introduction

Bupropion is an aminoketone that is structurally and chemically different from other antidepressants on the market. It is a weak inhibitor of neuronal uptake of dopamine, norepinephrine, and serotonin and does not inhibit monoamine oxidase.[1] Bupropion was first marketed as an oral antidepressant (Wellbutrin®) and was subsequently developed as a non-nicotine aid to smoking cessation (Zyban®).[2] Major depression among women of reproductive age is common[3], and women who smoke are encouraged to stop doing so when they become pregnant.[4] It is therefore not surprising that some women are treated with bupropion early in pregnancy.[5] Nevertheless, available data on the safety of such treatment in human pregnancy are limited.

The manufacturer, GlaxoSmithKline, established a Bupropion Pregnancy Registry in 1997 to follow the outcomes of pregnancies in which women took this drug. By the end of March 2008, congenital anomalies had been reported in 24 of 675 (3.6%) infants of women identified prospectively to have taken bupropion in the first trimester and reported to the Registry. These included 651 live births without birth defects, 18 live births with birth defects, 1 fetal death with a birth defect, and 5 induced abortions with birth defects. Congenital heart defects were observed in nine (1.3%) of these infants.[6] The Registry used voluntary recruitment and reporting, which may lead to incomplete or biased reporting of pregnancies or outcomes. Most outcome reports were from

[4] A version of this chapter has been accepted for publication. Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol.

clinicians who cared for the mother during her pregnancy but who may only have had information on birth defects diagnosed within a short time after birth, and the Registry did not collect data on a comparison group.

The Registry also received retrospective notification of bupropion-exposed pregnancies after their outcomes were known. Of 28 retrospectively-reported birth defects with maternal bupropion exposure (including 25 involving first trimester exposure), there were 12 reports of congenital heart defects.[6]

These findings raised concern about the possibility of an association between maternal bupropion use early in pregnancy and congenital heart defects in the infant,[7] which prompted the manufacturer to undertake a retrospective cohort study of claims records of a large managed care database. That study did not find an association with cardiovascular defects among infants of women who had received prescriptions for bupropion during the first trimester of pregnancy when compared to infants whose mothers had received prescriptions for other antidepressants during pregnancy or infants whose mothers received bupropion prescriptions outside the first trimester.[8]

We used data from the National Birth Defects Prevention Study (NBDPS), a population-based case-control study, to determine if maternal bupropion exposure in early pregnancy is associated with one or more selected categories of congenital heart defects in the infant. We also carried out an exploratory analysis to compare the prevalence of maternal bupropion use among the mothers of infants with six categories of non-cardiac defects.

4.2 Materials and methods

The NBDPS is an ongoing, multisite case-control study of environmental and genetic risk factors for more than 30 selected categories of major birth defects. Case infants were ascertained by population-based birth defects surveillance systems at 10 study sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas and Utah).[9] We used data on infants born on or after October 1, 1997, who had an estimated date of delivery on or before December 31, 2004. Case infants were either live births (all participating sites), fetal deaths greater than 20 weeks' gestation (Arkansas, California, Georgia, Iowa, Massachusetts, New York [since 2000], North Carolina, Texas and Utah), or electively terminated pregnancies with reliably-ascertained defects (Arkansas, California, Georgia, Iowa, New York [since 2000], North Carolina, Texas and Utah). Infants with recognized or strongly suspected chromosomal abnormalities or single-gene conditions were excluded from the study. Control infants were liveborn with no major birth defects, randomly selected from the same geographical populations using either birth hospital or vital records. Only one case or control infant was included from each multifetal pregnancy. This study received institutional review board approval at all participating sites.

To confirm eligibility, information on infants in each birth defect category was reviewed without knowledge of exposure status by clinical geneticists. In addition, case infants with heart defects were reviewed without knowledge of exposure status by a team of experts in pediatric cardiology and epidemiology of heart defects, and each case was assigned to one of 33 cardiac diagnostic subcategories, each of which was in turn placed into one or more of 9 major categories.[10] Not all types of heart defects were

included in the NBDPS; those that were excluded were either not well ascertained in infancy, very rare, often related to preterm delivery (e.g., patent ductus arteriosus or patent foramen ovale), vascular defects that are not true malformations of the heart, or heart defects that were associated with chromosomal abnormalities.[11] The proportion of infants with various categories of heart defects does not reflect their relative population frequencies because some infants with more common defects were not included because the number of infants with such defects that needed to be recruited for a particular year had already been reached.

Extensive information regarding demographics and pregnancy exposures was collected by standardized telephone interviews with mothers of case or control infants. The interviews were conducted in English or Spanish 6 weeks to 2 years after the estimated date of delivery.[9] Infants with incomplete maternal interviews were excluded. Mothers were asked during the interview whether or not they took any of a list of medications, including Wellbutrin® and Zyban®. Exposure was defined as reported use of bupropion anytime between one month before and three months after conception. Women were considered unexposed if they did not use any antidepressant at any time during pregnancy. Mothers who reported having depression but who did not report use of an antidepressant during their pregnancy were excluded.

Only heart defects or other birth defect categories that had at least 3 cases exposed to bupropion in the period from one month before to 3 months after conception were analyzed. Crude analyses were done using Pearson's chi-square tests, and odds ratios and Fisher's exact confidence limits were calculated with SPSS 11.0. The following potential confounders were evaluated: maternal age (<35, ≥35 years), maternal race (non-Hispanic white, other), maternal education (≤12 years, >12 years), maternal

obesity before pregnancy (body mass index [BMI] <30 kg/m^2, ≥30 kg/m^2), maternal smoking and alcohol use from 1 month before to three months after conception, use of a dietary supplement containing folic acid from one month before to one month after conception, annual family income (<$20,000, ≥$20,000), plurality (singleton, twins and above), and parity (no previous live births, ≥1 live births). Potential confounders were first evaluated for association with bupropion exposure and with the birth defects categories, and were excluded from the logistic regression if their removal resulted in a change in risk estimate of less than 10 percent. All confounders retained in the model for any of the defects were included in the final models for all defects. Infants of women with pre-gestational type 1 or 2 diabetes (304 case and 32 control mothers) were excluded from adjusted analyses because of the strong association of diabetes with birth defects.

4.3 Results

Seven subcategories of heart defects (which fell within 4 major categories) and 6 other categories of birth defects each met the inclusion criterion of at least 3 cases exposed to bupropion in the period between 1 month before and 3 months after conception. Of 18,534 case and control mothers available for study, we excluded 276 mothers who did not complete their interviews and 6 mothers who reported depression but did not report use of any antidepressant. A total of 12,383 case infants (including 6,853 diagnosed with at least one of the selected heart defects and 5,763 diagnosed with at least one of the 6 categories of non-cardiac defects studied) and 5,869 control infants were analyzed. Among all case and control mothers, 90 (0.5%) reported use of bupropion in the one month before to 3 months after conception.

Characteristics of case and control mothers included in the study are presented in Table 4.1. Mothers of case infants were significantly more likely to be older, have a higher education, to be obese, smoke early in pregnancy, and to have a lower family income compared to mothers of control infants. Having type 1 or 2 diabetes prior to pregnancy and having a multiple pregnancy were also reported more frequently among mothers of case infants than among mothers of control infants. Having at least one previous live birth and intending to become pregnant, on the other hand, were reported more frequently among mothers of control infants.

Table 4.2 presents crude and adjusted odds ratios comparing the prevalence of case mothers to control mothers exposed to bupropion between one month before to three months after pregnancy for each of the seven subcategories of heart defects analyzed.

Table 4.1. Characteristics of mothers of case and control infants, NBDPS 1997-2004.

	Mothers of case infants (N = 12,383) N (%)	Mothers of control infants (N= 5,869) N (%)	X^2 P-Value
Maternal race-ethnicity			
Non-Hispanic White	7481 (60.6)	3525 (60.3)	0.35
Other	4868 (39.4)	2323 (39.7)	
Maternal age			
< 35 years	10489 (84.7)	5051 (86.1)	**0.01**
≥ 35 years	1894 (15.3)	818 (13.9)	
Maternal education			
≤ 12 years	5546 (44.8)	2457 (41.9)	**<0.001**
> 12 years	6826 (55.2)	3402 (58.1)	
Maternal prepregnancy body mass index (BMI)			
Not obese (BMI < 30 kg/m^2)	9685 (81.3)	4738 (84.1)	**<0.001**
Obese (BMI ≥ 30 kg/m^2)	2223 (18.7)	898 (15.9)	
Maternal smoking in the period of 1 month before to 3 months after conception			
0/day	9687 (78.3)	4745 (80.9)	**<0.001**
1-14/day	1861 (15.0)	782 (13.3)	
≥15/day	826 (6.7)	337 (5.7)	
Annual family income			
< $20,000	3845 (33.9)	1679 (32.0)	**0.01**
≥ $20,000	7507 (66.1)	3574 (68.0)	
Type 1 or 2 Diabetes prior to pregnancy			
No	11125 (97.3)	5464 (99.4)	**<0.001**
Yes	304 (2.7)	32 (0.6)	
Maternal alcohol intake in the period of 1 month before to 3 months after conception			
No	7746 (62.9)	3677 (63.0)	0.47
Yes	4572 (37.1)	2164 (37.0)	
Maternal folic acid intake*			
No	6124 (49.5)	2883 (49.1)	0.34
Yes	6259 (50.5)	2986 (50.9)	

	Mothers of case infants (N = 12,383) N (%)	Mothers of control infants (N= 5,869) N (%)	X^2 P-Value
Plurality			
Singleton	11593 (93.7)	5689 (97.0)	**<0.001**
Multiple	775 (6.3)	174 (3.0)	
Parity			
No previous live births	5344 (43.2)	2352 (40.1)	**<0.001**
≥ 1 previous live births	7034 (56.8)	3514 (59.9)	
Pregnancy intendedness			
No	4448 (43.4)	1933 (40.7)	**0.001**
Yes	5800 (56.6)	2821 (59.3)	
Exposure to bupropion†			
No	11733 (99.5)	5626 (99.5)	0.27
Yes	64 (0.5)	26 (0.5)	

* Use anytime between 1 month before and 1 month after conception

† Exposure to bupropion was defined as reported use anytime between 1 month before to 3 months after conception. Women were considered not to have been exposed if they did not take an antidepressant anytime from 3 months before conception and through the end of pregnancy.

Some numbers do not add up because of missing data.

Factors found to influence the association between the birth defects analyzed and bupropion use were maternal race, obesity, smoking and family income, and these factors were included in the adjusted analyses.

A statistically significant association was observed between the occurrence of a left outflow tract heart defect in the infant and maternal bupropion use, based on 10 exposed pregnancies (adjusted odds ratio 2.6, 95% confidence interval 1.2 to 5.7). The main diagnoses assigned to the ten exposed cases were coarctation of the aorta in five cases (one of whom also had features of a hypoplastic left heart variant), hypoplastic

Table 4.2. Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for associations of self-reported maternal bupropion use in the period from one month before to three months after conception among infants with various categories of heart defects, NBDPS 1997-2004.

Heart defect (N)	Crude Analysis*		Adjusted Analysis†
	Exposed(N)	OR (95% CI)	OR (95% CI)
Controls (5,869)	26	-	-
Conotruncal heart defects (1,350)	4	0.7 (0.2-1.9)	0.9 (0.3-2.6)
Tetralogy of Fallot (598)	3	1.1 (0.2-3.7)	1.5 (0.4-5.1)
Left outflow tract heart defects (1,038)	10	**2.2 (1.0-4.8)**	**2.6 (1.2-5.7)**
Coarctation of aorta (546)	5	2.1 (0.6-5.5)	**2.6 (1.0-6.9)**
Hypoplastic left heart (310)	3	2.3 (0.4-7.5)	2.7 (0.8-9.1)
Right outflow tract heart defects (1,030)	4	0.9 (0.2-2.6)	1.2 (0.4-3.4)
Pulmonary valve stenosis (763)	3	0.8 (0.2-2.8)	1.1 (0.3-3.8)
Septal heart defects (3,033)	15	1.1 (0.5-2.2)	1.4 (0.7-2.8)
Perimembraneous VSD (1,214)	6	1.1 (0.4-2.8)	1.2 (0.5-3.4)
ASD secundum (1,320)	5	0.9 (0.3-2.3)	1.1 (0.4-3.0)
ASD nos (430)	3	1.6 (0.3-5.2)	2.2 (0.6-7.5)
All groups of heart defects in NBDPS (6,853)	34	1.1 (0.7-1.9)	1.4 (0.8-2.5)

* Fisher's exact confidence intervals.

† Adjusted for maternal race, obesity, smoking and family income. Cases and controls with pre-existing type 1 or 2 diabetes in the mother were excluded.

VSD: Ventricular septal defects, ASD: Atrial septal defects, nos: not otherwise specified.

left heart syndrome in three cases, and aortic stenosis in two cases. Out of the 10 exposed cases with left outflow tract defects, 7 were isolated cardiovascular defects, two also had multiple non-cardiac birth defects and one infant who had coarctation of aorta was suspected to have PHACE syndrome.[12] Mothers of all 10 cases reported taking Wellbutrin®. None of these ten mothers reported concomitant use of a medication with known teratogenic effects, although two also reported use of other

antidepressants (fluoxetine and paroxetine in one case and fluoxetine and sertraline in the other) in the first trimester.

Limiting the exposure to the period of two months after conception, when cardiac embryogenesis is most likely to be susceptible to a teratogenic effect, reduced the number of cases exposed to 7 but did not affect the point estimate for the odds ratio, and the association remained of borderline statistical significance (adjusted odds ratio 2.6, 95% confidence interval 1.0 to 6.4).

We also tested crude and adjusted associations of any congenital heart defect included in the NBDPS with maternal bupropion use, but exposure prevalence was not significantly different among cases when compared to controls (adjusted odds ratio 1.4, 95% confidence interval 0.8 to 2.5, N=34). Likewise, no significant association with maternal bupropion use was observed with any of the six non-cardiac defects categories analyzed (Table 4.3).

4.4 Discussion

A relatively large number of cases with congenital heart defects among mothers exposed to bupropion was noted among both prospective and retrospective reports to the Bupropion Pregnancy Registry.[7] Although no comparable reference group was available to permit statistical assessment of this observation, these results raised concern that maternal bupropion treatment early in pregnancy might be associated with an increased risk of congenital heart defects. We used data from a population-based case-control study to test this hypothesis. We found a positive association with maternal

Table 4.3. Crude and adjusted odds ratios (OR) and 95% confidence interval (CI) for associations of reported maternal bupropion exposure in the period of one month before to three months after conception among infants with various categories of birth defects not involving the heart, NBDPS 1997-2004.

Birth defect (N)	Crude Analysis*			Adjusted Analysis†
	Controls‡ (Number Exposed)	Number of Exposed Cases	OR (95% CI)	OR (95% CI)
Neural Tube Defects (1,043)	5869 (26)	4	0.9 (0.2-2.5)	1.3 (0.4-3.9)
Cleft lip with or without palate (1,552)	5735 (24)	7	1.1 (0.4-2.6)	1.3 (0.4-3.9)
Cleft palate (824)	5735 (24)	4	1.2 (0.3-3.4)	1.2 (0.4-3.6)
Hypospadias, 2nd or 3rd degree (1,147)	2951 (12)	9	1.9 (0.7-5.0)	2.3 (0.9-5.9)
Limb Deficiency (648)	5869 (26)	3	1.0 (0.2-3.4)	1.4 (0.4-4.8)
Gastroschisis (611)	5869 (26)	3	1.1 (0.2-3.7)	1.4 (0.4-5.1)

* Fisher's exact confidence intervals.

† Adjusted for maternal race, obesity, smoking and family income. Cases and controls with pre-existing type 1 or 2 diabetes in the mother were excluded.

‡ The number of controls is different for the oral clefts and hypospadias because data on oral clefts from Utah in 2003 were not available and only male control infants were included for infants with hypospadias.

bupriopion use during pregnancy among infants with left outflow tract heart defects but not among infants with other types of heart defects.

Our study has several important strengths. It is large and population-based, used consistent case definitions, and incorporates information on many potential confounders. The study sample provided adequate statistical power to evaluate the relationship between bupropion exposure and the risk for several individual types of cardiovascular birth defects.

However, the small number of exposed cases for each defect category remains a limitation. Because of the small number of cases exposed to bupropion overall, we were unable to stratify our analyses by type of bupropion exposure (Wellbutrin® vs. Zyban®), which would have enabled us to deal with confounding by indication (depression vs. smoking cessation). We cannot rule out the possibility that the association we observed with left outflow tract heart defects is actually related to depression, rather than to bupropion use, in as much as all women were taking bupropion for depression. However, the fact that previous studies of the infants of women who took SSRIs for depression during pregnancy have not shown an association with this type of heart defect[13] makes this explanation unlikely.

Furthermore, because data on dosage were unavailable, we were unable to evaluate a potential dose-response relationship. The use of bupropion was determined by maternal self-reports and was not validated through other sources, so the influence of recall bias on the results is difficult to assess. Although we calculated an overall odds ratio for all heart defect categories combined (Table 4.2), this estimate is not comparable to overall estimates from other studies because NBDPS collects data on selected major heart defects rather than all heart defects or heart defects in general, and the relative frequencies of various specific cardiac malformations in our pooled group differ from those in the general population.

The magnitude of the association with left outflow tract heart defects suggests a possible doubling of risk over baseline if the association is not due to chance or methodologic issues such as bias or confounding. Replication of these findings in other studies that address such methodologic considerations are warranted before inferences about a possible causal relationship between medication use and the occurrence of this

type of heart defects can be made with any degree of confidence. Even if there were a 2.6-fold increased risk for left outflow tract heart defects, the absolute risk of a cardiovascular malformation in the child of a pregnant woman who takes bupropion during the first trimester would be low. Based on the estimated prevalence for left outflow tract heart defects of 0.82/1,000 live births in the metropolitan Atlanta population in 1998-2005,[14] our findings are compatible with an absolute risk following first trimester maternal bupropion treatment of 2.1/1,000 births.

In their retrospective cohort study of healthcare claims records, Cole et al.[8] observed 13 infants with congenital heart defects whose mothers had received bupropion prescriptions in the first trimester of pregnancy, a frequency that was not significantly increased when compared to infants whose mothers had received prescriptions for other antidepressants or infants whose mothers received bupropion prescriptions outside the first trimester. Five of the 13 infants with congenital heart defects born to women who had received prescriptions for bupropion during the first trimester and 6 of 57 infants of women who had received prescriptions for other antidepressants during the first trimester in the study of Cole et al. had left outflow tract heart defects, which are estimated to account for about 10% of all heart defects in the general population.[14] Based on the data reported in the study by Cole and associates, we calculated a crude risk ratio for bupropion use compared to use of the other antidepressants of 3.2 (95% confidence interval 1.0 to 10.6), a value similar to that observed in our study.

A family history of congenital heart defects was not reported for any of the 10 infants with left outflow tract defects whose mothers reported taking bupropion early in pregnancy in our study. Familial clustering of this group of heart defects has been suggested in the literature,[15] indicating a genetic component in the etiology. Of course,

this does not preclude the involvement of teratogenic factors as well in a complex and probably etiologically heterogeneous disorder like congenital heart defects.

We found no increased odds of maternal bupropion use early in pregnancy among infants with neural tube defects, cleft lip with or without cleft palate, cleft palate alone, 2nd or 3rd degree hypospadias, or gastroschisis (Table 4.3). Maternal bupropion exposure in pregnancy was not found to be associated with other major birth defects in the retrospective cohort study of Cole et al.[8] or in a small prospective cohort study performed through a teratogen information service[16]. Similarly, the frequency of malformations was not increased among the offspring of rats or rabbits treated during pregnancy with the equivalent of 19-56 or 3-19 times the maximum human therapeutic dose of bupropion.[17] It is unclear how carefully the pups in this study were examined to determine the presence or absence of heart defects.

A critical question is whether the association we observed with left outflow tract heart defects is biologically plausible. This question cannot currently be addressed because so little is known about the effect of bupropion treatment on embryonic development in general or on cardiac morphogenesis specifically.

Our results are based on exploratory analyses of a case-control study, therefore our findings are not conclusive. Further studies are needed to confirm our findings in other datasets, to assess whether the risk extends to other birth defects, and to elucidate the underlying pathogenic mechanism(s).

The findings of the present study, along with recent evidence related to the effects of SSRIs in pregnancy,[13, 18-23] present healthcare providers with a dilemma regarding choice of antidepressant medications in pregnancy. It is important to note that the

absolute risk for left outflow tract heart defects we found associated with bupropion exposure is small. Nevertheless, risks and benefits of antidepressant medications need to be considered on a case-by-case basis and clearly presented to women who are pregnant or planning pregnancy so that they can make informed decisions in consultation with their physicians.

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5 BIRTH OUTCOME IN RELATION TO LOW FETAL CROWN RUMP LENGTH ON EARLY ULTRASOUND EXAMINATION[5]

5.1 Introduction

The frequency of birth defects is significantly increased among babies of low birth weight (<2500 g),[1, 2] and, conversely, the frequency of fetal growth restriction is significantly higher than expected among infants with birth defects[3]. Previous studies have found an association between crown rump length (CRL) of the embryo and subsequent birth weight by comparing dizygotic twin conceptions achieved through assisted reproductive techniques.[4] A larger study involving a cohort of over 4,000 women attending prenatal care at an institution in the United Kingdom also showed significant associations between smaller-than-expected embryo size as measured by ultrasound examination and low birth weight at term, birth weight below the 5th centile for gestational age, and prematurity, which were independent of maternal height, body mass index or smoking status.[5]

First trimester measurement of the crown-rump length is considered an accurate method for pregnancy dating[6] and is usually preferred to dating by last menstrual period (LMP) when menstrual cycles are irregular or recall is uncertain. Early fetal growth can usually be assessed by comparing the actual size of the embryo or fetus from CRL measurements on ultrasound examination to the size expected according to standard growth charts and menstrual age.[7]

[5] A version of this chapter will be submitted for publication. Alwan S, Janssen P, Gagnon A, Friedman JM. Birth outcome in relation to fetal crown rump length on early ultrasound examination.

In this study, we compared CRL measurements in the first trimester to standard fetal growth charts developed for pregnant women seen at British Columbia Women's Hospital.[8] We then determined the risk of various adverse reproductive outcomes among women whose embryos had low CRLs in comparison to women whose embryos had normal CRLs.

5.2 Methods

We conducted a retrospective cohort study of women who underwent at least one obstetrical ultrasound examination in the first trimester of their pregnancies with measurements of the CRL of the embryo or fetus at the Ultrasound Unit of BC Women's Hospital between April 1st, 2003, and June 21st, 2006. Only singleton pregnancies were included. Three measurements of the CRL were obtained for each case, and the average was reported. Because CRL measurements at 6-14 weeks are considered to be most accurate[9], measurements of embryos of less than 6 weeks or of fetuses over 14 weeks gestational age by menstrual dates were excluded. Cases with no heart beat detected at the ultrasound examination were also excluded. We also excluded all women who were noted to have irregular cycles, who were not menstruating (e.g., because of breastfeeding), or who were uncertain of the date of their last menstrual period.

Although pregnancies are routinely re-dated (i.e., the estimated gestational age is "corrected") for clinical purposes if gestational age according to ultrasound fetometry (GA_U) disagrees with the gestational age estimated from the date of the last menstrual period (GA_{LMP}) by 7 days or more, for this study we used the estimate of GA_{LMP} in all cases noted with a regular menstrual cycle. Where a discrepancy between the GA_U and

GA_{LMP} of > 7 days existed, CRL percentiles were re-calculated on the basis of GA_{LMP} according to British Columbia population standards[8] and gestational age at delivery was also re-adjusted accordingly.

Data on ultrasound examinations were linked to the BC Perinatal Database Registry (BCPDR), which contains detailed obstetrical and demographic information on fetal and neonatal outcomes after 20 weeks gestation delivered in the province of British Columbia. Because data on spontaneous abortions occurring before 20 weeks gestation were unavailable at the BCPDR, linkage to the BC Women's obstetrical database, which includes demographic and obstetrical information on all fetal and neonatal outcomes for women delivering at BC Women's Hospital, was also performed in order to get those data. 45% of cases were linked to both databases and 55% were retrieved from a single database.

Embryos and fetuses with CRL at the 10^{th} centile or less for GA_{LMP} between 6 and 14 weeks were defined as having low CRL. Embryos and fetuses with CRL between the 21^{st} and 80^{th} centile for GA_{LMP} between 6 and 14 weeks were considered to have normal CRL and were used for comparison. Birth defect diagnoses that were included in this analysis were major anomalies defined by the National Birth Defects Prevention Network (NBDPN).[10]

We calculated risks for occurrence of the following outcomes: major congenital anomalies noted after 20 weeks gestation, spontaneous abortions (less than 20 weeks gestation), neonatal death or stillbirth (after 20 weeks gestation), long neonatal hospital stay (> 7 days), neonatal intensive care unit (NICU) admission, requirement for assisted oxygen or ventilation at birth, premature delivery (<37 weeks gestation), or a low Apgar

score (< 7) at 1 minute. In addition, we compared birth weight, birth length and head circumference at birth as continuous variables in infants who had low CRL and infants who had normal CRL between 6 and 14 weeks gestation.

Crude analyses were evaluated using chi-square test for categorical variables and analysis of variance (ANOVA) for continuous variables. Weight, length and head circumference at birth were converted to standard Z-scores calculated through comparison to the appropriate gestational age- and gender-specific parameters for the population of British Columbia.[11, 12]

The following maternal characteristics were evaluated: Maternal age at delivery (categorized as <35 years, ≥35 years), maternal education (≤12 years, >12 years), maternal obesity before pregnancy (body mass index [BMI] <30 kg/m^2, ≥30 kg/m^2), parity (no previous live births, ≥1 live births) and presence or absence of gestational hyptertension or of type 1, 2 or gestational diabetes. Characteristics that were found to be associated with both low CRL and outcome were assessed as potential confounders and adjusted using logistic regression analyses.

The study received ethical approval from the University of British Columbia and Children's and Women's Hospital of British Columbia.

5.3 Results

A total of 1,260 women had at least one ultrasound examination at BC Women's Ultrasound Unit in the first trimester of pregnancy between April 1st, 2003, and June 21st, 2006. 1,115 of these pregnancies were singleton and were successfully linked to outcome from the BCPDR or had a documented spontaneous abortion before 20 weeks gestation. We excluded 38 women whose only early ultrasound examination was before

6 weeks or after 14 weeks according to GA_{LMP}, 32 women who reported irregular cycles or were not menstruating and 65 women with no LMP date reported. The remaining 976 women were included in the analyses.

BC Women's Hospital, the only tertiary maternity hospital in British Columbia, serves women with high-risk pregnancies from throughout the province as well as pregnant women in all risk categories who live in Vancouver. Because of this referral characteristic, the majority of our study population consisted of women greater than 35 years of age, who had a university degree and a BMI within the normal range (Table 5.1). The frequencies of malformations and other adverse neonatal outcomes were similar to those for all births in British Columbia.

Women with embryos having low CRL on early ultrasound examination were 10 times more likely to have a spontaneous abortion (AOR: 10.5, 95% CI: 3.5-30.9) and almost twice as likely to undergo a cesarean delivery (AOR: 1.8, 95% CI: 1.1-2.9) as women

Table 5.1. Characteristics of the study population (N=976)

Characteristic	Value
Age at delivery (y), mean (SD)	36.0 (5.0)
Pre-pregnancy BMI (kg/m^2), mean (SD)	23.9 (4.6)
Education (y), median (Range)	16 (0-22)
Birth weight (g), mean (SD)	3,343 (702)
GA at delivery (wk), median (Range)	39 (7-43)
≥ 1 previous livebirth (%)	52.6
Diabetes (I, II or gestational) (%)	11.3
Hypertension during pregnancy (%)	4.6
Neonatal outcomes (%):	
Major malformations	3.4
Preterm birth	13.2
Low birth weight < 2500 g	7.1

SD: Standard deviation

with normal CRL early in pregnancy (Table 5.2). Stillbirth, NICU admission, low Apgar score, ventilation/oxygen use at birth, long hospital stay and preterm delivery were not found to be associated with low CRL early in pregnancy. We found no association of low CRL with the occurrence of major malformations detected after 20 weeks gestation.

Table 5.2. Crude and adjusted odds ratios and 95% CI for associations of birth outcome and low crown rump length at or below the 10th centile detected at first trimester ultrasound examination.

Outcome	Low CRL ≤10th % N= 124 N (%)	Normal CRL 21st-80th % N= 620 N (%)	OR (95% CI)	AOR (95% CI)†
Major malformation*	4 (4.5)	20 (3.6)	1.3 (0.4-3.8)	1.2 (0.3-4.4)
Spontaneous abortion	10 (10.0)	6 (1.0)	**10.6 (3.8-30.0)**	**10.5 (3.5-30.9)‡**
Stillbirth	1 (1.1)	10 (1.7)	0.6 (0.1-5.1)	0.7 (0.1-5.5)
NICU admission	9 (7.3)	64 (10.3)	0.7 (0.3-1.4)	0.8 (0.4-1.7)
Low Apgar < 7	9 (9.9)	74 (12.6)	0.8 (0.4-1.6)	0.9 (0.4-1.9)
Ventilator/Oxygen	5 (5.5)	32 (5.5)	1.0 (0.4-2.7)	0.9 (0.3-2.5)
Long hospital stay > 7 days	7 (8.0)	34 (6.0)	1.4 (0.6-3.2)	1.5 (0.6-3.6)
Cesarean delivery	47 (51.6)	230 (39.2)	**1.7 (1.1-2.6)**	**1.8 (1.1-2.9)**
Premature delivery (<37 GA)	12 (13.2)	86 (14.4)	0.9 (0.5-1.7)	1.4 (0.5-3.9)

OR: odds ratio; AOR: adjusted odds ratio; CI: confidence interval

* Major malformation detected after 20 weeks gestation

† All associations were adjusted for maternal age and parity, except for spontaneous abortions, which was adjusted for maternal age and gravidity.

‡ Adjusted for maternal age and gravidity.

Figure 5.1 compares the distribution of birth weight (A), birth length (B) and birth head circumference (C) shown as age- and gender-standardized Z-scores between infants having a low CRL and those with a normal CRL in early pregnancy. The average birth weight and birth length among pregnancies with low CRL were significantly smaller than expected compared to those who had a normal CRL on early pregnancy ultrasound examination (mean Z-score = -0.30, $P < 0.001$; mean Z-score = -0.17 , $P = 0.01$, respectively). In contrast, the average head circumference at birth of fetuses who had a

CRL at the 10th centile or less was similar to that of fetuses who had a normal CRL (mean Z-score =0.20, *P*= 0.59).

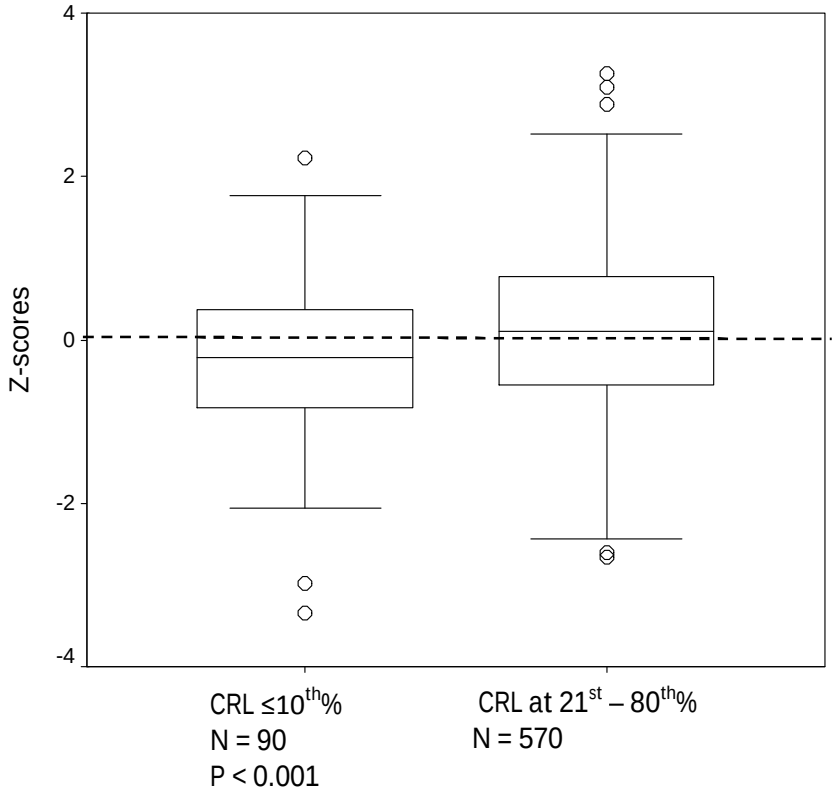
5.4 Discussion

In this retrospective cohort study, we found an increased risk for subsequent spontaneous abortion, cesarean delivery, lower than expected birth weight or smaller than expected birth length among embryos or fetuses who had a CRL below the 10th centile compared to embryos or fetuses who had a normal CRL on first-trimester ultrasound examination.

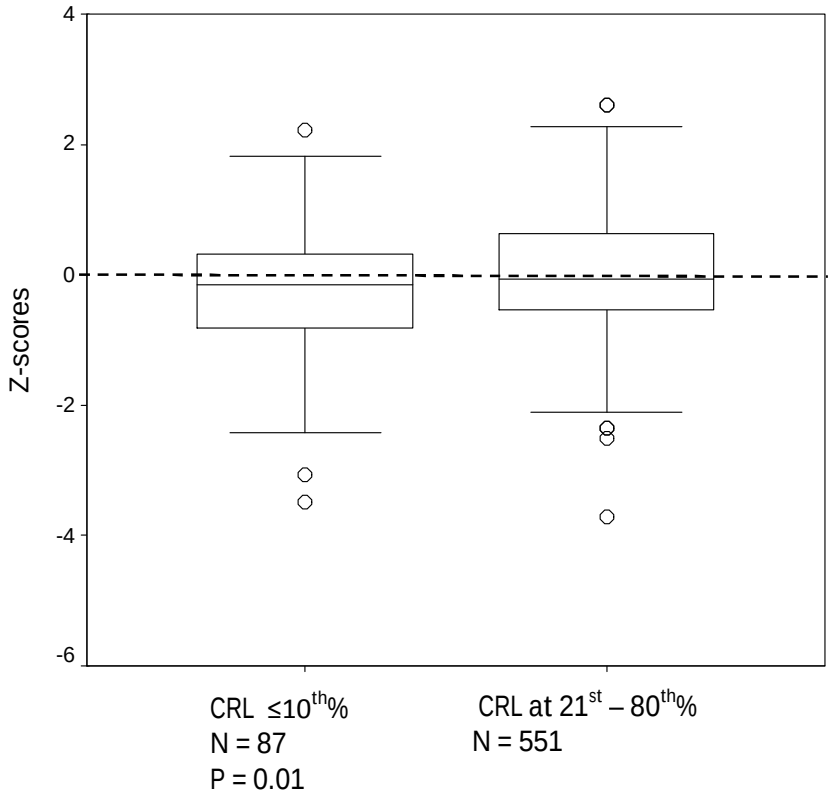
Our data do not support an association of a low CRL on early ultrasound examination with increased risk of having a newborn with a major malformation, but the statistical power of this analysis was limited. We could exclude a 5-fold increase in the rate of birth defects with 95% probability but not an increase that was 4-fold or smaller. Very few teratogenic effects increase the overall rate of birth defects 5-fold, and it would have been surprising to find such a large effect in this study. Larger studies are needed to determine if poor growth of the embryo or fetus early in pregnancy is associated with a clinically important increase in the risk of birth defects in the infant.

Figure 5.1. Box plots of Z-scores for (A) birth weight of 90 pregnancies with CRL ≤ 10th centile and 570 pregnancies with normal CRL (21st-80th centile), (B) birth length of 87 pregnancies with low CRL and 551 pregnancies with normal CRL and (C) birth head circumference of 87 pregnancies with low CRL and 552 pregnancies with normal CRL. For all graphs: The central horizontal line in the box indicates the median value of the data. The lower and upper edges of the box indicate the 25th and 75th centiles of the dataset, respectively. The whiskers represent the largest and smallest data values that are not defined as outliers, and the circles outside the whiskers are outliers with values that lie more than 1.5 times the interquartile distance from the median. The dotted line represents the mean (Z-score of 0.00). A significant association of low crown rump length with birth weight and birth length for gestational age is shown by the ANOVA *P*-value < 0.05 (A and B).

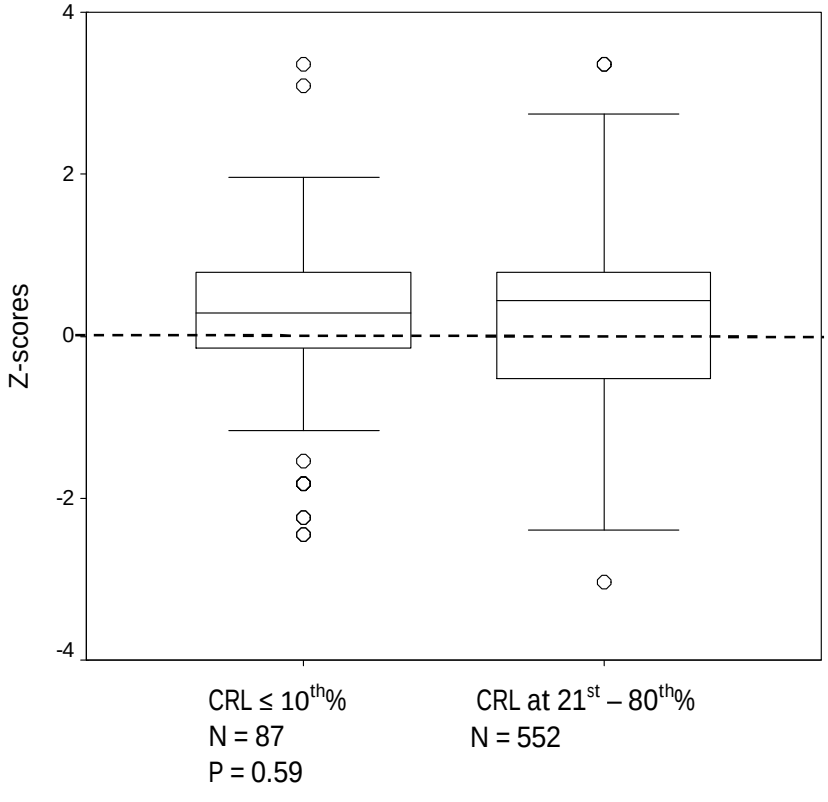
A



B


4
2
0
-2
-4
-6
Z-scores
CRL ≤10th%
N = 87
P = 0.01
CRL at 21st – 80th%
N = 551

C


4
2
0
-2
-4
Z-scores
CRL ≤ 10th%
N = 87
P = 0.59
CRL at 21st – 80th%
N = 552

A number of studies have examined first trimester growth restriction in chromosomally abnormal fetuses. A shortening of the CRL in aneuploidies with high postnatal mortality, notably embryos with trisomy 18[13-17] or trisomy 13,[14-16] but not trisomy 21, [14-17] has been shown, indicating that fetal growth restriction may occur in association with a chromosomal abnormality as early as the first trimester of gestation. In our study, there were 7 babies born with a congenital anomaly who had low CRL on early pregnancy ultrasound examination, but none of them was known to have a chromosomal abnormality. We did not have access to the results of maternal serum biochemical screening, which may detect an increased risk for certain aneuploidies or neural tube defects in the first trimester. We would assume that women who had an abnormal screening result and subsequently were found to have a fetus with a chromosomal abnormality or other major congenital anomaly may have opted for an induced abortion.

Our findings agree with those of previous studies that found CRL below the 10th centile in the first or second trimester to be a strong predictor of spontaneous abortion.[18, 19] In a prospective cross-sectional survey on singleton embryos conceived through assisted reproductive technology, Choong and associates demonstrated that a multivariate model combining measurements of mean-sac diameter, CRL, embryonic heart rate, maternal age and gestational age at the first transvaginal ultrasound scan had the highest prediction rate for pregnancies that were destined to abort spontaneously compared to univariate models such as low CRL alone.[20] We did not have data on mean sac diameter or embryonic heart rate. We also did not have information on the karyotypes of the spontaneous abortuses in our study, which may have added more insight into whether the abortion in low CRL embryos or fetuses was due to a chromosomal abnormality.

Several studies have shown a relationship between estimated fetal weight during the second or third trimester of gestation using fetal ultrasound measurements of head circumference, biparietal diameter, abdominal circumference or femur length and various adverse pregnancy outcomes. In a population-based prospective cohort study in Norway, Nakling and Backe found that fetuses who were smaller than expected at the mid-second trimester ultrasound examination have an increased risk for preterm birth, low birth weight, SGA and perinatal death.[21] A retrospective cohort analysis conducted among women with certain gestational age in California also showed that sonographically estimated fetal weight below the 5th percentile was a significant indicator for low birth weight, preterm birth, prolonged neonatal hospital stay, neonatal intensive care unit admission and stillbirth or neonatal death.[22] These authors also showed that estimated fetal weight as early as 13 gestational weeks was a stronger predictor of adverse pregnancy outcome than later estimated fetal weight. Another study found an association of low estimated fetal weight in the 2nd or 3rd trimester with preterm delivery.[23] Several other studies have reported that when GA_{LMP} is found to be larger than GA_U, there is an increased risk for low birth weight[24], Apgar score < 7 at 5 minutes[24], preterm birth[24], perinatal death[24-26] and other adverse pregnancy outcomes.[24, 26]

Our findings of a significant association between first trimester CRL and birth weight is supported by previous literature showing a relationship between early fetal growth and risk of delivering a small for gestational age infant.[5, 27, 28] Some authors postulated that the determining factor could be the prolonged interval between menstruation and conception rather than early intrauterine growth restriction.[29] However, Bukowski et al[27] used data from pregnancies resulting from assisted reproductive technology, where the

date of conception was known, and demonstrated that the association of first trimester embryonic size and birth weight is attributable to poor early growth.

Our study is limited by its small population size and therefore limited power to analyze endpoints like specific types of birth defects. Not including prenatally diagnosed fetal anomalies in which the pregnancy was terminated may have resulted in underascertainment of congenital anomalies. Data on some important confounders such as smoking or alcohol use that have been shown to be associated with adverse reproductive outcomes and restricted fetal growth[30, 31] were not available, and our inability to adjust for them is a limitation of this study. We also lacked data on race or ethnicity, which may have confounded our analyses of several birth outcomes. In a recent British Columbia study providing sex- and ethnicity-specific standards for weight[32], length and head circumference for term infants, Janssen and her associates found that ethnicity greatly affected variation in growth and that misclassification of size for gestational age at birth may occur when ethnic group is not taken into consideration. In addition, our study did not include data on second trimester ultrasound scans, which would have enabled estimation of fetal growth throughout pregnancy and provided more information on the presence of malformations.

In conclusion, low CRL in early pregnancy is a strong predictor of a subsequent miscarriage and having certain adverse pregnancy outcomes. Furthermore, we have demonstrated that low birth weight and length may originate from poor early fetal growth in some instances. These findings add more evidence to the existing literature that early fetal growth restriction affects later pregnancy outcome and indicate the importance of future surveillance and prevention. Detection of fetal growth restriction on early ultrasound examination might usefully be combined with first or first and second

trimester maternal serum screening results to identify pregnancies at high risk for pregnancy complications.

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6 GENERAL DISCUSSION

The importance of recognizing maternal drug treatments as causes of birth defects lies in their potential prevention. Pregnant women may require drug treatment to restore or protect their own health as well as that of the fetus. Choice of the safest therapy is not possible if the teratogenic risks of alternative treatments are unknown, and treatments that actually are teratogenic cannot be avoided unless they have been recognized as such. In other instances, inadvertent drug exposure occurs because a woman becomes pregnant while taking a medication. Such women may be greatly concerned about possible harm to their babies, and some women terminate their pregnancies because of fear of unknown risks.[1]

Furthermore, the importance of detecting an early signal for the presence of a fetal malformation or a higher risk for the development of other adverse outcomes also lies in the potential for surveillance and the possibility of timely intervention or prevention.

6.1 The teratogenic potential of antidepressant treatment

The risk of major depression among women is highest during the childbearing years,[2] with an estimated prevalence of up to 20% in pregnancy.[3] I used data from a large multi-site population-based case-control study to assess the risk of birth defects in the infants of mothers who reported taking an SSRI or bupropion, the two most commonly used antidepressant medications worldwide, in early pregnancy. The results showed an increased rate of SSRI use among mothers of infants with anencephaly, craniosynostosis or omphalocele compared to mothers of control infants. A *post-hoc* analysis showed that the association with craniosynostosis and omphalocele was even

stronger among women who were obese prior to pregnancy. Among women who were obese and taking an SSRI, associations were also found with conotruncal heart defects, septal heart defects and spina bifida in the infant. The risk for a different kind of heart defects, those of the left outflow tract, was significantly increased among the infants of mothers who used bupropion in early pregnancy.

The question remains as to whether the associations I observed are causal, i.e., whether SSRI or bupropion treatment actually causes birth defects. Several factors that determine the teratogenicity of an exposure have been set forth as the principles of teratology[4], as first put forward by James G. Wilson. These include but are not limited to the points discussed below in reference to my studies on antidepressants:

1. Abnormal development produced by a teratogenic exposure is manifested as death, malformation(s), growth retardation, or a functional disorder. In chapters 3 and 4, I used a case-control design, whereby the outcome (case infants) was specifically defined as selected categories of major malformations that were ascertained by population-based birth defects surveillance systems and were carefully reviewed by clinical geneticists who were unaware of the infant's exposure status. Furthermore, because some birth defects due to single-gene conditions or chromosomal abnormalities may not have had the necessary genetic testing to confirm the diagnosis, infants who were strongly suspected of having a specific single-gene condition or chromosomal abnormality were excluded, even if definitive testing had not been performed, so they would not obscure the association of exposure with a birth defect. In chapter 3 on the analyses of maternal SSRI exposure, the selected birth defects were further classified into isolated versus multiple defects to detect any differences in risk.

Finally, case infants were either liveborn, died at 20 weeks or more of gestation or reliably ascertained defects in electively terminated pregnancies, depending on which participating site the data were derived from.

2. A second principle of teratology states that susceptibility varies with the developmental stage at the time of exposure. In both studies of maternal use of SSRIs and bupropion, conception date was established as the estimated date of delivery minus 266 days. Data on the last menstrual period or whether the mother had a regular or an irregular cycle were not available. Since the time of conception could not be unequivocally established, the exposure definition for both studies was set as one month before to three months after conception in order to cover the critical period of organogenesis that peaks around the third to eighth weeks of gestation.[4] In the SSRI study, the exposure period was further restricted to the two months post conception for the analyses on all birth defect categories to exclude women who were only exposed outside the critical period of embryogenesis. Following the identification of an association between left outflow tract heart defects with bupropion exposure, the exposure was also limited to the two months after conception, when cardiac embryogenesis is most likely to be susceptible to a teratogenic effect.

   Several periods of susceptibility may exist for a single organ. For example, in the case of craniosynostosis, the critical period for development may extend beyond the first trimester, which is why an additional analysis was conducted to examine the association between SSRI use in the second and third trimester of pregnancy and craniosynostosis.

3. Susceptibility to a teratogenic exposure also depends on the fetal and maternal genotype, specifically with respect to drug metabolism. Unfortunately, genetic data were not available on either the mother or infant in my studies. However, with respect to SSRIs, some studies have implicated the effect of certain serotonin transporter (5-HTT) gene polymorphisms on differential gene expression and consequent differences in SSRI clinical effects in adults.[5] A 44 base pair insertion/deletion polymorphism in the promoter region of the 5HTT gene (*SLC6A4*) was examined with regard to its effect on the association between SSRI exposure in late pregnancy and adverse neonatal outcomes.[6] The authors found that one particular genotype (*ss*) was associated with reduced 5-minute Apgar scores, increased jitteriness and increased muscular tone, while a different genotype (*ls)* was associated with low birth weight, and the third genotype (*ll*) was associated with respiratory distress and tachypnea in prenatally-exposed infants. These findings suggest the possibility of a gene-environment interaction that influences the occurrence of adverse neonatal effects following maternal SSRI treatment late in pregnancy. It is possible that the same or other polymorphisms in the *5HTT* gene or variants of other genes affect the occurrence of certain birth defects following maternal SSRI use in early pregnancy.

   Genetic predisposition to the effects of several other teratogenic exposures have been intensively studied. Examples include the increased associations found between maternal smoking and risk of cleft lip and palate in the presence of a rare transforming growth factor alpha (*TGFA*) genotype[7] or a variation in the nitric oxide synthase (*NOS3)* gene in the infant.[8] Animal studies have also implicated

genetic susceptibility in the increased risk of birth defects with maternal hyperglycemia or anticonvulsant medications.[9]

4. Manifestations of abnormal development depend on dose and duration of a teratogenic exposure. In fact, both studies on maternal SSRI and bupropion exposure were limited by lack of information on dosage, and therefore inability to look at dose–response relationships. Only two previous studies assessed associations of birth defects with maternal SSRI dosage; one found an association of cardiac defects with the highest (but not lower) doses of paroxetine[10], while the other study failed to confirm an association with dose.[11] Only one case-control study nested within a cohort looked at duration of antidepressant use during the first trimester in relation to risk of congenital malformations.[12] No increase was observed in the risk with longer duration of exposure.

5. The fifth principle states that teratogenic exposures act in specific ways: Teratogenic mechanisms may involve inhibition of a specific biochemical or molecular process or involve cell death or decreased cellular proliferation. The existence of serotonin (5-HT) and serotonin-like substances in cells of the early embryo and the essential role of 5-HT in the regulation of cellular proliferation, migration, and differentiation and of neural crest cell morphogenesis have been extensively investigated in experimental animals.[13, 14] Studies in early murine embryos found that lipophilic 5-HT receptor antagonists can disrupt early cleavage divisions.[13] A specific role of serotonin in cardiac and craniofacial morphogenesis has been established in the mouse embryo.[15-17] Therefore, animal studies clearly indicate the potential for SSRI exposures to alter

> embryogenesis. The mechanism of action of bupropion, on the other hand, is unknown, and animal studies are scarce. In the one published study that provided an overview of the pre-clinical toxicology of bupropion in rats and rabbits, no evidence of teratogenicity was observed, precluding the ability to investigate pathogenetic mechanisms.[18]

It is important to note that my observation of an increased risk of birth defects associated with maternal SSRI use is somewhat consistent with findings in other high quality epidemiological studies that found an increased risk for any congenital malformation[10, 19, 20] or cardiac malformations.[10, 20-25] It is difficult, however, to compare the results of my study in detail to others, most of which have not used a case-control design and did not assess exposure in selected categories of birth defects. These differences may explain why increased risks for craniosynostosis or anencephaly have not been replicated in other studies. Louik et al[23], who used a similar design to my study, also detected an association between SSRI use and the occurrence of omphalocele.

It is important to note that in my studies assessing the risks of first trimester SSRI and bupropion use, no information was available on the medical condition for which these drugs were prescribed. This presented an important limitation for both studies, causing inability to address possible confounding by indication. However, it seems likely that in most instances treatment was given for depression. Little is known about the effect of maternal depression during pregnancy on the risk for malformations in the baby. Previous epidemiological studies of the teratogenicity of SSRI exposure suffered from the same limitation, except in one study where severity of maternal depression was controlled in a weighted regression model, although the authors found no effect on

depression itself on birth defects.[11] Maternal stress has been linked to a higher rate of cranial neural-crest malformations[26], orofacial clefts[27] and various other congenital anomalies in some studies.[27, 28] It is possible that the observed increase in risk of birth defects in my studies could be attributed to a mechanism that involves both the mother's underlying psychiatric condition and the pharmacological treatment.

Considered as whole, the evidence available from my study and others that have been reported suggests that maternal SSRI treatment may be weakly teratogenic to the fetus. As for bupropion, replication of the results observed in my study in other well-designed epidemiological studies is warranted before any definite conclusions can be made. In general, larger epidemiological studies that have sufficient power to assess the teratogenic potential of individual SSRIs, bupropion or other antidepressants are needed to clarify the magnitude and nature of the risks that may be associated with early SSRI exposure and to separate the effect of drug therapy from effects of the underlying maternal disease.

Untreated antepartum depression may be a predictor of adverse reproductive outcomes, such as caesarean or premature delivery, low birth weight and neonatal intensive care admission.[29-31] Treatment of maternal depression in pregnancy is, therefore, crucial. Interpersonal therapy or cognitive behavioural therapy may be used for mild to moderate depression in pregnancy, although there is very little research on the effectiveness of such methods. Pharmacological treatment is considered to be the optimal choice for pregnant women with more serious depression.[3, 32] Meanwhile, it is important that clinicians counsel pregnant women and those of childbearing age who require antidepressant treatment about the possible slight increase of malformations in

children whose mothers take SSRIs or bupropion early in pregnancy, while at the same time highlighting that no strong teratogenic risk has been detected.

Discontinuation of antidepressant treatment in pregnant women with serious depressive illness may have adverse effects on the mother and the baby.[33, 34] The increase in absolute risk observed with either SSRI or bupropion exposure in my study and others is small in comparison to the background risk of 2-3% of having a major malformation identified at birth (or 3-4% identified by 1 year of age) in an unexposed population, but this small increase may still be of concern to some patients. Switching to therapy with another type of antidepressant may be an option in some instances, although the teratogenic potential of other antidepressants in humans has not been as extensively studied as that of SSRIs. Consideration of termination of a pregnancy solely on the basis of exposure to an SSRI or bupropion in early gestation is not warranted on the basis of my data or those of other reported studies.

6.2 Early fetal growth impact on pregnancy outcome

In chapter 5, I linked data on first-trimester CRL measurements to their pregnancy outcomes to investigate whether small size of the embryo or fetus for gestational age early in pregnancy is associated with the occurrence of birth defects or other adverse reproductive outcomes. The results show that early restricted fetal growth is a strong indicator of subsequent miscarriage and some other adverse outcomes, including delivering through a cesarean section, low birth weight and low birth length.

My study did not detect an association of low crown rump length in the first trimester with the presence of a birth defect, but this may be a result of insufficient statistical power owing to the limited sample size. A previous study suggests that an association

of birth defects with intrauterine growth retardation (IUGR) defined at the time of delivery exists.[35] In that report, the authors proposed three mechanisms to explain the pathogenetic relationship between delayed fetal growth and the presence of a malformation: 1) The presence of a malformation predisposes the fetus to slowed growth; 2) IUGR predisposes the fetus to a malformation; or 3) IUGR and malformations coexist because of common underlying factors.

The high risk of subsequent spontaneous abortions noted amongst women who had embryos that were smaller than expected in size with the presence of a heartbeat at the time of the ultrasound examination in my study can be explained by either the first or the third proposed mechanism mentioned above. About 50% of spontaneous abortions occur as a result of chromosomal abnormalities,[36] and this could explain the association of low CRL with subsequent miscarriage that I observed, but miscarriages may also be caused by teratogenic exposures or intrinsic abnormalities in growth that impair development. If the latter were true, it would also explain the increased rates of low birth weight and length reported amongst pregnancies that survived to term after small initial CRL. Smith[37] supports the view that embryonic nutrition in early pregnancy originates from decidual glandular secretion, and that maternal intraplacental circulation or hemotrophic exchange is only established after embryogenesis is complete and the fetal metabolic requirements increase. This suggests that factors affecting early nutrition are different from those affecting fetal nutrition later in pregnancy, and, therefore, the associations found between early growth restriction of the embryo and later adverse outcomes might be explained by abnormalities in factors that affect embryonic nutrition in the very early stages of pregnancy.

My study had several limitations, including a small sample size and inability to adjust for important confounders such as smoking and alcohol, which are known to be risk factors for adverse birth outcomes and restricted fetal growth. Race or ethnicity is one of the main factors that affect fetal weight. The fact that data were unavailable for this important confounder may have led to misclassification as growth restricted of fetuses born to mothers who were constitutionally small because of their ethnic background.

My finding that embryonic growth restriction may affect later pregnancy outcome may have important implications in terms of prevention. Because several adverse outcomes contribute to increased morbidity and mortality, pregnancies with small embryonic size should be regarded as high risk and given close followup. Detection of poor growth of the embryo early in pregnancy might be incorporated into first trimester ultrasound screening programmes following proper evaluation of the sensitivity, specificity and predictive values.

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