**JOURNAL CLUB**

Prenatal Effects of Selective Serotonin Reuptake Inhibitor Antidepressants, Serotonin Transporter Promoter Genotype (*SLC6A4*), and Maternal Mood on Child Behavior at 3 Years of Age

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**Objectives:** To investigate whether prenatal selective serotonin reuptake inhibitor (SSRI) antidepressant exposure affects behavior in 3-year-olds of antenatally anxious or depressed mothers and whether risk was moderated by the serotonin transporter promoter (*SLC6A4*) genotype.

**Design:** Prospective longitudinal cohort design.

**Setting:** Vancouver.

**Participants:** Mothers and their 3-year-old children (n=33 SSRI exposed and n=42 nonexposed).

**Main Exposures:** Prenatal exposure to SSRI antidepressants and prenatal and postnatal maternal mood disturbances.

**Main Outcome Measures:** Parent report of child behavior (Child Behavior Checklist, ages 1.5-5 years) and the child *SLC6A4* genotype. The covariates used were maternal mood during the third trimester, 3 months post partum, and at the 3-year follow-up study and the child’s 5-minute Apgar score.

**Results:** Prenatal exposure to both maternal depressed mood and SSRI antidepressants were associated with increased internalizing behaviors during early childhood, whereas current maternal mood increased risk for externalizing behaviors. Increased child anxiety and depression symptoms were predicted by higher third-trimester maternal anxiety only in children with 2 short S alleles. In contrast, increased aggression and externalizing behaviors were predicted by third-trimester maternal anxiety only in children with 2 copies of the L allele.

**Conclusions:** Exposure to prenatal SSRIs and maternal mood had distinct effects on child behavior at 3 years of age, reflected in an increased level of internalizing behaviors. The impact of antenatal maternal anxiety on child mood was moderated by the child *SLC6A4* genotype. Despite SSRI treatment for prenatal maternal mood disturbances, childhood behavior at 3 years of age remained at risk.


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EXPOSURE TO MATERNAL MOOD disturbances during pregnancy may be one of life’s first adverse experiences that potentially sets a course of increased risk of childhood behavioral disturbances.1-4 In animal models, gestational stress is associated with behavioral disturbances and altered stress regulation in offspring.5-7 Similarly, in clinical studies,6,8 antenatal maternal mood disturbances set up developmental trajectories that affected cognitive, behavioral, and emotional outcomes throughout childhood, even when controlling for obstetric risk, psychosocial disadvantage, and postnatal maternal mood. Antenatal anxiety doubles the risk of hyperactivity and conduct and emotional problems during early childhood9 and school age.10 Together, such early adverse experience has a “fetal programming” effect on the developing brain.11 The magnitude of the effect is clinically significant, with approximately 15% of emotional behavioral problems in childhood attributable to antenatal anxiety.3

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Antenatal mood disorders are increasingly being managed with selective serotonin reuptake inhibitor (SSRI) antidepressants, which are prescribed with an
expectation that pharmacotherapy for maternal mood disturbances will “buffer” the developing child from the effects of maternal mental illness. Alternatively, because these medications alter central serotonergic (serotonin) tone during early brain growth, they may also contribute to developmental risk. Primarily, SSRIs act by blocking the serotonin transporter (5-HTT), consequently increasing extracellular serotonin levels. Because SSRIs readily cross the placenta and the blood-brain barrier, maternal SSRI treatment alters central serotonin signaling of the fetus. Undertreated antenatal maternal mood disturbances also alter neonatal serotonin levels, leaving critical questions unanswered about how the effects of prenatal SSRI exposure differ from the impact of the underlying maternal disorder.

Long before serotonin acts as a neurotransmitter, it has critical roles as a trophic factor directing neuronal growth. It is conceivable that altered serotonin levels during development affect subsequent serotonergic function and vulnerability to affective disorders. Genetically modified mice lacking the serotonin transporter (SERT), analogous to an SSRI-induced increase in intrasynaptic serotonin, are at increased risk for depressed and anxious behaviors in adulthood, suggesting links between early disrupted serotonin and subsequent behavioral disturbances. SERT, one of the key regulators of serotonin neurotransmission, is the membrane-bound 5-HTT protein that governs the reuptake of serotonin from the synaptic cleft, returning it to the presynaptic neuron. Altered 5-HTT and reduced serotonin levels have been associated with depression, and the function of this protein is closely tied to polymorphisms in the serotonin transporter gene (SLC6A4) promoter region (SLC6A4 OMIM 12182138; 5-HTT). Differences in transporter-dependent reuptake efficiency are related to 44–base pair (bp) insertion/deletion polymorphisms in a region of repetitive sequence in the proximal 5′ regulatory region in the promoter region of the SLC6A4 gene, leading to differential transporter gene expression and clinical differences in SSRI efficacy.

The short (S) variant is associated with reduced transcription of SLC6A4 and approximately 50% reduction in serotonin reuptake compared with the long (L) variant. The Il genotype is associated with increased SSRI efficacy compared with the ss genotype, although effects have been inconsistent. Individuals with 2 copies of the short allele of the serotonin transporter promoter, a condition associated with reduced SERT expression, have increased vulnerability to depression and other mood disorders after stressful events in early life. In SSRI-exposed neonates, risk of neonatal neurobehavioral disturbances may be moderated by reduced serotonin transporter (SHTT or SERT) expression (SLC6A4 genotype); however, this single polymorphism does not seem to account for all outcomes.

Beyond the newborn period, little is known about the impact of prenatal SSRI exposure on child development. For the most part, childhood behaviors seem to be best predicted by current levels of maternal mood and not by prenatal SSRI exposure; however, findings have been limited by the difficulty in accounting for prenatal and postnatal maternal mental health. Increased externalizing symptoms were observed in SSRI-exposed 4-year-olds with increased cord SSRI drug levels and a history of neonatal withdrawal, suggesting possible sustained links between fetal SSRI exposure and childhood neurobehavior. Altered serotonin levels during early periods of brain development, possibly via prenatal SSRI exposure or genetic variations that modify serotonin transport, may change serotonin-related neurobehavioral development.

This study was undertaken to examine associations between prenatal SSRI exposure and behavioral outcomes in early childhood controlling for prenatal and postnatal maternal mood. A secondary objective sought to examine whether such risk was moderated by the child SLC6A4 genotype, reflecting genetic variations in the capacity to control the severity of serotonergic tone. We expected that prenatal SSRI exposure, especially combined with 2 copies of the short S allele (thereby reducing SLC6A4 transcription and transporter activity), would increase the risk of behavioral disturbances in early childhood.

METHODS

PARTICIPANTS

With approval from the University of British Columbia Research Ethics Board and the Children’s and Women’s Health Centre of British Columbia Research Review Committee, and after receiving informed parent consent, we prospectively recruited a convenience sample of 98 mothers late in their second trimester (mean [SD], 24.2 [5.1] weeks) as part of a longitudinal study of the effects of antenatal SSRI exposure. Mothers were physician- and self-referred from the Reproductive Mental Health Clinic at British Columbia Women’s Hospital & Health Centre, a tertiary care referral service, community midwife clinics, and family physician practices in the greater Vancouver metropolitan area. All SSRI-treated mothers started taking medication based on clinical need, had a diagnosis of a mood disorder, and were already taking antidepressant medications at the time of conception. The criteria for recruitment were the presence or absence of SSRI antidepressant treatment rather than a threshold for mood symptoms. Women in the non-SSRI group were recruited from family or midwifery practices and had a range of mood symptoms (mean [SD] Hamilton Rating Scale for Depression [HAM-D] score, 5.6 [6.8]) at the time of recruitment. Cord and third-trimester maternal blood samples were obtained for DNA analysis. Of the original 98 pregnant mothers recruited, 4 withdrew before the baby was born, leaving 94 newborns in the longitudinal study. Four more children then withdrew from the study before the end of the first year of life, and an additional 15 children were unavailable for the 3-year study (11 families moved and could not be contacted, and 4 mothers refused consent to participate). At the 3-year follow-up visit, 75 children returned (33 children of depressed mothers treated with an SSRI during pregnancy and 42 children of non-SSRI–treated mothers). Mothers had been treated with 1 of 5 SSRIs, which included SSRIs and serotonin norepinephrine reuptake inhibitors. (For simplicity, the SSRI nomenclature is used). None of the mothers had taken other serotonergic medications or any other psychotropic or antidepressant medications during pregnancy.

SLC6A4 GENTYPING

Genomic DNA was extracted from whole venous blood using the Flexigene DNA Blood Kit (Qiagen, Valencia, California). The L and S alleles of SLC6A4 were identified as previously described. Polymerase chain reaction was performed with oligonucleotide primers flanking the polymorphism (correspond-
CHILD EMOTIONAL WELL-BEING AND BEHAVIOR

The Child Behavior Checklist (ages 1.5-5 years) (CBCL) was completed by the mother. This widely used and well-validated scale provides standardized ratings of behavior in children aged 1.5 to 5 years. The CBCL yields a total problem score, externalizing and internalizing scores, and subscale scores (emotionally reactive, depressed/anxious, withdrawn, somatic complaints, sleep problems, attention, and aggression). Scale scores were used in analyses. The CBCL also yields T scores, with the mean (SD) set at 50 (10). T scores were reported because of their widespread clinical application, and they were used only for descriptive purposes. Raw untransformed scores were used in the primary analyses.

MATEERNAL MOOD

Maternal mood was assessed during the third trimester of pregnancy, a mean of 33.7 weeks’ gestation, and again 3 months post partum using 4 instruments. During the pregnancy and 3 months post partum, the HAMD, a 21-item clinician-rated measure of anxiety with a score ranging from 0 to 63, and the Hamilton Rating Scale for Anxiety (HAMA), a 14-item clinician-rated measure of anxiety with a score ranging from 0 to 56 (minimal to severe levels), were used. At the time of the 3-year follow-up study, maternal mood was assessed using the Beck Depression Inventory, a 21-question multiple-choice self-report inventory for measuring depression with scores ranging from 0 to 63, and the Beck Anxiety Inventory, a 21-question multiple-choice self-report inventory used for measuring severity of anxiety during the last week with scores also ranging from 0 to 63. Total scores were used in the analyses.

STATISTICAL ANALYSIS

Analyses were undertaken in 2 stages. In the first stage, analyses of covariance were used to examine group (SSRI-exposed vs nonexposed) differences in child behavior using measures of prenatal (third-trimester) and postnatal (3-month and 3-year) maternal mood and neonatal risk (5-minute Apgar score) as covariates. Measures of maternal anxious and depressed mood were used in separate models. Because maternal mood measures varied between groups and during the antenatal and postpartum periods, they were used as continuous covariate measures. In the second stage, similar analytical models (analyses of covariance) were used to examine interactions between exposure group and SLC6A4 genotype (ss, sl, and ll), testing the role of genotype as a possible moderator of the effects of prenatal exposure on behavior. In this stage, measures of prenatal (third-trimester) and postnatal (3-month and 3-year) maternal mood and neonatal risk (5-minute Apgar score) were used as covariates. We calculated effect sizes (η²) to examine the strength of these associations because the statistical significance of the findings would be affected by sample size and potentially by multiple comparisons.

MATERLAL AND CHILD CHARACTERISTICS

Except for mood symptoms, educational level, and antidepressant medication use, maternal characteristics did not vary significantly between groups (P > .05) (Table 1 and Table 2). The SSRI-treated mothers had approximately 2.5 fewer years of higher education (F = 9.1; P = .03, η² = 0.09). Levels of maternal depression and anxiety symptoms during pregnancy and at 3 months post partum were 2 to 3 times higher in the SSRI-treated group than in the non-SSRI group (P < .001 for all), and they remained so 3 to 4 years post partum (P < .05 for all). All of the mothers took a prenatal vitamin containing the prenatal folic acid dose (0.8-1.0 mg). At the time of the 3-year study, most mothers in the prenatal SSRI-treated group were still taking medication, and 4 of the nonprenataelly treated mothers had begun to take an SSRI (Table 2). Mothers in both groups were equally concerned about their child’s development, and none of the children were taking psychotropic medications at the time of the study. No interactions between time and group for any measure were observed (P > .05 for all) (Table 3). At 3 years, 78% of SSRI-exposed and 79% of nonexposed children who had been studied as neonates returned for this follow-up study. Child characteristics did not differ significantly between those who were studied at 3 years and those who were not studied (P > .05) (Table 4).

MATERNAL AND CHILD CHARACTERISTICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>SSRI Exposed</th>
<th>Non SSRI Exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age at birth, mean (SD), y</td>
<td>31.9 (4.6)</td>
<td>33.3 (5.1)</td>
</tr>
<tr>
<td>Maternal education, mean (SD), y</td>
<td>15.3 (2.4)</td>
<td>18.0 (3.2)</td>
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<td>Cigarettes/smoking, yes/no, No.</td>
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<td>0</td>
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<tr>
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<tr>
<td>0</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>1-10</td>
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<td>42</td>
</tr>
<tr>
<td>&gt;10</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Cesarean delivery, %</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>Maternal SLC6A4 genotype, No.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ll</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>ls</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>ss</td>
<td>8</td>
<td>7</td>
</tr>
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<td>SSRI third-trimester dose, median (range), mg</td>
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<tr>
<td>Paroxetine (n=15)</td>
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<td>Sertraline (n=5)</td>
<td>50 (25-175)</td>
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</tr>
<tr>
<td>Venlafaxine (n=3)</td>
<td>75 (38-150)</td>
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</tr>
<tr>
<td>Citalopram (n=6)</td>
<td>25 (20-40)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; SSRI, selective serotonin reuptake inhibitor. 

a P < .05.

bDNA samples from 2 SSRI-exposed and 1 nonexposed mother were unavailable for genotyping.
SLC6A4 genotype ratios were distributed according to Hardy-Weinberg equilibrium for all 140 participants (68 children and 72 mothers: 7 child and 3 maternal samples were of poor quality and were not analyzed) together (allele frequency—children: L = 57.3% and S = 42.7%; maternal: L = 56.3% and S = 43.8%; and genotype frequency—child: I1 = 32.4%, I2 = 50.0%, and s2 = 17.6%; maternal: I1 = 33.3%, I2 = 45.8%, and s2 = 20.8%) and for mothers and infants separately (Tables 1 and 3). The allele frequency and genotype distribution was different between SSRI-exposed and nonexposed mothers. Mean daily dose and length of prenatal SSRI exposure did not vary significantly between genotypes (P > .05).

MODEL 1: CHILD BEHAVIORAL OUTCOMES

Internalizing Behaviors

Higher internalizing scores were associated with prenatal SSRI exposure and increased levels of maternal anxiety at the time of the 3-year study (F = 3.978, P = .05, η2 = 0.06 and F = 4.517, P = .04, η2 = 0.07, respectively), controlling for third-trimester anxiety (HAMA) scores, 5-minute Apgar scores, and 3-month postpartum HAMA scores (Table 5). When controlling for prenatal and postnatal maternal depressed mood (HAMD) and 5-minute Apgar scores in a separate model, higher levels of internalizing symptoms were predicted by higher levels of maternal depression symptoms 3 years post partum (F = 5.816, P = .02, η2 = 0.08) but not by prenatal SSRI exposure (F = 3.396, P = .07, η2 = 0.05).

Externalizing Behaviors

Increased levels of externalizing behaviors were also associated with 3-year postpartum levels of maternal anxiety (Beck Anxiety Inventory) and depression symptoms (Beck Depression Inventory) using prenatal and postnatal HAMA and HAMD measures (in separate models) and 5-minute Apgar scores as covariates (F = 4.562, P = .04, η2 = 0.07 and F = 6.75, P = .01, η2 = 0.11 for Beck Anxiety Inventory/HAMA and Beck Depression Inventory/HAMD, respectively). Neither prenatal SSRI exposure nor maternal years of education contributed to externalizing symptoms in either model (P > .25) (Table 5).

CBL Subscale Scores

Of the internalizing behavior subscales, prenatal SSRI exposure predicted increased levels of somatic complaints (F = 8.7, P < .01, η2 = 0.12) and sleep disturbances (F = 4.8, P = .03, η2 = 0.07). Increased maternal anxiety at the time of the 3-year study predicted child somatic (F = 7.918, P < .01, η2 = 0.11) and emotionally reactive (F = 5.8, P = .02, η2 = 0.08) symptoms. Similarly, in separate models, increased levels of maternal depressed mood at 3 years predicted increased emotionally reactive symptoms (F = 5.7, P = .02, η2 = 0.08), whereas withdrawal behaviors were not associated with prenatal SSRI exposure or maternal mood (P > .05). Externalizing subscale scores (aggression and attention)
were not associated with prenatal SSRI exposure or measures of maternal mood ($P > .05$).

**MODEL 2: EFFECT OF THE CHILD SLC6A4 GENOTYPE**

When the child SLC6A4 genotype was added to the model, significant interactions with maternal third-trimester measures of mood emerged. Increased externalizing symptoms at 3 years were predicated by an interaction between third-trimester maternal anxiety and the child SLC6A4 genotype ($F = 3.954$, $P = .03$, $\eta^2 = 0.13$). In particular, higher externalizing symptoms ($F = 5.945$, $P = .03$, $\eta^2 = 0.30$) and increased aggressiveness ($F = 4.97$, $P = .04$, $\eta^2 = 0.26$) were predicted by higher third-trimester maternal anxiety only in children with 2 long alleles (ll) (Figure 1).

Increased child anxiety and depression symptoms were predicted (in separate models) by the interaction between both third-trimester maternal anxiety and depression symptoms and the child SLC6A4 genotype ($F = 6.055$, $P < .01$, $\eta^2 = 0.19$ and $F = 6.328$, $P < .01$, $\eta^2 = 0.20$, respectively). Specifically, increased child anxiety and depression symptoms were predicted by higher third-trimester maternal anxiety and depression symptom scores only in children with 2 short alleles (ss) ($F = 7.128$, $P = .04$, $\eta^2 = 0.54$) (Figure 2). No interactions were noted between child genotype and SSRI exposure in either model.

Child behavior and prenatal maternal anxiety were not associated in children with 1 long and 1 short allele ($F = 0.048$, $P = .83$, $\eta^2 = 0.002$ for anxious/depressed behavior; $F = 0.324$, $P = .57$, $\eta^2 = 0.011$ for aggressive behavior). Neither child sex nor maternal SLC6A4 genotype affected behavioral symptoms.

**COMMENT**

Prenatal SSRI exposure and higher current maternal anxiety contributed to increased internalizing behaviors in 3-year-old children. Increased levels of externalizing behaviors were also observed, but they were associated with current levels of 3-year postpartum maternal mood. Beyond the effects of prenatal exposure to SSRIs and maternal mood, the child SLC6A4 genotype moderated the impact of exposure to third-trimester maternal mood. The SSRIs are often used to manage antenatal mood disturbances with the expectation that they optimize maternal mood. However, the results of this study suggest that the impact of SSRI exposure on child behavior may be influenced by the child’s SLC6A4 genotype.
ternal mental health, thereby reducing child behavioral risk. However, child behavioral disturbances were still observed at 3 years even after prenatal and postpartum SSRI treatment, suggesting that such maternal antidepressant therapy did not buffer the children from the ongoing effects of maternal mood disturbances. Although maternal education differed between exposure groups, this did not contribute to child behavioral outcomes.

Children with poor or inefficient transcription of \( SLC6A4 \) (ss genotype), resulting in reduced levels of serotonin transporter protein and potentially reduced serotonin reuptake, coupled with third-trimester exposure to maternal anxiety, were seen as more anxious or depressed by their mothers, even controlling for perinatal SSRI exposure, perinatal risk, and postnatal (3-month) and 3-year postpartum maternal mood. This may reflect an effect related to increased intrasynaptic prenatal serotonin exposure and receptor sensitivity at critical periods of development, consistent with an extreme manipulation in central serotonin using a \( SLC6A4 \) knockout animal model. A child with 2 short alleles may have received a higher “effective” prenatal “serotonin dose” during fetal brain development, secondary to reduced serotonin transporter, thereby increasing risk of anxiety or depression symptoms during early childhood. In contrast, increased externalizing and aggressive behaviors were predicted by third-trimester maternal mood in children with 2 copies of the long allele, presumably reflecting the effect of relatively “increased” serotonin reuptake, leading to a “deficiency” in intrasynaptic serotonin, coupled with late gestational maternal anxious and depressed mood. This could be analogous to the low central serotonergic tone coupled with genetic and early rearing experiences (parental deprivation) that have been reported in nonhuman primates with impaired impulse control, aggression, and low social dominance. Similarly, early central serotonin alterations secondary to SSRI-related serotonin reuptake blockade could, via a variety of genetic and neurotransmitter-related mechanisms, lead to sustained developmental and behavioral consequences. Although the effects of prenatal SSRI exposure, which presumably also affected intrasynaptic serotonin levels in the developing brain, were not modified by \( SLC6A4 \) genotype, a direct prenatal effect of SSRIs on 5-HTT function as an influence on central serotonergic tone could not be ruled out, as has been reported in animal models.

Beyond infancy, few studies report a main effect of SSRIs. Most such studies report that irrespective of prenatal exposure, maternal mood predicts childhood behavior. In SSRI-exposed infants aged 6 to 40 months, poorer psychomotor development (Psychomotor Developmental Index and Bayley Scales of Infant Development) was observed, although the contribution of postnatal maternal mood was unclear. Early gestational fluoxetine exposure did not affect IQ, language, or behavioral outcomes in preschool-aged children compared with children with other antidepressant (tricyclic antidepressant) exposure, although development was affected by longer or more frequent episodes of postnatal maternal depression. At age 4 years, internalizing and externalizing behaviors were predicted by current levels of maternal mood in perinatally exposed children; however, externalizing behaviors and reduced task persistence and increased aggressiveness were associated with increased cord drug levels and a history of neonatal withdrawal symptoms, suggesting that early neurobehavioral and pharmacologic factors may predict subsequent behavioral vulnerability.

Several limitations need mentioning. Measures of child behavior in this study were limited to maternal reports, which raises a key concern that child behavioral ratings may have been subject to reporter bias. Anxious and depressed mothers may have been more likely to either overreport or underreport behavioral disturbances. However, if such a bias existed, as has been previously observed, this would not explain the moderating effect of the \( SLC6A4 \) genotype. This study examined associations between antenatal exposure to SSRIs and maternal mood disturbances and, in this sense, was unable to address causality or direction of effect. The study cohort was a convenience sample, and several key unmeasured maternal characteristics may have affected child outcomes, such as social and family factors inherent to mental illness during and after pregnancy. Because the mothers in the SSRI-treated group were already symptomatic and taking SSRIs at the time of conception, there may have been factors that affected fetal development long before the mothers were recruited into this study or even before they conceived. Ideally, the use of a randomized controlled study design may be regarded as an appropriate study design; however, given the evanescent nature of perinatal maternal mood disorders, a randomized study examining the effects of prenatal antidepressant exposure was not considered appropriate for ethical, logistic, and medical reasons. Although differences between children lost to follow-up from the original cohort and those studied were nonsignificant, missing data may have introduced another limitation to the generalizability of these findings. Because we had no previous behavioral data, we did not impute the missing data.

In summary, prenatal exposure to both maternal mood and SSRI antidepressants were associated with in-
creased internalizing behaviors during early childhood, whereas current maternal mood increased risk for externalizing behaviors. The impact of third trimester maternal anxiety on child mood was moderated by the child SLC6A4 genotype. In offspring with reduced 5-HTT expression (short alleles), antenatal maternal mood predicted increased vulnerability to anxiety at 3 years, whereas 2 long alleles predicted aggressive behaviors, suggesting fetal genotype-specific serotoninergic programming. Even with prenatal maternal SSRI treatment, mothers continue to be symptomatic, and child behavior at 3 years of age continues to be at risk.

Accepted for Publication: January 6, 2010.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Oberlander and Grunau. Acquisition of data: Oberlander, Brain, and Misri. Analysis and interpretation of data: Oberlander, Papsdorf, Ross, and Grunau. Drafting of the manuscript: Oberlander and Papsdorf. Critical revision of the manuscript for important intellectual content: Oberlander, Papsdorf, Brain, Misri, Ross, and Grunau. Statistical analysis: Oberlander and Papsdorf. Obtained funding: Oberlander. Administrative, technical, and material support: Oberlander, Brain, Misri, and Ross. Study supervision: Oberlander.

Financial Disclosure: None reported.

Funding/Support: This research was funded by grant 12-FY01-30 from the March of Dimes Foundation and by grants MOP 54490 and 57837 from the Canadian Institutes of Health Research. Dr Oberlander is supported by a Human Early Learning Partnership Senior Career Award and is the R. Howard Webster Professorship in Child Development (University of British Columbia, Faculty of Graduate Studies).

Role of the Sponsors: The study sponsors had no role in the study design; in the data collection, analysis, or interpretation; in the writing of the paper; or in the decision to submit the paper for publication.

Online-Only Material: This article is featured in the Archives Journal Club. Go to http://archpediatrics.com to download teaching PowerPoint slides.

Additional Contributions: Mary Beckingham, Ari Sanders, BSc, and Wendy Frasca, BA, contributed to the organizing and facilitating of this research program. We are grateful to the mothers and their infants who participated and contributed to this work.

REFERENCES


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**Announcement**

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Pediatrics and Adolescent Medicine* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://clinicaltrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archpediatrics.com. ©2010 American Medical Association. All rights reserved.