FOLLOW-UP OF CHILDREN OF DEPRESSED MOTHERS EXPOSED OR NOT EXPOSED TO ANTIDEPRESSANT DRUGS DURING PREGNANCY

REGINA C. CASPER, MD, BARRY E. FLEISHER, MD, JULIE C. LEE-ANCAJAS, PHD, ALLYSON GILLES, BA, ERIKA GAYLOR, PHD, ANNE DEBATTISTA, MS, AND H. EUGENE HOYME, MD

Objective To compare the structural growth and developmental outcome of children born to mothers diagnosed with major depressive disorder during pregnancy who were exposed or not exposed to selective serotonin reuptake inhibitors (SSRIs) in utero.

Study design Children whose mothers were diagnosed with major depressive disorder in pregnancy and elected not to take medication (n = 13) were compared with children of depressed mothers treated with SSRIs (n = 31) on birth outcomes and postnatal neurodevelopmental functioning between ages 6 and 40 months. Children underwent blinded standardized pediatric and dysmorphology examinations and evaluations of their mental and psychomotor development with the use of the Bayley Scales of Infant Development (BSID II).

Results The Bayley mental developmental indexes were similar in both groups. Children exposed to SSRIs during pregnancy had lower APGAR scores and scored lower on the Bayley psychomotor development indexes and the motor quality factor of the Bayley Behavioral Rating Scale than unexposed children.

Conclusions The findings that SSRIs during fetal development might have subtle effects on motor development and motor control are consistent with the pharmacologic properties of the drugs. *(J Pediatr 2003;142:402-8)*.

Women are at the highest risk of having a major depressive disorder (MDD) during their childbearing years.[1] The treatment of a MDD during pregnancy presents unique challenges because it needs to minimize the risk to the fetus and to optimize the benefits for the mother.[2] Although psychotherapy is currently considered the safest approach to treat MDD in pregnancy,[3] women may not respond to psychotherapy or they might want to continue to take antidepressant drugs to avoid a worsening of their symptoms, even if the drugs' effects on fetal growth and development, in particular postnatal development, are incompletely known.

Nearly all drugs, including antidepressants and their metabolites, cross from the placenta into the fetus and can be identified in amniotic fluid, umbilical cord blood, or fetal serum.[4-6] Information about the reproductive safety of antidepressant drugs from birth outcome studies has shown no increase in the rate of major congenital malformations in newborn infants of mothers treated with antidepressant drugs during pregnancy.[7-11] Chambers et al,[12] however, have reported a higher frequency of minor structural anomalies in fluoxetine-exposed infants.

The possible long-term effects of in utero exposure to antidepressant drugs have been studied much less. Nulman et al[13] tested children between 1 and 7 years of age who had been exposed to tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressant drugs prenatally and found them not to be different from children of control mothers in their mental development or their verbal and language skills. Similarly, Mattson et al[14] reported no differences in the cognitive and neurobehavioral development of 4- to 6-year-

BDI	Beck Depression Inventory
BSID-II	Bayley Scales of Infant Development, Second Edition
BRS	Behavioral Rating Scale
MDD	Major depressive disorder
MDI	Mental Development Index
PDI	Psychomotor Development Index
SSRI	Selective serotonin reuptake inhibitor

From the Division of Medical Genetics, Department of Pediatrics; the Division of Neonatology and Developmental Medicine, Department of Pediatrics; and the Department of Psychiatry and Behavioral Sciences, Stanford University and Stanford University School of Medicine, Stanford, California.

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Reprint requests: Regina C. Casper, MD, Stanford University, Department of Psychiatry and Behavioral Sciences, 401 Quarry Rd, Room 2365, Stanford University School of Medicine, Department of Psychiatry and Behavioral Sciences, Stanford, CA 94305-5723. E-mail: rcasper@stanford.edu.

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old children of mothers treated with fluoxetine during pregnancy compared with children of control mothers.

Because the presence of a major depressive disorder and maternal depressive symptoms during pregnancy may affect pregnancy outcome and postnatal development,[15,16] this follow-up study was designed to include as a control group women diagnosed with MDD during pregnancy who remained medication-free and to compare the physical and mental development of their offspring with that of women diagnosed with MDD who used SSRI antidepressant drugs during pregnancy.

METHODS

Women who were in treatment in the Women's Wellness Clinic or with other clinicians and who met DSM-IV criteria[17] for Major Depressive Disorder during pregnancy were invited to participate in the follow-up study. They were recruited before or during pregnancy (71%) or after delivery (29%). The study was approved by the Panel on Human Subjects in Medical Research at Stanford University. All women signed consent forms that contained a description of the content and purpose of the study, with one form for themselves and one for the participating child. Thirteen women remained medication-free throughout their pregnancy and opted for psychotherapy only. Thirty-one women were taking SSRIs at referral or started SSRI antidepressant drugs during pregnancy.

Medication Use During Pregnancy

Of the 31 women who took SSRIs, 48% took sertraline; 23% took fluoxetine; 26% took paroxetine, and 3.2% took fluvoxamine (50 mg/d). The average daily doses of sertraline, fluoxetine, and paroxetine were 113.2 ± 72.3 mg, 20 ± 11.9 mg, and 17.2 ± 10.1 mg, respectively; 45% of the women took SSRIs throughout, 71% took SSRIs during the first trimester, and 74% took SSRIs during the third trimester. All women received supportive psychotherapy. For assessing alcohol consumption, one drink was defined as one glass of wine, one bottle of beer, or one mixed drink per day. Fewer than 9 drinks during pregnancy were not considered alcohol use.

All women were interviewed in person, with the Structured Clinical Interview for DSM-IV Axis I Disorders[18] used to confirm the diagnosis of a major depressive disorder. Women were asked to complete a Likert Scale (ranging from 1 [not depressed] to 10 [severely depressed]), summarizing their level of depression for each trimester of the pregnancy. We also asked women to complete the Beck Depression Inventory (BDI)[19] at a time during their pregnancy when they had significant depressive symptoms and selected each woman's highest BDI rating.

Each woman completed a questionnaire that contained sociodemographic information; medical, family, and psychiatric history; information about the index pregnancy; information about any drug exposure; the dose and timing of antidepressant drugs; and the use of vitamins, caffeine, alcohol, and nicotine, including dose and timing. Information regarding delivery and neonatal course were collected from obstetric and neonatal medical records.

Follow-up evaluation. Children ranged in age from 6 months to 40 months. All children underwent neurologic and dysmorphology examinations performed by a pediatric neurologist with certification in a standardized evaluation method for neurologic functioning[20] and a dysmorphologist, respectively. Pediatricians and psychologists who conducted the follow-up evaluations had no knowledge of the mothers' medication status. A standardized 130-item checklist was used by the dysmorphologist to record minor anomalies. Frequency calculations were based on first-trimester exposure only. Prematurity was defined as delivery at <37 weeks' gestation. The child's level of mental and motor development was tested by a clinical child psychologist by using the Bayley Scales of Infant Development, Second Edition (BSID-II).[21] The BSID-II consists of three scales: the Mental Development Index (MDI), the Psychomotor Development Index (PDI), and the Behavioral Rating Scale (BRS). The Mental and Motor Scales assess the child's current level of cognitive, language, personal-social, and fine and gross motor development. The BRS assesses qualitative aspects of the child's behavior during the testing situation by using a rating scale completed by the psychologist. The two psychologist raters are reliability certified on the BSID-II annually as part of a National Institutes of Health–funded collaborative neonatal outcome study.

Data Analysis

Statistical analyses were performed with the SPSS system (SPSS, Inc, Chicago, Ill), version 10.0. Outcome characteristics were compared by use of χ^2 tests. All tests were 2-tailed, with an α level of .05. Pearson moment correlations were used to test associations between variables. Analyses of covariance were used for group comparisons if a variable showed significant between group differences. The Cohen *d* was calculated to determine effect sizes.

RESULTS

The proportion of prospectively/retrospectively recruited women was similar in both experimental groups (χ^2 = .59; *P* =.44). There were no differences between prospectively and retrospectively studied patients on any of the demographic or outcome variables.

Maternal Characteristics During Pregnancy and Delivery

All but three women were white (Table I). All received early and regular prenatal care. No between-group differences were found for age at delivery, marital status, years of schooling, parity, weight gain, and self-rated levels of depression.

Based on self-report, none of the women used illicit drugs during the pregnancy. No woman smoked. Three women in the medication-free group and 3 in the medicated group reported fewer than 9 drinks. Three medicated women reported totals of 24, 24, or 54 drinks while pregnant.

Breast-Feeding and Drug Exposure

Mothers nursed their infants for an average duration of 6.4 ± 5.9 months in the unmedicated group and for 8.5 ± 7.2

Table I. Maternal characteristics during pregnancy and delivery

Variables	Women not taking medication (n = 13)	Women taking medication (n = 31)		
	Frequency (%)		χ^2	*P* value
Married	11/13 (85)	28/31 (90)	6.06	.11
Miscarriages	7/13 (54)	9/31 (29)	2.44	.19
Alcohol use	0/13 (0)	3/31 (10)	1.35	.25
Tobacco use	0/13 (0)	0/31 (0)	—	—
Illicit drug use	0/13 (0)	0/31 (0)	—	—
Prenatal vitamins	13/13 (100)	26/31 (84)	2.37	.12
Vegetarian diet	0/13 (0)	3/30 (10)	1.39	.24
Illness or flu during pregnancy	4/13 (31)	10/31 (32)	0.01	.92
Exercise	7/13 (54)	25/31 (81)	3.32	.07
Cesarean delivery	4/13 (31)	8/31 (26)	0.11	.74
	Mean (SD)		*t*	*P* value
Age at delivery (y)	36.6 (3.5)	34.9 (3.8)	1.38	.17
Education (y)	17.0 (1.4)	16.8 (2.8)	0.33	.74
Parity	1.62 (.9)	1.65 (1.1)	0.09	.93
Hours in labor	7.34 (7.1)	10.1 (7.4)	1.14	.26
Weight gain during pregnancy (lb)	30.6 (11.6)	30.0 (14.8)	0.14	.89
Depression ratings (Likert scale):				
1–3 mos	4.2 (2.5)	5.0 (2.5)	1.06	.29
4–6 mos	5.4 (3.2)	5.0 (2.8)	0.39	.70
7–9 mos	6.1 (2.3)	4.8 (3.0)	1.41	.17
BDI maximum score	24.0 (8.2)	21.3 (7.9)	0.57	.58

months in the medicated group (t = 0.85; P = .4, Table II). Three previously unmedicated mothers took sertraline for postpartum depressive disorder and breast-fed for an average of 3.8 ± 3.8 months (average dose, 58.3 ± 38.2 mg). Among the medication-exposed mothers, 10 took sertraline (119.4 ± 75.8 mg; 11.9 ± 9.5 months), 4 took paroxetine (28.6 ± 14.3 mg; 7.8 ± 7.3 months), and 3 took fluoxetine (23.3 ± 15.3 mg; 3 ± 1.7 months).

Birth Outcome and Follow-up Evaluation

There were no stillbirths. No differences between the groups were observed for gestational age, premature births, birth weight and/or length (Table II). Drug-exposed children had lower APGAR scores at 1 and 5 minutes than unexposed children. There was a trend for more drug-exposed children to be admitted to neonatal intensive care units compared with their unexposed peers. All mothers of infants admitted to neonatal intensive care units had taken antidepressant drugs during the third trimester. Reasons for admission included respiratory distress in six newborn infants and meconium aspiration in four; one infant was admitted for a cardiac murmur.

Neurodevelopmental Examination at Follow-up

Weight, height, and fronto-occipital head circumference expressed as percentage were similar in both groups of children (Table II). The groups had similar sex distributions (χ^2 = 0.64; P = .43). Two children whose mothers took medication were noted to have slight hypotonia; one had slight gross motor delay and one had slightly increased tone at the hips. One child whose mother did not take medication exhibited intermittent toe walking.

Dysmorphology Examination

Regarding major structural anomalies, a bilateral lacrimal duct stenosis that required surgical correction occurred in a child whose mother had taken no antidepressant drugs during pregnancy and a small asymptomatic ventricular septal defect that had required no intervention at age 3 was observed in a medication-exposed child (χ^2 = 0.13; P = .72). Fifty-four percent of unexposed and 76% of exposed children had minor structural anomalies (χ^2 = 0.18; P =.17). Three or more minor structural anomalies were observed in 15% of unexposed and 29% of exposed children (χ^2 = 0.19; P = .37).

Table II. Physical characteristics of the infants of depressed mothers at birth and at follow-up examination

	Children not exposed to medication during pregnancy (n = 13)	Children exposed to medication during pregnancy (n = 31)		
At birth	**Frequency (%)**		χ^2 **or** *t*	***P* value**
Preterm	1/13 (8)	1/31 (3)	.39	.53
First born	5/13 (38)	15/31 (48)	4.02	.55
Admission to neonatal intensive care units	0/13 (0)	7/31 (23)	3.62	.06
Breast-feeding	11/13 (85)	28/31 (90)	.30	.59
SSRI medication while breast-feeding	3/13 (23)	17/31 (55)	3.73	.05
	Mean (SD)			
Gestational age (wk)	38.7 (1.5)	39.1 (1.1)	.88	.38
Birth weight (g)	3363 (498.5)	3394 (432.2)	.21	.84
Birth length (cm)	49.7 (7.2)	50.3 (2.5)	.29	.78
APGAR at 1 min	8.2 (1.2)	7.0 (1.9)	2.07	.05
APGAR at 5 min	9.0 (0)	8.4 (1.0)	3.20	.00
At follow-up:				
Age (mo)	17.7 (8.7)	12.9 (9.6)	1.57	.12
Weight (%)	46.7 (27.4)	48.4 (29.4)	.18	.86
Height (%)	49.7 (30.1)	41.9 (28.0)	.82	.42
Fronto-occipital circumference %	50.3 (28.1)	54.2 (25.9)	.45	.66

Mental and Psychomotor Developmental Outcomes

Mental and psychomotor developmental outcomes were assessed by the BSID II[22] and are set forth in Table III. There were no significant differences in MDI between unexposed and exposed children. Drug-exposed children, however, were rated significantly lower than unexposed children on the psychomotor index (PDI) and on the BRS. Examination of the BRS factor scales revealed specifically lower scores for behavioral motor quality in SSRI-exposed children. The differences were notable for tremulousness and for fine motor movements. After adjusting for APGAR scores at birth, at 5 minutes the between-group differences in the PDI and in motor quality were weaker, but they remained significant.

DISCUSSION

The current study found that children exposed to SSRI antidepressant drugs in utero did not differ on most birth outcome and follow-up measures from children of depressed mothers who elected not to take medication during pregnancy. Drug-exposed newborn infants were found to have lower APGAR scores. At follow-up examination, the mental development of drug-exposed children was similar to that of unexposed children. However, we found evidence that prenatal SSRI exposure may have subtle effects on motor development and motor control.

The healthy lifestyle of the women in our study (eg, use of prenatal vitamins, no smoking, little alcohol use, and regular exercise) makes this sample different from that of other published pregnancy outcome studies and might have contributed to the finding that antidepressant drugs did not increase the risk of prematurity or low birth weight.[22] Such overall good health in the mothers contrasts with studies that have found depressive symptoms to be associated with poor health behaviors, which by themselves adversely affect pregnancy outcome, such as increased life stress, poor weight gain, smoking, or alcohol use.[15] Indeed, other outcome studies have found an excess of smoking, alcohol use, or higher maternal ages among women using antidepressant drugs.[9,10,12,22] Some birth outcome studies[7,8,23] have not included data on maternal nicotine or alcohol use. Screening for alcohol use during pregnancy is indispensable in view of reports from the Centers for Disease Control and Prevention[24] that drinking among women of childbearing age has risen again in the 1990s and because moderate exposure to alcohol can be associated with fetal malformations.[25]

The finding that children of medicated mothers had lower APGAR scores at birth compared with children of medication-free mothers is consistent with a recent report by Simon et al,[22] who found lower APGAR scores after third-trimester exposure to antidepressant drugs. The trend toward increased frequency of admissions to neonatal intensive care

Table III. Neurodevelopmental test results of children exposed or not exposed to SSRI antidepressant medication in utero using the Bayley Scales of Infant Development (BSID-II)

	Children not exposed (n = 13)	Children exposed (n = 31)					
Bayley scales	**Mean (SD)**		***t***	***P* value**	***F****	***P* value**	***d*†**
MDI	94.3 (7.5)	91.0 (13.3)	0.83	.41	2.12	.15	0.27
PDI	98.2 (9.1)	90.0 (11.4)	2.30	.03	5.55	.02	0.76
BRS	89.5 (15.4)	76.0 (24.6)	2.18	.04	2.57	.12	0.72
BRS factor scales							
Attention arousal	94.0 (7.1)	76.6 (25.6)	0.92	.38	1.20	.31	0.30
Orientation/engagement	76.6 (30.1)	73.0 (27.2)	0.34	.74	0.02	.88	0.11
Emotional regulation	87.5 (25.3)	78.3 (27.6)	0.92	.37	0.07	.79	0.30
Motor quality	88.8 (20.2)	68.6 (29.0)	2.62	.01	4.02	.05	0.87
Motor quality factor items							
Gross motor movement	4.77 (.44)	4.43 (.68)	1.93	.06	2.01	.17	0.64
Fine motor movement	5.00 (0)	4.71 (.46)	2.83	.01	2.22	.15	0.94
Control of movement	4.77 (.44)	4.60 (.56)	0.96	.34	0.55	.46	0.32
Tremulousness	5.00 (0)	4.87 (.34)	1.82	.08	3.37	.08	0.60
Slow and delayed movement	4.92 (.28)	4.83 (.38)	0.77	.45	0.06	.81	0.25
Frenetic movement	5.00 (0)	4.87 (.43)	1.68	.10	2.14	.15	0.56
Hypertonicity	5.00 (0)	4.97 (.18)	0.65	.52	0.74	.40	0.22
Hypotonicity	4.92 (.28)	4.90 (.31)	0.23	.82	0.05	.83	0.08

*Analysis of covariance, corrected for APGAR scores at 5 minutes.
†Cohen *d* = effect size.

units in exposed newborn infants also indicates poorer perinatal adjustment. Indeed, several other investigators[12,23] have found higher rates of special care nursery admissions in infants with third-trimester exposure or recorded a higher rate of postnatal complications.[8] All medicated mothers in our study whose newborn infants were admitted to the neonatal intensive care unit had taken antidepressant drugs during the last trimester. Taken together, these observations suggest that SSRIs taken in the last trimester may put the newborn infant at risk for perinatal complications, either through direct toxic effects or through effects from drug withdrawal.[26]

Importantly, at follow-up, the children's mental development and their attention, orientation, and emotional regulation were comparable in both groups. Two other follow-up studies have reported normal neurobehavioral development in children exposed in utero to fluoxetine.[13,14] In particular, Nulman et al,[13] who used the BSID-II[21] as well as other instruments, described similar mental developmental index scores and similar temperamental and language development in exposed children compared with children of "mothers who had not been exposed to any agent known to affect the fetus adversely." However, Nulman et al[13] did not report data for the PDI or the BRS of the BSID-II.

Our observation that SSRI-exposed children were slightly delayed in their psychomotor development and displayed subtle changes in motor movement control at follow-up compared with unexposed children is intriguing. The clinical implications of these findings are not known. Motor changes after SSRI exposure would be consistent with studies that have found the serotonin system to be the oldest and most expansive system within the vertebrate CNS with well-documented regulatory influence on muscle tone and other motor output.[27] Specifically, the findings of tremulousness and inappropriate fine motor movements in exposed children are consistent with reports describing a higher frequency of tremor and hyperkinesia in SSRI-treated children as opposed to placebo-treated children.[28,29] Results of the statistical correction for differences in APGAR scores suggest an association between APGAR scores at birth and motor functioning at follow-up. Nonetheless, differences between the exposed and unexposed groups in psychomotor development and motor quality remained significant after controlling for APGAR scores, and the effect sizes were moderate to large.

The current study demonstrates how difficult it is to control confounding variables, since, just as in other published outcome studies, the design tends to be influenced by the clinical needs of the patients. In this study, three children of previously unmedicated mothers were exposed to medication during breast-feeding. The amounts of drug

reaching the infant through breast milk would be expected to be small, from 1% to 10% of the maternal dose,[30-32] and their effects would have attenuated any between-group differences. On the other hand, we cannot rule out that SSRI exposure during breast-feeding, which occurred in about half of the exposed children, might have contributed to the findings in motor development. The issue of whether antidepressant drugs in breast milk have potential long-term effects on infants' health and behavior has so far received little attention. Yoshida et al[33] observed normal development at 1 year in 4 breast-fed infants whose mothers were taking fluoxetine, whereas Chambers et al[34] reported reduced growth curves for the first 6 months in nursing infants whose mothers took fluoxetine.

Study Limitations

The use of different types of SSRI antidepressant drugs and the doses and timing of the medication were outside the investigators' immediate control. Second, because of its sample size, the study had insufficient statistical power to detect differences in the incidence of major and minor structural malformations between exposed and unexposed children and to detect statistically significant differences in neonatal care unit admissions. Third, although unlike previous studies, this study controlled for the presence of a major depressive disorder, the depressive symptom self-ratings provide at best an estimate of depression levels during the pregnancy. Last, the fact that the children, albeit not significantly different in mean age, were not age-matched but were tested at differing ages, raises the possibility that greater variances in motor skills could have influenced the results of the PDI, since motor abilities are scored by age on standardized instruments. By contrast, ratings of motor qualities, such as tremor or inappropriate fine motor movements, might be expected to be less age-dependent.

This study is best viewed as a pilot investigation. Our results highlight the importance of including comprehensive assessments of motor development in follow-up studies of children with intrauterine exposure to SSRI antidepressant drugs. The information from this and two other studies[13,14] that the children were not affected in their cognitive and emotional development by prenatal exposure to SSRI antidepressant drugs is reassuring.

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50 Years Ago in *The Journal of Pediatrics*

CHOICE OF AN ANTIBIOTIC: AN INTERPRETIVE REVIEW

Karelitz S. J Pediatr 1953;42:478-504

How far we have NOT come! Fifty years ago, Karelitz wrote this brief review of the principles for prescribing antimicrobials together with details on how these drugs should be used in the treatment of the prevalent diseases of the day. Rereading this article is a reminder of the difficulties of translating principles into practice, despite good science and understanding.

The principles themselves have remarkably stood the test of time. By contrast, the applications of the principles in this review are dated. For example, penicillin has not replaced silver nitrate for opthalmia neonatorum, as Karelitz predicted. As expected, many details have changed because of the emergence of resistant organisms, occurring largely because of the exposure to antibiotics to which they were initially sensitive.

However, the widespread changes in bacterial sensitivity to antimicrobials is just what makes reading this article enlightening and somewhat sobering. Karelitz comments that "Uncontrolled sales of these agents would result in many more instances of toxicity, and in all probability many more resistant strains of bacteria." He relates that, quite commonly in that era, parents would pressure their pediatrician to prescribe in circumstances where the physician's better judgment would determine otherwise. This scenario occurs no less frequently today. "The omission of antibiotics or sulfonamides often requires a long and detailed explanation to the parents that there are definite and specific indications for the use of antibiotics, that these drugs may be harmful, and that drug resistance is becoming a more serious problem." Everything has changed, but nothing has changed.

The statement in the current Red Book[1] that "The spread of antimicrobial resistance is an issue of increasing concern to patients as well as health care professionals" (p 647) sounds a bit tired considering the remarkable persistence of this problem. The Centers for Disease Control and Prevention continues to conduct a campaign to professionals and the public to increase awareness of the appropriate use of antibiotics and the dangers of misuse. Information for patients is available on the web at: http://www.cdc.gov/drugresistance/community/files/html_versions/Your_Child_and_Antibiotics.htm. We must work to be more effective in the next 50 years than we have during the last.

Thomas P. Green, MD
Department of Pediatrics
Children's Memorial Hospital
Northwestern University
Chicago, IL 60614
YMPD182
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1. Red Book 2000. Report of the Committee on Infectious Diseases. 25th edition. Pickering LK, editor. Elk Grove Village (IL): American Academy of Pediatrics; 2000.