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Fetal, neonatal and developmental outcomes of lithium-exposed pregnancies

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ABSTRACT

Introduction: Many women with a bipolar disorder are of reproductive age and will need to continue lithium treatment during pregnancy. The teratogenic and perinatal effects of lithium are known, but not the long-term effects of lithium on neurodevelopment of the children. This study investigates growth, neurological, cognitive and behavioral development of children exposed to lithium in utero.
Method: In an observational retrospective cohort study 15 children who were exposed to lithium in utero were investigated at 3–15 years of age. Neurological development was tested using the Hempel or Touwen examination. Cognitive development was assessed with the Bayley Scales of Infant Development III, Wechsler Preschool and Primary Scale of Intelligence or the Wechsler Intelligence Scale for Children. Parents completed the Child Behavior Checklist to assess behavioral development and a standard questionnaire about general development of the child since birth.
Results: One child had signs of a minor neurological dysfunction, but without further clinical implications. The results of the cognitive tests were within normal limits, although most children had lower scores on the performance IQ subtest. Growth, behavior and general development were within the normal range.
Conclusions: Continuing lithium therapy during pregnancy did not cause adverse effects on growth, neurological, cognitive and behavioral development of exposed children.

1. Introduction

Since the 1950s lithium is the most important drug in the pharmacological treatment of bipolar disorder. Bipolar disorder is common in women in their reproductive age, which raises the question whether intrauterine exposure to lithium affects neurodevelopmental outcome of exposed children [1]. Discontinuation of lithium use during pregnancy is contraindicated as this is associated with a twofold greater risk of recurrence of a new episode of mania or depression [2–4].

Lithium entirely readily crosses the placenta and the fetus receives 100% of the drug during pregnancy. High serum lithium levels at delivery are associated with a higher incidence of neonatal complications and have led to interruption of lithium therapy or use of lower doses of lithium shortly before delivery [5].

The risk of congenital disorders of children who received lithium in utero has been extensively investigated. A retrospective analysis of data from the Danish Register of Lithium Babies in 1976 suggested a high risk of Ebstein's anomaly (6 out of 225 exposed children versus an incidence of 1 in 20,000 in the general population) [6], but this turned out to be a gross overestimation due to a voluntary reporting bias. The Motherisk Program performed two studies on the potential teratogenic effect of lithium and found a relative risk for all congenital disorders of 1.2 and for cardiac disorders of 1.1 and no association of lithium use with Ebstein's anomaly [7,8]. A review of the epidemiologic data by Cohen et al. concluded that the teratogenic risk of first-trimester lithium exposure is lower than previously suggested [9].

Many case reports describe neonatal lithium toxicity which often presents as a “floppy infant syndrome” characterized by lethargy, poor sucking, tachypnea, tachycardia, respiratory distress syndrome, cyanosis and hypotonie [10]. Other neonatal problems include structural and functional cardiovascular problems, macrosomia, hyperbilirubinemia, diabetes insipidus, and hypothyreoidism [10]. However, an elevated risk of these adaptation problems and complications has never been significantly proven and most of them are transient and without long-term consequences [11].

Although lithium does not seem to cause major congenital disorders, there is a realistic possibility of long-term effects on the developing fetal brain during pregnancy [12,13]. The first trimester is the

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most critical period for drug-induced disorders, but the brain is developing throughout pregnancy and highly vulnerable to the latent cognitive and neurological impact of drugs [14]. Youngs et al. investigated long-term effects of lithium on the developing rat brain and found long-lasting increases in anxiety-like behavior [15]. Except for a follow-up questionnaire reported by Schou, long-term effects of exposure to lithium in utero have not been studied in humans [16,17]. This lack of knowledge causes fear in women who use lithium and are pregnant, or are planning a pregnancy [18].

The objective of this study was to investigate growth and neurological, cognitive and behavioral development of children who were exposed to lithium in utero.

2. Method

2.1. Participants

The Perinatal Center of the Leiden University Medical Center (LUMC) prospectively collected perinatal data on all mothers treated with lithium (target maintenance serum lithium levels 0.6–0.8 mmol/L) for bipolar disorder during pregnancy and their children in the period between 1-1-1994 and 31-12-2007. Mothers with a bipolar disorder without lithium therapy were not identified in the defined period. Twenty-one mothers of 30 children born alive in the LUMC between 1-1-1994 and 31-12-2007 were asked by their psychiatrist or obstetrician for permission to examine their children for follow-up purposes. The psychiatrist or obstetrician called the mothers to inform them about the study and ask them if they wanted to participate. If they agreed, information about the study and follow-up questionnaires were sent and the physical and psychological examination scheduled. The ethics committee of the hospital approved the study and informed consent was obtained from the parents.

2.2. Study design

Growth and neurological, cognitive and behavioral outcome of lithium-exposed children were assessed using standard tests, validated in the Dutch population. Data collection was done during the neonatal period and between November 2008 and December 2009. The visit of the children with one of their parents to the hospital lasted about 4 h.

2.3. Assessments

2.3.1. Neonatal assessment

The neonatal database provided [1] data on the medical and obstetric history of the mothers, including use of medications during pregnancy, serum lithium values, method of delivery, and perinatal complications, and [2] data collected during the 24 h observation of each child after birth, including birth weight; 1 and 5 min Apgar scores; umbilical cord blood lithium levels; chest X-ray, ECG, and echocardiography (if indicated); blood glucose, serum electrolytes, and thyroid function.

2.3.2. Developmental assessment and growth

Physical and mental development of the child was screened using a questionnaire to be filled in by the mother. Items that were asked were growth, illnesses, behavioral problems, motor problems and developmental milestones. Growth of the children was assessed by measurement of height, weight and head circumference and plotted in the Dutch growth curves.

2.3.3. Neurological examination

Children between 2 and 5 years of age were assessed according to the Hempel examination [19]. Outcome of this test is divided into 3 groups: normal, simple minor neurological dysfunction (MND) when dysfunction is detected in 1 cluster, and complex MND when dysfunction is found in more than 1 cluster. For older children the Touwen protocol for neurological examination was used [20,21]. Outcome for that test is 0 (normal), 1 (simple MND), 2 (complex MND), 3 (Complex Pathology, CP).

2.3.4. Cognitive testing

Cognition was assessed by a child psychologist. Children between 16 and 30 months old were tested with the Bayley Scales of Infant Development (BSID III) [22] and older children were tested with the Wechsler Preschool and Primary Scale of Intelligence or the Wechsler Intelligence Scale for Children (WPPSI/WISC) [23]. The BSID reports a Developmental Score, the WPPSI/WISC consists of a verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ) and total intelligence quotient (TIQ). All tests have a mean score of 100 and a standard deviation of 15.

2.3.5. Behavioral assessment

Behavioral development of the children was tested by having the mothers complete the Child Behavior Checklist (CBCL) for children from 1.5 to 5 or 6–18 years [24]. Outcome of this test consists of T-values on 6 different areas of the DSM-IV: affective problems, anxiety problems, attention deficit/hyperactivity problems, oppositional defiant problems, conduct problems, pervasive problems (1.5–5 year old) or somatic problems (6–18 year old). Results of these scores are divided into 3 categories, with T-values of 50–64.5 being normal, 64.5 to 69.5 subclinical and 69.5–100 clinical.

2.3.6. Statistical analysis

Data are presented as means ± standard deviation (SD) or as median (range).

3. Results

None of the 30 lithium-exposed children were born with congenital anomalies known to be associated with maternal lithium use. Mean ± SD birth weight was 3384 ± 510 g, mean gestational age was 38.0 ± 1.2 weeks and none of the children was asphyxiated (5 min Apgar score <7) or needed respiratory support at birth. Seventeen out of 30 children were born by normal vaginal delivery. Ten children (of whom five were seen for follow-up) showed signs of neonatal toxicity: 4 had respiratory symptoms, 4 nausea and vomiting (retching, refusal of nutrition), 2 hypoglycemia, 1 hypotonia and 1 hyperbilirubinemia. Two children had serum lithium values >0.8 mmol/L, of whom one had signs of neonatal toxicity. In addition to lithium, 9 out of 30 children were exposed to other psychotropic medications (4 were exposed to antidepressants, 4 to benzodiazepines and 1 to an antipsychotic drug). One child had a ventricular septal defect with coarctation of the aorta and underwent successful surgical repair. Serum electrolytes, renal function and thyroid hormones were normal in all.

Six mothers (8 children) could not be reached for follow-up because they had moved without leaving a forwarding address or moved out of the country, 3 mothers (5 children) refused participation and 2 mothers (2 children) were not available on test dates. Ten mothers were left, with a total of 15 children, to participate in the study. In Fig. 1 a flowchart can be seen of participating children and mothers.

Table 1 shows the baseline characteristics of the 15 children who participated in the follow-up study. No significant differences were found in baseline characteristics comparing participating and non-participating children in the follow-up study.

Results of the neurological and physical examinations are presented in Table 2. One child had a minor neurological dysfunction (MND), but this result was without further clinical implications. In all other cases no neurologic abnormalities were found. Growth measurements were all within the normal range.

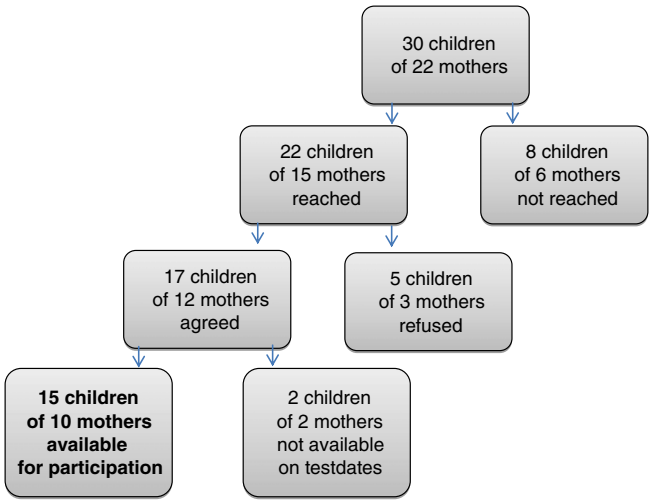

Fig. 1. Flowchart of participating children in follow-up study.

Table 2 also reports the results of the psychological examinations. Testing of cognition with WISC-III-NL, WPPSI-R and Bayley tests did not demonstrate any abnormality. One child had a low VIQ and TIQ, but the PIQ was normal. All other data were within the normal range. Most children had a lower score on the performance tests, especially on the subtest Block patterns, but this was not a significant deprivation. The child tested with the WPPSI-R had above average scores, so did one child tested with the Bayley test.

The results of the CBCL-questionnaire showed no abnormalities in the areas of Affective Problems, ADH, Conduct Problems and Pervasive Disorders and all scores were within the normal range. In the area of Anxiety Problems two children scored in the subclinical range, one of whom also scored in the subclinical range in the area of Somatic Problems. One child was in the subclinical range in the area of Oppositional Problems.

Developmental milestones were normal in all children. Parents mentioned hyperactivity and concentration problems in 3 children. Medical histories frequently reported viral upper airway infections, eczema in 4 children and allergies in 2. Two children received physical therapy when they were 1.5 to 4 years old to improve their gross motor skills. One child had transient motor problems at the age of 7.

4. Discussion

This study reports the long-term outcome of 15 children who were exposed to lithium in utero and were not breastfed. Neurological screening and growth measurements did not show significant abnormalities in the children, all were well within the normal range. Intelligence tests detected lower scores in the performance tests, especially in the Block pattern subtest, in nearly all children, but the difference with a control general population was not significant. Motor and behavioral development showed no significant abnormalities, based on the CBCL and developmental questionnaire.

The only study on follow-up of lithium exposed children was done by Schou in 1976 [16]. In this follow-up study a questionnaire was sent to the psychiatrist or the general practitioner of the mothers of 60 children who had been exposed to lithium in utero. These doctors were requested to ask the mothers if any problems in physical or mental development had occurred in the lithium-exposed children and their non-lithium-exposed siblings who served as a control group. No significant differences were found between both groups. However, this study was based on the subjective report of the mothers, never a study was done where a pediatrician and a psychologist examined the children. Our study comprised growth measurements and formal testing of neurological, cognitive and behavioral outcome in 15 children 3–15 years of age and shows that outcome of these children is indeed within normal limits.

Limitations of this study are the relatively small sample size, lack of a suitable control group, and use of other psychotropic medications. Because of the observational character of the study, no specific hypothesis was formulated in advance. Small differences may be difficult to detect due to the small group of children tested and the intrinsic limitations of the standard screening instruments for behavioral development [25]. A possible negative finding may be the lower scores on the performance IQ (PIQ) tests, but further and more specific research needs to be done on this subject. As the lower scores of PIQ were not statistically significant, it was not necessary to investigate the role of potential confounding factors on cognitive development (maternal IQ, socioeconomic status, use of alcohol and tobacco). No suitable control group could be found, because it is almost impossible to identify children who were raised in the same situation and family, but without in utero exposure to lithium. This type of controls was not available to us. However, normal values of tests for psychological and behavioral development are based on a large cohort of children from the general population, which functions like a control group.

Table 1
Baseline characteristics of children who participated in the follow-up study.

Patient #	Gravida/ para	Age of mother (years)	Other psychotropic medication	Gestational age (weeks)	Delivery*	Gender (Male, female)	Birth weight (g)	Apgar scores		Lithium cord blood level > 0.8 mmol/L	Neonatal toxicity
								1 min	5 min		
1	G1P0	34		39	VE	F	3820	8	9		
2	G2P1	37		39	VE	F	4740	9	10		X
3	G1P0	34		39	VE	M	3720	9	10		
4	G2P1	36		38	V	F	2870	10	10		X
5	G1P0	37		38	V	M	3130	8	9		X
6	G2P1	28	Fluoxetine	37	V	F	3500	8	9		
7	G1P0	36		37	VE	M	3240	8	9		
8	G1P0	29		40	VE	M	3655	5	8		
9	G2P1	40		40	CS	F	3665	8	9		
10	G1P0	32		40	CS	M	3766	8	9		X
11	G2P0	35	Haloperidol	39	VE	F	3585	8	10		
12	G2P1	31		38	V	F	3835	10	10		
13	G3P1	38	Nortriptyline	36	V	F	2675	7	9		
14	G2P1	36	Lorazepam	39	CS	F	3715	9	9	X	
15	G1P0	35		37	V	F	3290	9	10	X	X

*: V: vaginal delivery; VE: vacuum extraction; CS: cesarean section.

Table 2
Neurological and growth assessments and psychological examinations at follow-up.

Patient #	Age (years)	Neurological and growth assessment				Psychological examination				
		Neurological outcome[1]	Height (cm)	Weight (kg)	Head circumference (cm)	WISC-III-NL and WPPSI-R[2]			BSID-III	
						VIQ	PIQ	TIQ	DS	95% CI
1	15	Normal	183.7	62.8	55	122	105	116		
2	13	Normal	172	49.3	54	108	99	105		
3	11	Normal	154	42.0	57	115	96	107		
4	10	Normal	147.5	36.2	55	122	118	123		
5	9	Normal	128.7	24.9	52	103	91	97		
6	9	Normal	133.5	26.8	51	83	88	84		
7	7	Simple MND	132.8	26.5	53	107	107	108		
8	8	Normal	132	27	53	106	86	96		
9	7	Normal	125.2	22.5	51	105	88	96		
10	6	Normal	124	24.8	54	122	110	119		
11	6	Normal	119	24.3	51	107	99	104		
12	6	Normal	118	22	50	126	121	128		
13	4	Normal	98	15.5	49	109	137	126		
14	3	Normal	96.5	15.5	50				139	126–139
15	3	Normal	99.4	16.4	48.6				105	97–113

1. Neurological and growth examination → Normal: normal neurological development. MND: minor neurological dysfunction. Patients 1–9: Touwen exam; patients 10–15: Hempel exam.
2. Psychological examination → WISC-III-NL: Wechsler Intelligence Scale for Children (patients 1–12); WPPSI-R: Wechsler Preschool and Primary Scale of Intelligence (patient 13); BSID-III Bayley Scales of Infant Development.
Outcomes → VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; TIQ: total intelligence quotient; DS: developmental score; 95% CI: 95% confidence interval.

Based on our results we conclude that the children are developing normally after being exposed to lithium in utero and that no major developmental problems have evolved. This supports the thesis that continuing lithium therapy during pregnancy does not adversely affect the development of a child, and that it is rather safe to do so. This information may provide the counseling doctor and the bipolar woman more confidence in planning a safe pregnancy and continuing lithium treatment.

Conflict of interest statement

The authors report no financial relationships with commercial interests.

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