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A Prospective Study Evaluating the Effects of SSRI Exposure on Cardiac Size and Function in Newborns

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Abstract

Background: Selective serotonin reuptake inhibitors (SSRIs) are antidepressants prescribed in 10% of pregnancies in the United States. We have previously shown in preclinical studies that sertraline exposure impacts cardiomyocyte development, leading to reductions in left ventricular size and cardiac function.

Objectives: We hypothesized that *in utero* SSRI exposure will lead to reduced left ventricular dimensions and cardiac function on echocardiography immediately after birth.

Methods: Twenty term infants with and twenty-one term infants without *in utero* exposure to SSRIs underwent echocardiograms to assess cardiac size and function. Exclusion criteria for infants included prematurity, small or large for gestational age, any respiratory or cardiovascular support needed after birth, and any major congenital malformation.

Results: Infants exposed to *in utero* SSRIs had significantly reduced right ventricular dimensions in diastole [Control 1.0 (0.86, 1.20) cm, SSRI 0.89 (0.730, 1.05) cm, $p=0.03$], and left ventricular lengths in diastole and systole [Diastole: Control 3.4 (3.25, 3.65) cm, SSRI 3.25 (3.10, 3.45) cm, $p=0.03$; Systole: Control 2.9 (2.65, 3.05) cm, SSRI 2.6 (2.50, 2.85) cm, $p=0.01$]. No differences were observed in cardiac function. Importantly, there were no differences in maternal conditions or infant birth weight, body surface area, or gestational age.

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Author Contributions

Deidra Ansah: Dr. Ansah collected and reviewed the data, assisted with the data analysis, drafted the initial manuscript and approved the final manuscript as submitted.

Benjamin E. Reinking: Dr. Reinking assisted in study design, reviewed all of the echocardiograms as the blinded cardiologist, reviewed and revised the manuscript and approved the final manuscript as submitted.

Tarah T. Colaizy: Dr. Colaizy assisted in study design, performed and critically reviewed all of the statistics, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Robert D. Roghair: Dr. Roghair assisted in study design, reviewed and revised the manuscript and approved the final manuscript as submitted.

Sarah E. Haskell: Dr. Haskell conceptualized and designed the study, applied for the study funding, assisted with and critically reviewed data analyses, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

Conclusions: Our findings suggest an association between *in utero* exposure to SSRIs and ventricular size in infants. Given the increasing use of SSRIs during pregnancy and the importance of early life programming on future cardiovascular health, larger studies need to be completed to determine if *in utero* SSRI exposure impacts ventricular size.

Keywords

ventricular size; cardiac function; selective serotonin reuptake inhibitors; fetal exposure

INTRODUCTION

As many as 18.4% of pregnant women are depressed during pregnancy, with as many as 12.7% having an episode of major depression [1]. Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed therapy for depression and approximately 10% of pregnant women in the United States take an SSRI [2, 3]. The management of maternal depression during pregnancy is accompanied by difficult decisions regarding the risks and benefits of medication therapy for both mother and baby.

GlaxoSmithKline released a statement in 2005 identifying an increased risk of congenital heart disease in infants of mothers taking the SSRI paroxetine. Multiple subsequent studies have been performed to evaluate this association of SSRI exposure and congenital heart defects. Several studies support a mildly increased risk of septal defects [4–7] with SSRI exposure during pregnancy, however studies may be affected by methodological weaknesses and confounding variables including maternal depression [7]. A recent systemic meta-analysis of individual SSRIs suggests paroxetine is the only SSRI associated with an increased risk of cardiac malformations [8]. SSRI use in pregnancy is also associated with a modest increased risk for persistent pulmonary hypertension in newborns, independent of structural defects [9]. Despite these associations, SSRI use during pregnancy has steadily been increasing over the last decade.

Given the prevalence of depression and SSRI use during pregnancy, it is important to improve our current knowledge on the effects of SSRIs on cardiac development. Preclinical studies are instrumental in understanding the potential mechanisms of how SSRIs influence cardiac development while eliminating confounding variables. While no cardiac malformations have been observed in our preclinical models, we have demonstrated that sertraline exposure decreases the proliferation and cross-sectional area of neonatal cardiomyocytes and increases neonatal cardiac fibrosis, resulting in significant reductions in cardiac size and function [10]. Based on these data, we hypothesized that human infants exposed to *in utero* SSRIs would have reduced ventricular size and cardiac function shortly after birth. To our knowledge this is the first study specifically designed to prospectively assess ventricular size and function in newborn infants following SSRI exposure.

MATERIALS AND METHODS

This study was approved by the University of Iowa Institutional Review Board. We conducted a prospective observational study of infants with or without *in utero* SSRI exposure and their mothers. Mothers were recruited through the University of Iowa

Women's Wellness Center, Obstetric or Family Medicine clinics, during their delivery hospitalization, or in response to study announcement. Mothers were consented for the study at the time of their admission for labor and delivery. As all SSRIs work by inhibiting the reuptake of serotonin, we chose to include mothers taking any SSRI during pregnancy.

Population

Inclusion criteria for the mothers included age 18–45 years of age and delivering infants at the University of Iowa. For women included in the study who were on SSRIs, medication lists were reviewed and verified with the mother. All mothers in the exposure group were on SSRIs at the time of delivery. Inclusion criteria for infants were term gestation, appropriate for gestational age and less than 7 days of life. Exclusion criteria for both non-exposed and SSRI-exposed infants included requirement of respiratory or cardiovascular support, or any major congenital malformations including cyanotic congenital heart disease.

Maternal and Infant Data Collection

Demographic data was collected using electronic medical records at the University of Iowa. Prenatal clinic notes, medication history, delivery documentation, and the infant admission and progress notes were reviewed. The following data was collected for all mothers enrolled in the study: maternal age, pregnancy health status, co-morbid conditions, and Patient Health Questionnaire-9 survey (PHQ-9) results. The PHQ-9 is a 9-item questionnaire widely used to screen for depression. Each item is rated on a 4-point Likert scale, with a score of 5–10 suggesting mild depression, 11–16 suggesting moderate depression, and > 16 suggesting severe depression. For mothers taking SSRIs during pregnancy, information was obtained on the type of SSRI, dosage, and duration of SSRI therapy. For all infants, gestational age, gender, birth weight and birth length were collected. Body surface area (BSA) was calculated using the following equation: $BSA (m^2) = Height(cm)^{0.725} \times Weight(kg)^{0.425} \times 0.007184$ [11]. APGAR scores and delivery complications were also reviewed.

Echocardiography

All of the infants underwent an echocardiogram within the first two days of life. Echocardiograms were performed using the Phillips iE33 ultrasound machine equipped with a standard transducer. (Phillips Healthcare, Andover, MA, USA). The echocardiogram images obtained adhered to the American Society of Echocardiography (ASE) protocols for transthoracic pediatric echocardiograms [12–14]. This included 2D imaging, color Doppler, and spectral Doppler in the subcostal, parasternal short axis, parasternal long axis, apical four chamber (4C), and suprasternal notch views. Additionally, we employed protocols approved by ASE for newborns during the transition period [12–13]. All echocardiograms were performed by one of four registered diagnostic cardiac sonographers with pediatric echocardiography certification. Each sonographer had >10 years of experience in pediatric cardiology. Post-processing of the obtained images was performed on Phillips Xcelera, a multi-modality cardiovascular image management system. All images were reviewed by a blinded pediatric cardiologist twice and the parameters are listed in detail below with corresponding equations in Table 1.

Standard ASE M-mode views were obtained. Left ventricular (LV) volumes at end diastole and end systole were measured in the apical 4C view. Stroke volumes were calculated based on the formulas of Teicholz et al. as validated by Kronik et al. [15]. The specific geographic measurements to evaluate ventricle size included: tricuspid valve and mitral valve annuli, right ventricular (RV) basal diameter, RV mid cavity diameter, RV length, antero-inferior dimension of the RV cavity, LV basal diameter, LV length, LV area, and LV mass. LV mass was calculated by two methods: M-mode [16] and 2D echo using the area/length method [17]. Ventricular function was evaluated in accordance with ASE recommendations [12–14]. Fractional area of change (FAC) was used as a marker of RV systolic function [18]. Ejection fraction (EF) was calculated using both Simpson's method and the bullet method. The LV long axis was obtained in the 4C view as the distance between from the mitral annulus to the endocardial apex in end diastole [19]. For diastolic functional assessment, pulse wave Doppler was placed at the tip of the tricuspid or mitral wave to obtain E and A waves. The E/A ratio was calculated. Calculations were performed by built in software in Xcelera.

Sample Size Calculation and Analysis

This power analysis was based on LV internal diameter in diastole data retrieved from our group's animal studies on SSRI exposure [20]. Assuming equal variance between the groups and setting alpha at 0.05, we estimated a sample size of 20 controls and 20 subjects would provide >80% power to detect a difference in means equal to one standard deviation, and therefore set our goal for recruitment according to this analysis. Data are presented as median (interquartile ranges) or proportions as appropriate. Statistical analysis was performed using Wilcoxon rank sum test for all continuous variables due to non-normality, and Chi-Square or Fisher's exact test for categorical variables, as appropriate. Analysis was performed using SAS 9.4. P value <0.05 was considered statistically significant.

RESULTS

Our cohort consisted of 21 mother-infant pairs without SSRI exposure and 20 mother- infant pairs with exposure to SSRIs. None of the women reported a personal or family history of congenital heart disease, and no pregnancy was complicated by the presence of twins or multiples.

Demographics

Maternal age was 30 (25, 34) years in the control group and 32.1 (30, 35) years in the SSRI-treated group ($p=0.0714$). Mothers in the two groups were not different when comparing common maternal comorbidities (Table 2). There was a difference in the PHQ-9 score between the SSRI-treated mothers compared to controls [Control 1(0–3); SSRI 3.5 (2–5), $p=0.028$]. Both groups were categorized as minimal to mild depression according to the PHQ-9 classifications. Both groups had PHQ-9 score ranges from 0–16. Seventy-five percent of mothers (15/20) started an SSRI before the time of conception. One mother (1/20, 5%) initiated her SSRI during the first trimester, three mothers (3/20, 15%) during the second trimester, and one mother (1/20, 5%) during the third trimester. The most commonly prescribed SSRI was sertraline (11/20, 55%). The remaining SSRIs used included:

fluoxetine (4/20, 20%), and citalopram or escitalopram (5/20, 25%). No mothers discontinued SSRI therapy at any time during their pregnancy.

There were no differences between the infant groups in regard to gestational age, sex, birth weight, body surface area, 1 and 5 minute APGARs, or day of life echocardiograms were performed (Table 3). The SSRI group was smaller in length.

Echocardiography

Echocardiogram data are summarized in Table 4. By M-mode, SSRI exposed infants had significantly smaller RV dimensions in diastole. LV lengths measured to the epicardium in both systole and diastole were significantly reduced in SSRI-exposed infants. No differences were observed in cardiac function. As expected, several infants in both groups had a physiologic patent ductus arteriosus (Controls 10, SSRI 9, $p=1$) and/or patent foramen ovale (Control 16, SSRI 18, $p=0.41$). Three infants in the control group had small, asymptomatic muscular ventricular septal defects (VSDs) where no infants with SSRI exposure had VSDs ($p=0.23$).

DISCUSSION

Serotonin has been implicated in cardiac development [21] and SSRIs impact extracellular serotonin. Due to the prevalence of maternal depression and common use of SSRIs during pregnancy, it is important to understand the risk profile of SSRIs on perinatal outcomes to properly advise expectant mothers. Epidemiological studies have described a relationship between SSRI exposure and cardiac malformations [4–8]. However, these studies focus primarily on structural defects, not ventricular size or function.

In this study, we found that SSRI-exposed infants had a 5–10% decrease in LV lengths in systole and diastole in comparison to non-SSRI exposed infants. We also found that RV internal diameters during diastole were 10% smaller in SSRI-exposed infants. We are the first to report an effect on ventricular size in SSRI-exposed infants. There was no difference in cardiac function between the groups. Thus, the smaller LV lengths in SSRI-exposed infants did not render a functional or physiological difference in the left ventricle at least in the otherwise healthy newborn. While the possible mechanisms for these findings are unclear, our preclinical work and that of others suggest SSRIs decrease cardiomyocyte proliferation [10, 22]. The impact of heart size at birth is currently not well studied. Preterm infants with fetal growth restriction have hypertrophied hearts and reduced cardiac function within a few days after birth [23]. Furthermore, children and adults with a history of preterm delivery have cardiac dysmorphology with foreshortened hearts and increased resting heart rates [24, 25]. This establishes an important foundation for longitudinal studies to assess if the difference in ventricular size will have a functional or physiological effect later in life. It is important to note that the majority of infants in our study had their echocardiograms performed on day of life 1 and 19/41 (46%) of infants had a PDA. As asymptomatic newborns rarely undergo echocardiography, our findings are similar to those reported in the literature [13, 26]. Jain et al. recently noted that 44% of term newborns who underwent echocardiograms had a PDA present within the first 24 hours of life [13]. As important physiologic changes occur after birth, more accurate ventricular measurements might be

obtained outside of this immediate transition period. However, protocols utilized for this investigation are particular to the transition time when it is common for the ductus to still be present [13].

In our population, 3/41 (7.3%) had VSDs which is similar to the 5.3% prevalence reported by Roguin et al. in neonates [27], but higher than the reported 0.42% prevalence of VSD in a metropolitan surveillance system [28]. The current literature demonstrates septal defects are one of the more common findings identified in SSRI-exposed infants [4–7]. However, the VSDs in our study were in the control population. Our limited sample size likely contributes to the notable difference in congenital heart defects and highlights the need for larger numbers.

To eliminate any potential confounding factors, we excluded infants that needed any early respiratory or cardiac support. SSRIs have been associated with respiratory distress [29]. As such, it is possible that a stronger cardiac phenotype could have been identified if potentially symptomatic infants were included in our study. Given that we observed changes in LV lengths and RV volumes with our strict inclusion criteria, it is important to evaluate the effects on ventricular size in a larger population including those that may have other SSRI-associated symptoms.

In this cohort, the median PHQ-9 score for each group was consistent with minimal depression, suggesting that the effect of maternal depression itself on cardiac development was controlled and unlikely to be a potential confounder. Maternal depression is considered one of the biggest challenges in interpreting epidemiologic studies on the risks of SSRIs in pregnancy, in that maternal depression alone has been associated with changes in neonatal outcomes [30, 31]. Studies are frequently limited by controlling for depression, timing and dosage of SSRI therapy, and other psychotropic medications. Because the mechanism of action is the same across all SSRIs, we chose to include any SSRI used during pregnancy. While we did not control for the dosage or duration of exposure, 75% of mothers in our study were on SSRIs pre-conception through delivery. Only one mother who was on an SSRI took an additional psychotropic medication and no mothers in the control group were on SSRIs or psychotropic medications.

SSRI-exposed infants in our study had similar birth weight and body surface area, however significant differences in their birth length were noted. There have been reports of decreased birth length caused by SSRI use during pregnancy [32, 33]. While our findings may corroborate these reports, infant length was not a primary study outcome. As such, length measurements were not via an infant length board which is the gold standard for length measurements.

Several limitations do exist in this study. Importantly, we do not know if the women on SSRI therapy were compliant as no drug levels were measured, either in mothers or infants. Data was obtained via medical record and current medication lists which were verified by the mother. Therefore, if mothers were not compliant with medications, their infants could be misclassified as exposed when they were not. This could bias our results toward the null hypothesis. Importantly, other factors that potentially contribute to an increased risk of

SSRI-associated congenital heart defects were not considered including genetic polymorphisms, and genetic variants in folate, homocysteine, or transsulfuration pathways [34, 35]. We were unable to evaluate if a dose-dependent effect was present or further parse out the effects of the particular SSRI due to our limited sample size, and lack of variability in agent used, as most mothers were taking sertraline. While the primary outcome (LV internal diameter in diastole) was chosen a priori, and the sample size calculated based on our preclinical data, no power calculations were obtained for the other echocardiogram measurements, and no adjustment for multiple comparisons was conducted. Therefore, there is potential for Type 2 errors in the other echocardiogram measurements. These data (outside of the primary outcome) should be considered exploratory, and will help guide future larger studies in this area, both in humans and animal models. Lastly, the infants in our cohort were asymptomatic and in the normal newborn nursery but we did not control for different hemodynamic variables which could influence echocardiogram measurements.

CONCLUSION

This investigation is one of the first prospective analyses to evaluate the effects of SSRI on ventricular size and function. Our findings suggest an association between *in utero* exposure to SSRIs and reductions in ventricular size in infants. While we recognize there are limitations to the study, our findings suggest closer monitoring and further research to better ascertain the role of SSRI exposure on cardiac development. Given the increasing use of SSRIs during pregnancy and the importance of early life programming on future cardiovascular health, larger studies need to be completed to determine if *in utero* SSRI exposure impacts ventricular size.

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Table 1.**Echocardiography Calculations**

LV Mass by M-mode	$0.8 \times 1.04 \times [IVS_d + LVID_d + PWT_d]^3 - LVID_d^3 + 0.6$
Fractional area of change	$[(RV \text{ end diastolic area} - RV \text{ end systolic area}) / RV \text{ end diastolic area}] \times 100$
Ejection Fraction	$EF = (EDV - ESV) / EDV$
Shortening Fraction	$FS = (LVEDD - LVESD / LVEDD) \times 100$
Sphericity Index	$EDV / (4/3 \times (D/2)^3)$ D= the LV end diastolic length

Table 2.**Maternal Comorbid Conditions**

	Controls (N=21)	SSRI Subjects (N=20)	P value
Obesity (BMI ≥ 30)	6	6	1
Overweight (BMI > 25 and <30))	8	6	0.59
Chronic Hypertension	3	1	0.61
Gestational Hypertension	0	3	0.11
Diabetes	2	3	1
Tobacco Use	3	1	0.61
Alcohol Use	0	1	0.49
Hypothyroidism	3	1	0.61
Hyperthyroidism	0	0	--
Maternal Infection	4	2	0.66
Anemia	2	3	0.66
Advance Maternal Age	3	4	0.70
Hx of Congenital Heart Disease	0	0	--

Table 3.

Infant Demographics

	Controls (N =21)	Subjects (N=20)	P value
Gestation Age (weeks)	40 (39, 40)	39.29 (38.43, 39.5)	0.32
Male Sex	12	7	0.16
Birth Weight (g)	3475 (3210, 3690)	3287 (3155, 3635)	0.29
Length (cm)	52 (50.8, 53.3)	50 (48.8, 51)	0.003
Body Surface Area (m ²)	0.221 (0.215, 0.233)	0.214 (0.210, 0.229)	0.18
1 minute Apgar	8 (7, 9)	8 (6, 9)	0.85
5 minute Apgar	9 (9,9)	9 (8,9)	0.13
Age at echocardiogram (d)			
0	3/21	3/20	0.89
1	16/21	14/20	
2	2/21	3/20	

Data are reported as absolute number for male sex, day, and as median (IQR) for all other variables

Table 4.**Echocardiogram Measurements**

	Controls (N=21)	Subjects (N = 20)	P value
M-mode			
Right ventricular diameter, diastole (cm)	1.0 (0.86, 1.20)	0.89 (0.73, 1.05)	0.03*
Interventricular septum diameter, diastole (cm)	0.35 (0.30, 0.42)	0.36 (0.31, 0.43)	0.79
Interventricular septum diameter, systole (cm)	0.46 (0.35, 0.56)	0.42 (0.38, 0.50)	0.67
Left ventricular internal diameter, diastole (cm)	1.7 (1.6, 1.8)	1.75 (1.6, 1.85)	0.23
Left ventricular internal diameter, systole (cm)	1.02 (0.9, 1.2)	1.05 (0.96, 1.17)	0.74
Left ventricular posterior wall, diastole (cm)	0.32 (0.28, 0.37)	0.29 (0.28, 0.34)	0.22
Left ventricular posterior wall, systole (cm)	0.45 (0.37, 0.52)	0.41 (0.37, 0.46)	0.48
Aortic root diameter (cm)	0.95 (0.87, 1.0)	0.92 (0.84, 1.0)	0.27
Left atrium diameter (cm)	1.40 (1.2, 1.5)	1.35 (1.25, 1.45)	0.81
Aortic root z-score	-0.21 (-1.1, 0.23)	-0.48 (-1.0, 0.05)	0.56
Left atrium: Aortic root	1.48 (1.15, 1.73)	1.53 (1.31, 1.64)	0.66
LV Mass (g)	8.2 (6.8, 10.2)	8.0 (7.1, 9.3)	0.68
Volumetric Data			
Left ventricular volume, diastole (mL)	4.1 (3.6, 4.7)	3.95 (3.3, 4.4)	0.46
Left ventricular volume, systole (mL)	1.7 (1.2, 1.9)	1.4 (1.15, 1.6)	0.09
Stroke volume (mL)	2.4 (2.1, 3.0)	2.45 (2.09, 3.0)	0.91
Geometrical data			
Tricuspid valve annulus (cm)	1.2 (1.15, 1.25)	1.2 (1.13, 1.25)	0.92
Mitral valve annulus (cm)	1.06 (0.99, 1.1)	1.05 (1.02, 1.15)	0.84
Right ventricular basal diameter, end diastole (cm)	1.3 (1.16, 1.35)	1.3 (1.25, 1.35)	0.58
Right ventricular mid cavity diameter, end diastole (cm)	1.23 (1.06, 1.30)	1.14 (1.03, 1.25)	0.14
Right ventricular length, end diastole (cm)	2.85 (2.65, 3.05)	2.83 (2.6, 3.0)	0.58
Antero-inferior diameter of the RV cavity area (cm)	1.45 (1.35, 1.63)	1.55 (1.43, 1.7)	0.20
Left ventricular basal diameter, end diastole (cm)	1.35 (1.3, 1.5)	1.4 (1.3, 1.6)	0.62
Left ventricular length to endocardium, diastole (cm)	3.30 (3.0, 3.4)	3.05 (2.8, 3.25)	0.09
Left ventricular length to endocardium, systole (cm)	2.35 (2.2, 2.5)	2.25 (2.0, 2.45)	0.21
Left ventricular length to epicardium, diastole (cm)	3.4 (3.25, 3.65)	3.25 (3.1, 3.45)	0.03*
Left ventricular length to epicardium, systole (cm)	2.9 (2.65, 3.05)	2.6 (2.5, 2.85)	0.01*
Left ventricular area, diastole (parasternal short axis to papillary muscle) (cm ²)	2.5 (2.25, 2.85)	2.35 (2.1, 2.65)	0.30
Left ventricular area, diastole (parasternal short axis to mitral valve) (cm ²)	2.85 (2.6, 3.1)	2.85 (2.65, 3.1)	1.0
Left ventricular area, systole (parasternal short axis to mitral valve) (cm ²)	1.6 (1.5, 1.8)	1.55 (1.45, 1.65)	0.47
Left ventricular mass (indexed g/m ²)	36.8 (33.6, 41)	40.25 (34.75, 43.40)	0.26
Functional Data			
Fractional area of change (RV)	0.36 (0.32, 0.40)	0.35 (0.315, 0.43)	0.81
Ejection Fraction, Simpson's (%)	0.60 (0.55, 0.66)	0.63 (0.61, 0.68)	0.16

	Controls (N=21)	Subjects (N = 20)	P value
Ejection Fraction, Bullet (%)	59.14 (53.97, 65.64)	59.99 (54.5, 62.31)	0.79
Shortening Fraction (%)	35.29 (31.58, 43.75)	39.44 (35.09, 45.0)	0.27
Sphericity Index	0.26 (0.19, 0.33)	0.27 (0.22, 0.32)	0.68
Tricuspid Valve E/A	0.74 (0.58, 0.89)	0.88 (0.58, 1.10)	0.94
Mitral Valve E/A	1.02 (0.87, 1.51)	1.12 (0.96, 1.36)	0.16