

NEURODEVELOPMENT OF CHILDREN EXPOSED IN UTERO TO ANTIDEPRESSANT DRUGS

IRENA NULMAN, M.D., JOANNE ROVET, PH.D., DONNA E. STEWART, M.D., JACOB WOLPIN, PH.D., H. ALLAN GARDNER, M.D., JOCHEN G.W. THEIS, M.D., NATHALIE KULIN, B.Sc., AND GIDEON KOREN, M.D.

ABSTRACT

Background Many women of reproductive age have depression, necessitating therapy with either a tricyclic antidepressant drug or a drug, such as fluoxetine, that inhibits the reuptake of serotonin. Whether these drugs affect fetal neurodevelopment is not known.

Methods We studied the children of 80 mothers who had received a tricyclic antidepressant drug during pregnancy, 55 children whose mothers had received fluoxetine during pregnancy, and 84 children whose mothers had not been exposed during pregnancy to any agent known to affect the fetus adversely. The children's global IQ and language development were assessed between 16 and 86 months of postnatal age by age-appropriate Bayley Scales of Infant Development or the McCarthy Scales of Children's Abilities (for IQ) and the Reynell Developmental Language Scales.

Results The mean (\pm SD) global IQ scores were 118 ± 17 in the children of mothers who received a tricyclic antidepressant drug, 117 ± 17 in those whose mothers received fluoxetine, and 115 ± 14 in those in the control group. The language scores were similar in all three groups. The results were similar in children exposed to a tricyclic antidepressant drug or fluoxetine during the first trimester and those exposed throughout pregnancy. There were also no significant differences in temperament, mood, arousability, activity level, distractibility, or behavior problems in the three groups of children.

Conclusions In utero exposure to either tricyclic antidepressant drugs or fluoxetine does not affect global IQ, language development, or behavioral development in preschool children. (N Engl J Med 1997;336:258-62.)

©1997, Massachusetts Medical Society.

AN estimated 8 to 20 percent of women have depression at some time in their lives, most commonly during childbearing years and often requiring drug therapy.^{1,2} The decision to continue or initiate pharmacotherapy for depression during pregnancy is complicated by the need to balance maternal well-being with fetal safety. Although the first trimester of pregnancy, in particular weeks 2 to 8 after conception, is the most critical period for drug-induced malformations, the brain develops throughout pregnancy, and injury may occur after the first trimester.³

There is ample evidence that discontinuation of antidepressant-drug therapy in patients with medica-

tion-responsive illness may be detrimental, with high relapse rates.⁴ The main drugs currently used in treating major depression are tricyclic antidepressant drugs and agents that selectively inhibit the reuptake of serotonin. The latter have fewer anticholinergic and cardioarrhythmic effects,⁵ but cause anxiety, nausea, and insomnia in a substantial proportion of patients.⁶⁻⁸

Both tricyclic antidepressant drugs and fluoxetine cross the placental barrier. In studies of these drugs in animals, doses much larger than those used in humans did not induce malformations.⁹⁻¹¹ Several small studies in humans have suggested that tricyclic antidepressant drugs are not teratogenic,¹²⁻¹⁷ but the studies were not controlled for various confounders, such as coexisting diseases and maternal lifestyle, that may affect the outcome of pregnancy. In a comparison of 74 children exposed in utero to tricyclic antidepressant drugs, 128 exposed to fluoxetine, and 128 matched children who were not exposed to such medications, exposure to drugs during the first trimester was not associated with an increased risk of major malformations.¹⁸ More recently, Chambers and colleagues reported similar rates of major malformations among children exposed in utero to fluoxetine and unexposed infants; however, the offspring of women who took fluoxetine in the third trimester were at increased risk for perinatal complications.¹⁹ The study did not control for coexisting diseases and did not correct for the more severe nature of depression among women who needed the drug throughout pregnancy.

Despite the wide use of tricyclic antidepressant drugs and fluoxetine by women of reproductive age, the paucity of information on fetal effects has not allowed physicians to reassure women that either exposure during the first trimester or continuous therapy throughout gestation is safe. This lack of data has created anxiety among women planning pregnancies and pregnant women, as well as among their families and physicians. Although neither tricyclic antidepressant drugs nor fluoxetine causes major

From the Motherisk Program (I.N., J.W., J.G.W.T., N.K., G.K.), the Division of Clinical Pharmacology and Toxicology (I.N., J.G.W.T., N.K., G.K.), the Department of Pediatrics (I.N., J.R., J.G.W.T., G.K.), Research Institute (J.R., G.K.), and the Department of Psychology (J.R.), Hospital for Sick Children and University of Toronto, Toronto; Women's Health Program, Toronto Hospital and University of Toronto, Toronto (D.E.S.); and Oshawa General Hospital, Oshawa, Ont., Canada (H.A.G.). Address reprint requests to Dr. Koren at the Division of Clinical Pharmacology, the Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada.

malformations, the possibility of long-term damage to the developing central nervous system may deter women from taking these drugs, even when clinically indicated.²⁰ This study was designed to assess prospectively cognitive and language development and behavior in children exposed in utero to tricyclic antidepressant drugs or fluoxetine.

METHODS

The Motherisk Program

The Motherisk Program is an information and consultation service for women, their families, and health professionals regarding exposure to drugs, chemicals, radiation, and infectious agents during pregnancy and lactation. Women with major depression who contact the program are invited to visit the clinic to be counseled by a physician.

Selection of Patients

We recruited three groups of mother-child pairs for this study. Two of the groups included the children of all women counseled by the program during the first trimester of pregnancy regarding therapy with either a tricyclic antidepressant drug or fluoxetine. We excluded from the study women in whom antidepressant-drug therapy had been discontinued before conception, those who took more than one antidepressant drug or were exposed to known teratogens during the pregnancy, and those who were unwilling to participate in our follow-up program. We also studied a group of mothers not exposed to any drug, chemical, radiation, or infection known to affect the fetus adversely. This group, also assembled prospectively, consisted of women who had taken innocuous drugs such as acetaminophen or oral penicillin or who had had dental x-ray films obtained during pregnancy. The control mothers were chosen from this list of women whose clinic appointments were closest (within two months) to those in the other two groups. The study was approved by the hospital's research ethics board, and informed consent was provided by all women.

Assessments

Antenatal Assessment

During the initial assessment, at the diagnosis of pregnancy or within several weeks thereafter, we obtained a medical history of each woman, including data on alcohol ingestion, use of medicinal and recreational drugs, smoking status, lifestyle, medical and nutritional status, and sexually transmitted diseases. A detailed genetic and obstetrical history was also obtained. Information concerning the time of drug therapy was recorded, as were the doses of tricyclic antidepressant drugs or fluoxetine and of any concomitantly administered drugs.

Postnatal Assessment

The first postnatal assessment occurred six to nine months after delivery. During this interview the mother was questioned about the course of her pregnancy after the initial meeting and was asked to verify the duration of treatment with tricyclic antidepressant drugs or fluoxetine during gestation, the dose of the drug, illnesses during pregnancy, and perinatal and postnatal complications. Details about the type of delivery, the perinatal period, and the times at which her child reached developmental milestones were also collected. This assessment also included a written report from the physician caring for the child.

Neurobehavioral Testing

All children were assessed by a psychometrician who did not know the nature of the intrauterine exposure. To assess neurocognitive development, children between 16 and 30 months of age were tested with the Bayley Scales of Infant Development²¹

and older children were tested with the McCarthy Scales of Children's Abilities.²² The temperament and behavior of children up to 24 months of age were evaluated with age-appropriate Carey Temperament Scales,^{23,24} and in children older than 24 months, the age-appropriate Achenbach Behavior Checklist²⁵ was used. Language skills were assessed in all children with the Reynell Developmental Language Scales.²⁶ Maternal IQ was assessed with the Wechsler Adult Intelligence Scale-Revised,²⁷ and socioeconomic status with the Hollingshead Four Factor Index.²⁸

The mother's level of depression and function from the birth of the infant to the time of the neurobehavioral assessment were evaluated with the Global Assessment Scale, which rates a subject's lowest level of functioning by selecting the lowest range that describes his or her functioning on a continuum of mental illness²⁹; the Center for Epidemiologic Studies Depressed Mood Scale, a 20-item scale that measures symptoms of depression for both epidemiologic research and clinical purposes³⁰; and the Index of Parental Attitudes, a 25-item scale designed to measure the extent, severity, or magnitude of problems in the parent-child relationship as seen and reported by a parent.³¹ As part of these assessments we recorded whether the mother continued drug therapy in the postpartum period, and if so, for how long.

Statistical Analysis

The outcome measures in each of the three groups were compared by one-way analysis of variance and Tukey's multiple-range test. All statistical tests were two-tailed. Subsequently, multiple regression analysis was conducted to determine the effects of potential confounders on the outcome measures. Differences in proportions among the groups were compared by the chi-square test.

RESULTS

A total of 129 pregnant women who were taking a tricyclic antidepressant drug have been counseled by the Motherisk Clinic since 1985. Twenty-four were lost to follow-up, 8 declined to participate, 3 were exposed to known teratogens, 12 had spontaneous abortions, and 2 had therapeutic abortions. Thus, the group comprised 80 women and 80 infants. Of the 80 women, 62 were treated for depression and 18 for other indications, including migraine (9 women), pain (6 women), and bladder control (3 women). Forty women took a tricyclic antidepressant drug during the first trimester, 36 throughout pregnancy, 2 during the first and second trimesters, and 2 during the first and third trimesters. Twenty-nine women took amitriptyline, 20 imipramine, 10 clomipramine, 9 desipramine, 8 nortriptyline, and 1 each maprotiline, doxepin, amoxapine, and trimipramine.

Eighty-eight pregnant women who were taking fluoxetine have been counseled since the introduction of the drug in Canada in 1988. Six were lost to follow-up, 8 declined to participate, 12 had spontaneous abortions, and 7 had therapeutic abortions. This group therefore consisted of 55 women and 55 infants — 37 whose mothers had taken fluoxetine during the first trimester and 18 whose mothers had taken the drug throughout pregnancy. The control group consisted of 84 pairs of mothers and children.

The characteristics of the women in the three groups are shown in Table 1. As compared with the other two groups, the women in the fluoxetine group

TABLE 1. CHARACTERISTICS OF WOMEN WHO WERE TAKING TRICYCLIC ANTIDEPRESSANT DRUGS OR FLUOXETINE DURING PREGNANCY AND PREGNANT CONTROL SUBJECTS.*

CHARACTERISTIC	TRICYCLIC ANTIDEPRESSANT DRUGS (N=80)	FLUOXETINE (N=55)	CONTROL (N=84)	P VALUE†
Age at conception (yr)	31±4	31±4	30±5	0.39
Gravidity	2±1	3±2	2±1	0.001 (fluoxetine vs. the other 2 groups)
Parity	1±1	1±1	0.4±0.6	0.001 (control vs. the other 2 groups)
Previous spontaneous abortion	0.3±0.6	0.2±0.5	0.2±0.4	0.61
Previous therapeutic abortion	0.3±0.6	0.6±1.1	0.1±0.4	0.001 (fluoxetine vs. the other 2 groups)
Weight gain during pregnancy (kg)	16±6.5	16±8	14±6	0.39
Socioeconomic-status score	46±12	40±13	44±13	0.04 (fluoxetine vs. the other 2 groups)
IQ	100±14	97±13	97±14	0.34
Alcohol use during pregnancy (no. of women)‡				
None	36	19	56	0.001 (control vs. the other 2 groups)
Light	44	34	27	
Heavy	0	2	0	
Cigarette smoking during pregnancy (no. of women)§				
None	54	29	65	0.001 (control vs. the other 2 groups)
Light	25	25	18	
Heavy	1	1	1	
Severity of depression¶				
Global Assessment Scale	62±15	60±15	—	0.10
CES Depressed Mood Scale				
Score on best days	10±9	13±10	—	0.08
Score on worst days	33±16	35±15	—	0.48
Index of Parental Attitudes	11±10	11±9	—	0.81

*Plus-minus values are means ±SD.

†The P values correspond to the overall heterogeneity of the three groups, or in the case of the severity of maternal depression, the two drug groups, according to Tukey's multiple-range test. Significant differences between specific groups are noted in parentheses.

‡Light alcohol ingestion was defined as the consumption of up to two drinks per week, and heavy alcohol ingestion as the consumption of more than two drinks per week. Information was not available for one woman in the control group.

§Light cigarette smoking was defined as smoking of up to five cigarettes per day, and heavy cigarette smoking as smoking of more than five cigarettes per day.

¶The score on the Global Assessment Scale can range from 1 (indicating the need for constant supervision) to 100 (indicating normal function). The score on the Center for Epidemiologic Studies (CES) Depressed Mood Scale can range from 0 (normal) to 60 (severe depression). The score on the Index of Parental Attitudes can range from 0 (no problems) to 100 (major attitudinal problems), and scores above 30 are considered to indicate clinically important problems.

had had more pregnancies and more previous therapeutic abortions and were of lower socioeconomic status. The women in both drug groups consumed more alcohol and smoked more cigarettes during the index pregnancy than the women in the control group. The women treated for depression in the two drug groups had similar scores on the three tests used to quantify their levels of depression and function after the birth of the index child (Table 1).

At birth and at the time of testing the percentiles of weight, height, and head circumference of the children in the three groups were similar (Table 2), and there were no significant differences in the rates

of perinatal complications. The incidence of major malformations among the three groups was also similar: three among the children exposed to tricyclic antidepressant drugs in utero (ventricular septal defect, hypospadias, and pyloric stenosis), two among those exposed to fluoxetine (ventricular septal defect and patent ductus arteriosus), and two among the control group (cyanotic heart disease and ventricular septal defect).

The mean global IQ values in the three groups of children were similar, for both younger children (tested with the Bayley Scales of Infant Development) and older ones (tested with the McCarthy

TABLE 2. PHYSICAL CHARACTERISTICS OF INFANTS AT BIRTH AND AT THE TIME OF TESTING, ACCORDING TO WHETHER THEY WERE EXPOSED IN UTERO TO ANTIDEPRESSANT DRUGS.*

CHARACTERISTIC	TRICYCLIC ANTIDEPRESSANT DRUGS (N=80)	FLUOXETINE (N=55)	CONTROL (N=84)	P VALUE†
	Gestational age at birth (wk)	39±2	39±2	40±1
Birth weight (g)	3490±642	3567±683	3373±540	0.18
Weight at testing (percentile)	58±30	54±30	51±31	0.32
Height at testing (percentile)	52±29	47±27	49±31	0.62
Fronto-occipital circumference at testing (percentile)	46±26	45±28	48±27	0.80

*Plus-minus values are means ±SD. Testing occurred between 16 and 86 months of age (mean, 33±14).

†The P values correspond to the overall heterogeneity of the three groups.

TABLE 3. RESULTS OF NEUROBEHAVIORAL TESTS IN INFANTS ACCORDING TO WHETHER THEY WERE EXPOSED IN UTERO TO ANTIDEPRESSANT DRUGS.*

TEST†	TRICYCLIC ANTIDEPRESSANT DRUGS (N=80)	FLUOXETINE (N=55)	CONTROL (N=84)	ADJUSTED DIFFERENCES (95% CI)‡	
				TRICYCLIC ANTIDEPRESSANT DRUGS VS. CONTROL	FLUOXETINE VS. CONTROL
				score	
Bayley Mental Development Index	118±17	117±17	115±14	2.4 (-4.5 to 9.4)	2.1 (-5.0 to 9.2)
McCarthy General Cognitive Index	117±10	114±16	114±13	2.7 (-2.3 to 7.6)	4.7 (-4.0 to 13.4)
Reynell Verbal Comprehension Scale	1.3±0.8	1.2±1.2	1.1±0.9	0.3 (-0.1 to 0.5)	0.3 (-0.1 to 0.6)
Reynell Expressive Language Scale	0.3±0.9	-0.2±1.0	0.1±1.0	0 (-0.3 to 0.3)	-0.1 (-0.4 to 0.3)

*Plus-minus values are means ±SD.

†The children were tested between 16 and 86 months of age (mean, 33±14). The Bayley and McCarthy scores are typical for this age. The normal range for both tests is 100±1 SD. Lower scores mean lower cognitive function. The mean Reynell score in normal children of this age is 0±1 (range of possible scores, -3 to +3).

‡Multiple regression analysis was used after adjustment for children's age; maternal IQ, socioeconomic status, score on the Center for Epidemiologic Studies Depressed Mood Scale, and score on the Global Assessment Scale; and duration of exposure to drug (first trimester vs. entire pregnancy). CI denotes confidence interval.

Scales of Children's Abilities) (Table 3). After adjustment for independent variables that may affect language development, the scores on the Verbal Comprehension and Expressive Language portions of the Reynell scales were similar in the three groups.

There was no significant difference in temperament in either drug group as compared with the control group. Similarly, there were no significant differences in scores of mood, arousability, activity level, distractibility, or behavior problems. Multiple regression analysis of the effect of the duration of an-

tididepressant-drug therapy (first trimester vs. the entire pregnancy) revealed no significant differences on any of the neurobehavioral tests in either group of children exposed to antidepressant drugs, as compared with the control children. Eighteen women took tricyclic antidepressant drugs during pregnancy for conditions other than depression. Their children's IQ scores, Reynell scores, and scores for temperament, mood, arousability, activity level, and distractibility were not different from those of the rest of the group (data not shown).

DISCUSSION

In planning our study we wished to address potential confounders that may affect a child's achievement on standard neurocognitive development and behavioral tests regardless of the type of therapy the mother received during pregnancy, including maternal IQ and socioeconomic class. Because the mother usually raises the child, the child's emotional, cognitive, and behavioral development may be adversely affected as a result of postnatal interactions with a mother who is depressed. For example, disturbances in the regulation of affect, attachment, and temperament; depression; and inferior development of cognitive and other skills have all been described in the children of depressed mothers.³² To address these potential confounders, we quantified the mother's depression and her resulting function with widely used research tools.²⁹⁻³¹ Despite wide variability in the degree of depression, the mean scores of the women receiving tricyclic antidepressant drugs and those receiving fluoxetine were similar on the three tests. In a similar manner, we quantified other maternal factors known to affect a child's scores on standard cognitive tests, including socioeconomic status and maternal IQ.

We found no significant differences in cognitive, language, and behavioral development among the children who were exposed to antidepressant drugs in utero and those who were not. Because half the pregnancies in North America are unplanned, many women take a tricyclic antidepressant drug or fluoxetine during the first few weeks of pregnancy. However, reassuring women that exposure to these drugs in the first trimester will not affect brain development in their unborn babies is not likely to reassure those who need continuous therapy throughout pregnancy. When maternal depression is not optimally controlled, there is ample evidence of adverse outcomes in infants and young children in a variety of domains, including cognitive, language, and behavioral, as well as higher rates of perinatal risks.³³

In our study one third of the women taking fluoxetine and almost half of those taking a tricyclic antidepressant drug continued the drug throughout pregnancy, allowing us to compare the effects of first-trimester exposure to these drugs with those of exposure during the entire pregnancy. We found that exposure to either type of drug throughout gestation did not affect the IQ or language and behavioral development of the offspring, as measured during the preschool years. In summary, in utero exposure to either tricyclic antidepressant drugs or fluoxetine does not adversely affect the neurodevelopment of preschool children.

Supported by the Motherisk Research Fund, Ciba Geigy Canada, Toronto, and a grant from the Medical Research Council and the Pharmaceutical Manufacturers Association of Canada.

We are indebted to Deborah Altmann for testing and to Jelena Pavlovic and Heather Rovet for scoring and analysis.

REFERENCES

- Weissman MM, Bruce ML, Leaf PJ, Florio LP, Holzer C III. Affective disorders. In: Robins LN, Regier DA, eds. *Psychiatric disorders in America: the Epidemiologic Catchment Area study*. New York: Free Press, 1991:53-80.
- Kessler RC, McGonagle KA, Swartz M, Blazer DG, Nelson CB. Sex and depression in the National Comorbidity Survey. I. Lifetime prevalence, chronicity and recurrence. *J Affect Disord* 1993;29:85-96.
- Koren G, ed. *Maternal-fetal toxicology: a clinician's guide*. 2nd ed. New York: Marcel Dekker, 1994.
- Cohen LS, Heller VL, Rosenbaum JF. Treatment guidelines for psychotropic drug use in pregnancy. *Psychosomatics* 1989;30:25-33.
- Potter WZ, Rudorfer MV, Manji H. The pharmacologic treatment of depression. *N Engl J Med* 1991;325:633-42.
- Gram LF. Fluoxetine. *N Engl J Med* 1994;331:1354-61. [Erratum, *N Engl J Med* 1995;332:343.]
- Pande AC, Sayler ME. Adverse events and treatment discontinuations in fluoxetine clinical trials. *Int Clin Psychopharmacol* 1993;8:267-9.
- Borys DJ, Setzer SC, Ling LJ, Reisdorf JJ, Day LC, Krenzlok EP. Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 1992;10:115-20.
- Shepard TH. *Catalog of teratogenic agents*. 5th ed. Baltimore: Johns Hopkins University Press, 1986.
- Nulman I, Koren G. The safety of fluoxetine during pregnancy and lactation. *Teratology* 1996;53:304-8.
- Vorhees CV, Acuff-Smith KD, Schilling MA, Fisher JE, Moran MS, Buelke-Sam J. A developmental neurotoxicity evaluation of the effects of prenatal exposure to fluoxetine in rats. *Fundam Appl Toxicol* 1994;23:194-205.
- Sim M. Imipramine and pregnancy. *BMJ* 1972;2:45.
- Crombie DL, Pinsent RJ, Fleming D. Imipramine in pregnancy. *BMJ* 1972;1:745.
- Possible teratogenicity of tricyclic antidepressants. *Lancet* 1972;1:838-9.
- Idanpaan-Heikkilä J, Saxen L. Possible teratogenicity of imipramine-chloropyramine. *Lancet* 1973;2:282-4.
- Kuenssberg EV, Knox JD. Imipramine in pregnancy. *BMJ* 1972;2:292.
- Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991;21:157-71.
- Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993;269:2246-8.
- Chambers CD, Johnson KA, Dick LM, Felix RJ, Jones KL. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996;335:1010-5.
- Koren G, Bologna M, Long D, Feldman Y, Shear NH. Perception of teratogenic risk by pregnant women exposed to drugs and chemicals during the first trimester. *Am J Obstet Gynecol* 1989;160:1190-4.
- Bayley N. *Bayley Scales of Infant Development*. 2nd ed. San Antonio, Tex.: Psychological Corporation, 1993.
- McCarthy D. *McCarthy Scales of Children's Abilities*. New York: Psychological Corporation, 1972.
- Fullard W, McDevitt S, Carey W. *Toddler Temperament Scale: for 1 to 3 year old children*. Philadelphia: Temple University Press, 1978.
- McDevitt SC, Carey WB. The measurement of temperament in 3-7 year old children. *J Child Psychol Psychiatry* 1978;19:245-53.
- Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington: University of Vermont Department of Psychiatry, 1991.
- Reynell JK. *Reynell Developmental Language Scales manual*. 2nd rev. (Huntley M.) Windsor, England: NFER-NELSON Publishing, 1985.
- Wechsler D. *Wechsler Adult Intelligence Scale*. Rev. ed. New York: Psychological Corporation, 1981.
- Hollingshead AB. *Four factor index of social status*. New Haven, Conn.: Yale University Department of Sociology, 1975.
- Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment Scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 1976;33:766-71.
- Radloff LS. The CES-D Scale: a self-report depression scale for research in the general population. *Appl Psychol Meas* 1977;1:385-401.
- Hudson WW. *The clinical measurement package: a field manual*. Homewood, Ill.: Dorsey Press, 1982.
- Goodman SH. Understanding the effects of depressed mothers on their children. *Prog Exp Pers Psychopathol Res* 1992;15:47-109.
- Morrison HL, ed. *Children of depressed parents: risk, identification, and intervention*. New York: Grune & Stratton, 1983.