NEURODEVELOPMENT OF CHILDREN EXPOSED IN UTERO TO ANTIDEPRESSANT DRUGS

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 (±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.

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 neuro-cognitive development, children between 16 and 30 months of age were tested with the Bayley Scales of Infant Development [21] 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 Checklist[25] 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 illness[29]; the Center for Epidemiologic Studies Depressed Mood Scale, a 20-item scale that measures symptoms of depression for both epidemiologic research and clinical purposes[30]; 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.

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

CHARACTERISTIC	TRICYCLIC ANTI-DEPRESSANT DRUGS (N = 80)	FLUOXETINE (N = 55)	CONTROL (N = 84)	P-VALUE†
			TRICYCLI	
Age at conception (yr)	31+/-4	31+/-4	30+/-5	0.39
Gravidity	2+/-1	3+/-2	2+/-1	0.001 (fluoxetine vs other 2)
Parity	1+/-1	1+/-1	0.4+/-0.6	0.001 (control vs other 2)
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 other 2)
Weight gain during pregnancy(kg)	16+/-6.5	16+/-8	14+/-6	0.39
SES Score	46+/-12	40+/-13	44+/-13	0.04 (fluoxetine vs other 2)
IQ	100+/-14	97+/-13	97+/-14	0.34
Alcohol use during pregnancy# (number of women)				
None	36	19	56	0.001
Light	44	34	27	(control vs other 2)
Heavy	0	2	0	
Cigarette smoking during pregnancy¶				
None	54	29	65	0.001
Light	25	25	18	(control vs other 2)
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		0.48

*Plus-minus values are means +/- SD.

†The P-values correspond to the overall heterogeneity of the three groups, or in the case of the 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 the consumption of more than two drinks per week. Information was not available in the control group.

¶ Light 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.

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 ANTI-DEPRESSANT DRUGS (N = 80)	FLUOXETINE (N = 55)	CONTROL (N = 84)	P-VALUE†
Gestational age at birth (wk)	39+/-2	39+/-2	40+/-1	0.10
Birth weight (g)	3400+/-642	3567+/-683	3373+/-54	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
ipital circumference at testing (percentile)	46+/-26	45+/-28	48+/-27	0.80

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*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 ANTI-DEPRESSANT DRUGS (N = 80)	FLUOXETINE (N = 55)	CONTROL (N = 84)	ADJUSTED DIFFERENCES (95% CI) **	
				TRICYCLIC vs CONTROL	FLUOXETINE vs CONTROL
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	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)

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* Plus-minus values are mean +/- 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 ion analysis was used after adjustment for children's age; maternal IQ, socioeconomic status, score on the 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.