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ARTICLE

# Antenatal Use of Selective Serotonin-Reuptake Inhibitors and QT Interval Prolongation in Newborns

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**What's Known on This Subject**

SSRIs are the most widely used class of antidepressants by pregnant women. Several reports of SSRI-induced QT prolongation in adults exist, and we previously reported such a case of prolonged QT after maternal fluoxetine use. No studies have examined the effects of maternal SSRI use in pregnancy and neonatal QT prolongation.

**What This Study Adds**

The mean QTc was significantly longer in the group of newborns exposed to SSRI antidepressants as compared with control subjects. Ten percent of SSRI-exposed newborns had a markedly prolonged QTc interval (>460 milliseconds) compared with none of the unexposed newborns. The longest QTc interval observed was 543 milliseconds.

## ABSTRACT

OBJECTIVES. Prolongation of the QT interval is a risk factor for sudden death. Selective serotonin-reuptake inhibitor antidepressants can prolong the QT interval and are widely used by pregnant women. Whether antenatal exposure to selective serotonin-reuptake inhibitor causes QT prolongation in offspring is unknown. The aim of this study was to determine the effect of maternal use of selective serotonin-reuptake inhibitor antidepressants during pregnancy on the QTc interval of the offspring.

METHODS. Between January 2000 and December 2005, we collected data on all of the newborns born at a single tertiary care hospital. Electrocardiograms of infants exposed to selective serotonin-reuptake inhibitor antidepressants in utero were compared with those of healthy control newborns matched on gestational age. The tracings were interpreted by a pediatric cardiologist who was unaware of the drug exposure.

RESULTS. We identified 52 newborns exposed to selective serotonin-reuptake inhibitor antidepressants in the immediate antepartum period and 52 matched control subjects. The mean QTc was significantly longer in the group of newborns exposed to antidepressants as compared with control subjects (409 ± 42 vs 392 ± 29 milliseconds). Five (10%) newborns exposed to selective serotonin-reuptake inhibitor antidepressants had a markedly prolonged QTc interval (>460 milliseconds) compared with none of the unexposed newborns. The longest QTc interval observed among exposed newborns was 543 milliseconds. All of the drug-associated repolarization abnormalities normalized in subsequent electrocardiographic tracings.

CONCLUSIONS. Antepartum use of selective serotonin-reuptake inhibitor antidepressants is associated with QTc interval prolongation in exposed neonates. Additional research using a standardized protocol is needed to determine whether exposure to selective serotonin-reuptake inhibitor antidepressants in late pregnancy is also associated with arrhythmias. *Pediatrics* 2008;122:e710–e715

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**Key Words**
pregnancy, antidepressant, adverse drug events, electrocardiography, long-QT syndrome

**Abbreviations**
SSRI—selective serotonin-reuptake inhibitor
ECG—electrocardiography

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PROLONGATION OF THE QT interval is associated with an increased risk of malignant arrhythmias and sudden death.[1] Drug-induced QT prolongation is the most common reason for the withdrawal of medications from market or the imposition of restrictions on their use.[2] Prominent recent examples of drugs removed from widespread use because of QT prolongation include terfenadine, astemizole, cisapride, and grepafloxacin.[3]

It has been estimated that ≥25% of women have symptoms of depression during pregnancy,[4] most often in the second and third trimesters.[5] Although some do not seek medical attention, a large proportion of depressed pregnant women receive antidepressant medication because of the well-documented negative impact of untreated depression on pregnancy outcomes.[5] Since their introduction ~2 decades ago, selective serotonin-reuptake inhibitor (SSRI) antidepressants have become the most widely used class of antidepressants by pregnant women. A recent report from

the National Birth Defects Prevention Study[6] revealed that SSRIs represent ~80% of antidepressants used in pregnancy; given that treatment often continues into the second and third trimesters, every year ~92 000 newborns are exposed to these medications before delivery. Recent studies question the safety of these drugs during pregnancy, with the main focus being adverse neonatal outcomes.[7–12]

SSRI antidepressants alter cardiac repolarization by inhibiting the human ether-a-go-go potassium channel.[13,14] In adults, these drugs have been associated with prolongation of the QT interval and torsades de pointes during therapeutic use[15–21] and after overdose.[22,23] However, little is known about the effects of SSRIs on cardiac repolarization in neonates. After the observation of a single case of QTc prolongation in a neonate born to a fluoxetine-treated mother,[24] we explored the potential association between antenatal exposure to SSRI antidepressants and prolongation of the QTc interval in the first days of life.

## METHODS

The Rabin Medical Center Department of Neonatology in Israel has been affiliated with the International Clearinghouse for Birth Defects Monitoring System since 1974, and, hence, much attention is given to drug use during pregnancy. At this institution, all of the newborns of mothers treated with psychoactive or cardiovascular medications undergo a detailed physical examination, close cardiorespiratory monitoring, routine serum biochemistry, and 12-lead electrocardiography (ECG) within the first days of life. Data on all of the newborns of mothers receiving SSRI antidepressants (paroxetine, fluoxetine, fluvoxamine, citalopram, or sertraline) or venlafaxine before the onset of labor, in the period from January 1, 2000, to December 31, 2005, were prospectively collected. Although venlafaxine also inhibits norepinephrine reuptake at high doses,[25] its clinical indications and effects on cardiac repolarization are similar to those of SSRI antidepressants.

We identified all of the neonates with a gestational age of ≥35 weeks born to women receiving treatment with an SSRI antidepressant at the onset of labor and extracted their medical charts and ECG tracings. We excluded neonates born to women treated with any other chronic medication during pregnancy (whether known as QT prolonging or not), as well as those with gestational diabetes or hypothyroidism. We also excluded neonates with Apgar scores <7 (either 1 or 5 minutes), because asphyxia is a known risk factor for QT prolongation,[2] and those with cardiac structural abnormalities identified by echocardiography.

The comparison group consisted of newborns born to healthy mothers who took no medications before delivery. These infants were born during the same 6-year period in our center and underwent electrocardiography because of the detection of a systolic murmur during the first postnatal examination. Infants with any abnormality on echocardiography were excluded from the comparison group. Normal infants were stratified by gestational age, and then a random match for each exposed infant's gestational age was chosen from the potential control subjects within that gestational age stratum. Exposed and unexposed neonates were matched on gestational age, because advancing fetal age is associated with changes in the duration of ECG intervals.[26]

For the purpose of this study, ECGs were interpreted by a single experienced pediatric cardiologist (Dr Fogelman), who was blinded to drug exposure. The pediatric cardiologist measured the RR, PR, QRS, and QT intervals and defined whether the ECG was otherwise normal. The QT intervals were corrected for rate (QTc) using Bazett's correction[27,28] and subsequently replicated using the Fridericia formula.[29] The mean of 2 consecutive ECG complexes in lead II[30] was calculated, and a prolonged QTc was defined as an interval >460 milliseconds.[31,32] Although there is no consensus regarding the definition of prolonged QTc in neonates, 460 milliseconds is a widely used upper limit cited by authorities in both pediatric cardiology[31] and neonatology[32] and is 3 SDs higher than the mean of the general healthy newborn population.[28] To test the robustness of our findings, we replicated our analysis using a less stringent cutoff (440 milliseconds), corresponding with the upper 2.5% of QTc values found in healthy newborns.[28] This threshold was adopted recently by the European Society of Cardiology.[33] The study was approved by the hospital's institutional research ethics board.

We compared continuous variables by using Student's *t* test or Mann-Whitney *U* test, as appropriate, and proportions by using Fisher's exact test. We used the Kruskal-Wallis test to compare the QTc intervals after exposure to different SSRI agents. Pearson's correlation (*r*) was used to assess the relationships between the QTc interval and various clinical and laboratory variables. For all of the analyses, *P* values were 2-sided and used a type I error rate of .05 as the cutoff for statistical significance. All of the statistical analyses were performed by using a standard statistical package (SPSS 15.0 [SPSS Inc, Chicago, IL]).

## RESULTS

We identified 52 newborns exposed to SSRI antidepressants in the immediate antepartum period and 52 unexposed newborns matched on gestational age. Their clinical and ECG data are shown in Table 1. Thirty-one newborns in the exposed group were boys compared with 29 in the control group ($P = .84$). Paroxetine was the most commonly used antidepressant ($n = 25$), followed by citalopram ($n = 13$), fluoxetine ($n = 12$), fluvoxamine ($n = 1$), and venlafaxine ($n = 1$). The time from delivery to first ECG ranged from 3 to 96 hours postpartum. ECGs were performed on days 1, 2, 3, and 4 in 22%, 18%, 10%, and 2% in the SSRI group, respectively, and in 8%, 12%, 20%, and 12% in the control group, respectively. We found no association between the age at which the ECG was performed (in hours) and the QTc interval within the entire study group, the SSRI-exposed group, or the control group.

The mean QTc interval was significantly longer among neonates exposed to SSRI antidepressants as compared with unexposed neonates (409 ± 42 vs 392 ±

TABLE 1 **Clinical and ECG Data of SSRI-Exposed and Unexposed Neonates**

| Variable | SSRI-Exposed Group ($n = 52$) | | Comparison Group ($n = 52$) | | $P$[a] |
|---|---|---|---|---|---|
| | Mean ± SD | Range | Mean ± SD | Range | |
| Boys, *n* | 29 | NA | 31 | NA | .84 |
| Gestational age, wk | 39 ± 1 | 35–42 | 39 ± 1 | 35–42 | .86 |
| Birth weight, g | 3135 ± 431 | 2215–4075 | 3365 ± 561 | 2340–4970 | .04 |
| Heart rate, bpm | 129 ± 18 | 95–162 | 138 ± 22 | 105–194 | .01 |
| PR interval, ms | 98 ± 16 | 70–140 | 100 ± 19 | 60–140 | .31 |
| QRS duration, ms | 51 ± 9 | 40–70 | 52 ± 11 | 40–80 | .28 |
| QT interval, ms | 280 ± 31 | 200–360 | 261 ± 25 | 210–320 | <.001 |
| QTc interval, ms | 409 ± 42 | 320–543 | 392 ± 29 | 332–460 | .02 |
| JT interval, ms | 229 ± 30 | 160–310 | 209 ± 24 | 170–260 | <.001 |

NA indicates not applicable; bpm, beats per minute.

[a] Data are from Student's *t* test except gender distribution, for which Fisher's exact test was used.

29 milliseconds; $P = .02$). The mean uncorrected QT interval was 7.5% longer (280 ± 31 vs 261 ± 25 milliseconds; $P < .001$), and the mean JT interval was 10% longer (229 ± 30 vs 209 ± 24 milliseconds; $P < .001$) among newborns exposed to SSRI antidepressants. We found similar mean QTc intervals among the most commonly used SSRI antidepressants, including paroxetine (406 ± 44 milliseconds), fluoxetine (420 ± 50 milliseconds), and citalopram (408 ± 23 milliseconds; $P = .59$), suggesting a "drug-class" effect. We found consistent results after replicating the analysis using the Fridericia formula to further adjust the QT interval for the heart rate (data not shown).

Five neonates (10%) born to SSRI antidepressant-treated mothers had a pathologically prolonged QTc interval (range: 462–543 milliseconds) as compared with none in the control group ($P = .057$; Table 2). Three of the infants with prolonged QTc were exposed to paroxetine and the other 2 to fluoxetine. Follow-up ECG showed normalization of the QTc intervals to ≤390 milliseconds within 48 hours in 3 of these infants, whereas the other 2 neonates had normal QTc intervals (390 and 412 milliseconds) on follow-up testing after hospital discharge. These 2 prolonged intervals were identified only during the chart review for this study. Families were contacted immediately; the children were ~1 year old and were reported to be completely healthy. Repeat ECGs were performed by their pediatricians, and tracings were blindly interpreted by the pediatric cardiologist for the study (Dr Fogelman).

We found consistent results when we repeated the analysis using a value of 440 milliseconds as the threshold for QTc prolongation.[28,33] Using this cutoff, 6 (12%) newborns in the antidepressant-exposed group had prolonged QTc as compared with 1 (2%) among the control subjects.

We found no association between QTc interval and birth weight ($r = -0.13$, $P = .2$ for all cohorts; $r = -0.06$, $P = .6$ for SSRI group; $r = -0.13$, $P = .4$ for control group), which was lower in exposed newborns and serves as a surrogate marker of long-term use of antidepressants by their mothers.[12] Among the antidepressant-exposed group, no infant had abnormalities in serum sodium, potassium, calcium, or magnesium, and

TABLE 2 **Clinical and Laboratory Data of SSRI Antidepressant-Exposed Neonates With a Prolonged QTc Interval**

| Variable | Infant 1 | Infant 2 | Infant 3 | Infant 4 | Infant 5 |
|---|---|---|---|---|---|
| Gender | Female | Female | Female | Male | Male |
| Gestational age, wk | 36 | 40 | 39 | 39 | 38 |
| Birth weight, g | 3020 | 2975 | 2650 | 3440 | 3058 |
| Drug name (dosage, mg/d) | Paroxetine (20) | Fluoxetine (30) | Paroxetine (20) | Paroxetine (20) | Fluoxetine (60) |
| Age at ECG recording, h | 22 | 30 | 3 | 72 | 29 |
| Plasma glucose, mmol/L | 3.3 | 3.5 | 4.1 | 2.5 | 2.5 |
| Plasma $Na^+$, mmol/L | 140 | 141 | 137 | 143 | 142 |
| Plasma $K^+$, mmol/L | 4.7 | 5.7 | 4.6 | 5.2 | 5.4 |
| Plasma $Ca^{2+}$, mmol/L | 2.4 | 2.4 | 2.6 | 2.2 | 2.3 |
| Heart rate, bpm | 118 | 136 | 146 | 140 | 133 |
| PR interval, ms | 90 | 90 | 90 | 90 | 80 |
| QRS duration, ms | 50 | 50 | 60 | 50 | 40 |
| QT interval, ms | 360 | 360 | 320 | 320 | 310 |
| QTc interval, ms | 504 | 543 | 500 | 488 | 462 |
| Repeat QTc interval, ms | 407 | 377 | 404 | 390 | 412 |
| Timing of normal QTc interval | 2 d | 1 d | 2 d | 1 y[a] | 1 y[a] |
| Degree of prolongation, % | 24 | 44 | 24 | 25 | 12 |

bpm, beats per minute.

[a] See text.

we found no correlation between QTc interval and any of these values. Finally, we found no significant differences in gender distribution, Apgar scores, QRS duration, or PR interval duration between the 2 groups.

## DISCUSSION

In the present study, we found that exposure to SSRI antidepressants in the immediate antepartum period was associated with prolongation of the QTc interval in neonates. Ten percent of exposed neonates displayed clinically significant QTc prolongation, which, in some instances, was dramatic. Similarly, QT and JT intervals were also significantly longer among SSRI antidepressant-exposed neonates, reflecting delayed cardiac repolarization. In adults, prolongation of the QTc interval by >30% of baseline predisposes to torsades de pointes.[15] The 5 abnormal QTc intervals identified in the antidepressant-exposed newborns were prolonged by 12%- to 44% compared with their subsequent (baseline) ECG tracings. Whether there is also an increased risk for clinical events and dysrhythmias remains to be examined in larger studies.

Several observations in the present study support a causal relationship between antenatal exposure to SSRI antidepressants and neonatal QTc prolongation. First, SSRI medications and their active metabolites cross the placenta to the fetus and appear in the amniotic fluid, allowing for possible absorption through fetal gastrointestinal and respiratory tracts.[34–36] Second, reversible QT prolongation has been described previously in adults and children receiving SSRI antidepressants, particularly after large doses. Third, the high incidence of long QTc observed among neonates exposed to antidepressants (10%) far exceeds that anticipated by chance, because only 1% of healthy newborns have QTc intervals >460 milliseconds.[28] Finally, repolarization abnormalities in 3 exposed newborns were shown to normalize shortly after delivery, coincident with the cessation of drug exposure. This reversibility supports a causal relationship between antenatal drug exposure and QTc prolongation in neonates and also suggests that congenital "long QT syndrome" (which affects ~1 in 10 000 individuals,[37] a 1000-fold lower figure compared with our study incidence) is not a competing explanation for our findings. Additional QT-prolonging drugs, such as amiodarone and methadone, have also been reported to cause neonatal QT prolongation in the same mechanism after maternal use during pregnancy.[38,39]

It should be noted that we identified no alternative explanation for the reversible QTc prolongation. The differential diagnosis for QTc prolongation in a neonate includes familial long QT syndrome, hypoxia, brain injury and hemorrhage, medications, endocrine causes, and electrolyte disturbances.[32,40] All of the infants in this study were healthy, born to healthy mothers, with no family history suggestive of long QT syndrome, no evidence of hypoxia, and with normal electrolyte levels. Neonates born to mothers with other known drug and nondrug causes of QT prolongation were a priori excluded from enrollment to further minimize any other potential confounding mechanism of repolarization abnormalities.

Although SSRI-induced QT prolongation in adults is relatively uncommon, a large proportion of neonates in our study had abnormally prolonged QTc intervals. It should be noted that this drug effect has probably occurred in utero as well and was only identified after birth. Prenatal magnetocardiograms could be used to identify such intrauterine QT changes in future studies.[41] Although the mechanisms for enhanced effects of SSRIs on the newborn's heart are not yet fully elucidated, several compelling explanations exist. These involve ontogeny of the CYP2D6 (the main metabolic pathway of SSRIs) and CYP2C9 (involved in the metabolism of fluoxetine), as well as altered protein binding and CYP2D6 polymorphism.

Limited CYP2D6 protein amount and activity at 30% have been documented in the fetal liver.[42] In the first month of life, CYP2D6 activity increases to reach approximately two thirds of adult values between 1 month and 5 years of age. On an individual basis, altered pharmacodynamic impact because of CYP2D6 polymorphism may also play an important role in reduced SSRI clearance.[43] CYP2C9 catalytic activity expression is at 1% to 2% of mature values during the first trimester and progressively increases during pregnancy to reach ~30% of mature values at birth.[44] Lower CYP2D6 and CYP2C9 activities in neonates can result in higher circulating SSRI levels at this age, thereby partially explaining the increased rate of QTc prolongation observed in this study.

Another mechanism that contributes to enhanced systemic exposure in newborns is their lower serum levels of binding proteins and, as a result, higher free drug levels compared with adults.[45] For example, fluoxetine is highly bound (94%–95%) to serum $\alpha$-1-acid glycoprotein,[46] which is present at lower levels in neonates. A third mechanism for the high rate of QTc prolongation is that the neonatal heart might be more sensitive than that of adults to drugs that interfere with the delayed rectifier current.[47]

## CONCLUSIONS

We identified a very high incidence of QTc interval prolongation among newborns whose mothers were treated with SSRI antidepressants immediately before delivery. Although these infants were free of serious adverse effects, additional research is necessary to determine whether antenatal use of SSRIs is associated with malignant arrhythmias in the first days of life. In the interim, clinicians should be aware of this phenomenon, given the widespread use of these drugs during pregnancy. We do not believe that there is currently sufficient data to restrict SSRI use during pregnancy and merely suggest that screening ECGs be considered in newborns exposed to SSRI antidepressants. In instances when the QTc interval is markedly prolonged, continuous cardiac monitoring may be advisable until the abnormality resolves.

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