Article

Pregnancy Outcome Following In Utero Exposure to Lithium: A Prospective, Comparative, Observational Study

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Objective: The authors conducted a prospective, comparative observational study to evaluate the risk of major anomalies following exposure to lithium during pregnancy.

Method: A total of 183 lithium-exposed pregnancies of women who contacted the Israeli Teratology Information Service were followed up (90.2% in the first trimester) and compared with 72 disease-matched and 748 nonteratogenic-exposed pregnancies.

Results: There were significantly more miscarriages (adjusted odds ratio=1.94, 95% CI=1.08–3.48) and elective terminations of pregnancy (17/183 [9.3%] compared with 15/748 [2.0%]) in the lithium-exposed group compared with the nonteratogenic exposure group. The rate of major congenital anomalies after exclusion of genetic or cytogenetic anomalies was not significantly different between the three groups (lithium-exposed in the first trimester: 8/123 [6.5%]; bipolar: 2/61 [3.3%]; nonteratogenic: 19/711 [2.7%]). Cardiovascular anomalies occurred more frequently in the lithium group exposed during the first trimester when compared with the nonteratogenic exposure group (5/123 [4.1%] compared with 4/711 [0.6%]) but not after excluding anomalies that spontaneously resolved (3/123 [2.4%] compared with 2/711 [0.3%]). Ebstein's anomaly was diagnosed in one lithium-exposed fetus and in two retrospective lithium cases that were not included because contact with the information service was made after the prenatal diagnosis by ultrasound. The rate of noncardiovascular anomalies was not significantly different between the groups. The rate of preterm deliveries was higher in the lithium group compared with the nonteratogenic exposure group (18/131 [13.7%] compared with 41/683 [6.0%]).

Conclusions: Lithium treatment in pregnancy is associated with a higher rate of cardiovascular anomalies. Women who are treated with lithium during organogenesis should undergo fetal echocardiography and level-2 ultrasound.

(Am J Psychiatry 2014; 171:785–794)

Lithium salts were introduced into psychiatry for the treatment of mania and are effective mood stabilizers. Bipolar disorder has a lifetime prevalence of ≥1% and carries significant morbidity. Women with the disorder are typically young at onset, placing them at risk for episodes throughout their reproductive years. Recurrence risk is greater among women who discontinue their mood stabilizer treatment during pregnancy, compared with those who continue, with a shorter time to first recurrence and longer illness period (1). The anticonvulsant mood stabilizers valproic acid and carbamazepine are both known human teratogens. Lithium freely crosses the placenta equilibrating between maternal and cord serum (2). Amniotic fluid concentrations exceed cord serum levels (3). Results reported in animal reproductive studies of lithium have been inconsistent. Malformations were not produced with lithium carbonate in some studies performed in mice, rats, rabbits, and monkeys (4, 5). In contrast, lithium salts were teratogenic in other studies in mice and rats, resulting in various anomalies. The anomalies observed in the rodent studies included neural tube, palate, eye, ear, kidney, skeletal, heart, and pericardium malformations (6–11).

An association between Ebstein's anomaly and lithium has been suggested in several human studies and case reports (12–15). The Lithium Baby Register that was established in Denmark in 1968 to retrospectively collect information on children born to mothers who had been treated with lithium at least some time during the first trimester of pregnancy (from Scandinavia, the United States, and Canada), based on a voluntary physician reporting system, supported this association (16–18). Eight percent (18/225) of the offspring were born with cardiovascular malformations (six with Ebstein's anomaly [2.7%], compared with a background risk of approximately 1:20,000 [0.005%] according to Nora et al. [12]) (18). However, the reports from the Lithium Baby Register were subject to recall bias resulting in overestimation of adverse outcome data. Källén and Tandberg (19) reported four cases of serious heart defects (although none had Ebstein's anomaly) among 59 infants born to women who used lithium during early pregnancy, suggesting a 7% risk. Their data on lithium use during pregnancy were collected prospectively. However, based on most prospective studies, the risk associated with lithium use during pregnancy is

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lower than previously suggested (20–22). Several case-control studies, mostly negative, have been published on the association between Ebstein's anomaly and lithium use in pregnancy (23–27). A follow-up study on the development of children exposed in utero to lithium did not reveal an increased frequency of either physical or neurodevelopmental anomalies (28). Various neonatal adverse effects, mostly transient, have been described in infants born to mothers treated with lithium during pregnancy (29).

The primary objective of the present study was to prospectively evaluate the rate of major anomalies after pregnancy exposure to lithium compared with the rate in two comparison groups: 1) pregnant women with bipolar disorder but not treated with lithium during pregnancy and 2) pregnant women counseled for nonteratogenic exposure. Secondary endpoints of interest were pregnancy outcome, birth weight, gestational age at delivery, and neonatal complications.

Method

In this prospective observational study, pregnant women who contacted the Israeli Teratology Information Service (Jerusalem) with regard to gestational exposure to lithium, between the years 1994 and 2010, were enrolled. The lithium-exposed group was compared with the following two groups: 1) pregnant women with bipolar disorder and no exposure to lithium who were counseled by the Israeli Teratology Information Service between the years 1999 and 2010 and who were untreated during pregnancy or treated with antipsychotics (e.g., haloperidol, risperidone) and/or antidepressants (e.g., duloxetine) or treated with mood stabilizers other than lithium, such as carbamazepine, valproic acid, lamotrigine, or topiramate; and 2) pregnant women randomly selected from the Israeli Teratology Information Service database who were counseled during pregnancy between 1994 and 2010 with regard to exposures known not to be teratogenic at a 1:4 ratio. Verbal consent to participate in the study was given by the women at initial contact. Since the study was observational, it was exempt from institutional review board approval. Details of exposure (dosage, duration and timing in pregnancy, and additional exposures) are routinely collected at the initial contact and before pregnancy outcome is known using a structured questionnaire (unpublished data available upon request from Diav-Citrin et al.). In addition, maternal demographic information and medical and obstetrical histories are recorded. Retrospective cases were not included in the comparative study, but are reported separately in the text. After the expected date of delivery, we actively sought pregnancy outcome in the lithium-exposed group and the two comparison groups. Follow-up was conducted by telephone interview to obtain details of pregnancy outcome, gestational age at delivery, birth weight, congenital anomalies, and neonatal complications. When the mother reported a malformation, she was asked to check medical documents verifying the diagnosis. In most cases with anomalies, a subsequent interview with the mother was carried out by a certified pediatrician. The offspring follow-up evaluation was performed between the neonatal period and 7 years of age. However, in most cases it was carried out within the first 2 years of life. Additionally, lithium or other exposures were ascertained. Data collection was similar in all three groups.

The primary outcome of interest was the rate of major anomalies. Major anomalies were defined as structural anomalies in the offspring that have serious medical, surgical, or cosmetic consequences. Significant neurodevelopmental or functional problems were also considered to be major anomalies, even in the absence of a structural abnormality, when they required special education or interventions. Anomalies such as mild hypospadias not requiring an intervention, functional problems without any morphological changes (e.g., systolic heart murmur with normal echocardiography, slight developmental delay), or complications of preterm delivery were not considered to be major anomalies. Cardiovascular anomalies, such as septal defects, were initially considered major anomalies and were reanalyzed excluding those that resolved spontaneously. In cases of cardiovascular anomalies not requiring an intervention, the women were repeatedly contacted for follow-up purposes to find out whether these anomalies resolved as time passed. Abnormalities detected by prenatal ultrasonography (if verified postnatally or by autopsy) were included in our study, since antenatal screening for major anomalies is routinely performed in Israel. The classification of anomalies was done by a certified pediatrician blinded to the exposure group. A certified medical geneticist was consulted in case of classification difficulty. Thus, the analysis of major congenital anomalies was performed in all live-born infants, as well as in stillbirths and in elective terminations of pregnancy as a result of prenatally diagnosed anomalies. In the case of multifetal pregnancies, each live-born offspring was included in the analysis. In order to increase the power of the study, the rate of major anomalies was also compared between larger lithium- and nonteratogenic-exposed groups after adding data collected by two additional services: MotherSafe (Sydney, Australia) and the Motherisk Program (Toronto), between the years 2000–2011 and 2001–2005, respectively. The three participating centers are members of the Organization of Teratology Information Specialists, an organization of counseling services pertaining to environmental exposures during pregnancy, and use similar methodologies. Secondary endpoints were the rates of live birth, miscarriage, pregnancy termination, stillbirth, ectopic pregnancy, preterm delivery (<37 completed weeks), gestational age at delivery, birth weight, and neonatal complications.

Statistical Analysis

Categorical data were compared using chi-square or Fisher's exact tests when appropriate. Continuous data were compared using analysis of variance or Kruskal-Wallis test, depending on whether or not the data followed normal distribution for three groups, or using student t or Mann-Whitney tests for two groups. The data are presented as ratios and percentages for categorical data. Normally distributed continuous data are presented using mean with standard deviation, while data that did not follow normal distribution are presented using median with interquartile range. The p values presented in Tables 1 and 2 are for a comparison between the three groups. Two-tailed tests were applied. For pairwise comparisons, Bonferroni method was applied, and statistical significance was set at a p value <0.017 for a two-group comparison. Logistic regression analysis was used to evaluate the relative contribution of various predictors to the differences in the rate of miscarriages or major malformations. Statistical calculations were performed using SPSS Version 19 (SPSS, Chicago) or Epi Info 2000 software (Centers for Disease Control and Prevention, Atlanta Epidemiology Program Office, Atlanta).

Results

A total of 183 lithium-exposed pregnancies recorded by the Israeli Teratology Information Service were prospectively followed up. The exposure was at least in the first trimester of pregnancy in 90.2% of this lithium-exposed

group. The mean daily lithium dose was 906 mg (SD=342). The medication was taken throughout pregnancy in 58.5% of these pregnancies. The reported indications for treatment with lithium were as follows: bipolar disorder (65.9%), depression (16.7%), schizoaffective disorder (6.8%), schizophrenia (3.8%), mania (1.5%), and psychosis (2.2%). Concurrent psychiatric medications were taken by 66.1% of women in this cohort. The comparison groups consisted of 748 pregnancies of women counseled by the Israeli Teratology Information Service for nonteratogenic exposure and 72 pregnancies of women, counseled by the same service, with bipolar disorder not treated with lithium during the gestation period.

A comparison of maternal characteristics and obstetrical history between the three groups is presented in Table 1. The median age of women in the lithium-exposed group was 2 years older than that of women in the nonteratogenic exposure group. There were more multiparous women in the lithium-exposed group. A higher proportion of women in the lithium-exposed group had four or more children or had one or more previous elective terminations of pregnancy compared with women in the nonteratogenic exposure group. A lower proportion of women in the lithium group made contact with the teratology service during their second, third, or fourth pregnancy or had one to three children compared with women in the nonteratogenic exposure group. The gestational age at initial contact was 4 weeks earlier in the lithium group and 5 weeks earlier in the bipolar group compared with initial contact in the nonteratogenic exposure group. A higher proportion of women in both the lithium and bipolar groups smoked 10 or more cigarettes per day compared with women in the nonteratogenic exposure group. A higher proportion of women in the bipolar group did not have children, while a lower proportion had one to three children, compared with women in the nonteratogenic exposure group.

A comparison of pregnancy outcome between the three groups is presented in Table 2. There was a 2.9-fold increase in the crude rate of miscarriages and a 4.7-fold increase in the rate of elective terminations of pregnancy in the lithium group compared with the nonteratogenic exposure group. The rate of preterm deliveries was 2.3-fold higher in the lithium group compared with the nonteratogenic exposure group. There were no significant differences in birth weight between the three groups.

The rate of major anomalies between the lithium, bipolar, and comparison groups is presented in Table 3. The overall rate of major congenital anomalies was not significantly different between the three groups. The analysis of major anomalies was repeated among those offspring exposed to lithium during the first trimester and after exclusion of genetic or cytogenetic anomalies, and no significant difference was found. However, cardiovascular anomalies were significantly more common in cases of lithium exposure during the first trimester when compared with the nonteratogenic group (χ^2=12.1, df=1, p=0.005; crude relative risk=7.23, 95% CI [confidence interval]= 1.97–26.53]), but there was no significant difference after excluding those anomalies that spontaneously resolved (relative risk=5.78, 95% CI=0.82–40.65). The rate of noncardiovascular anomalies was not significantly different between the three groups.

In an attempt to increase the power of the study by increasing the number of exposed pregnancies, a multicenter design was applied. A comparison of the rate of major anomalies between the lithium and nonteratogenic exposure groups was performed including data from two additional teratology information services, one in Australia (MotherSafe, 2000–2011) and one in Canada (the Motherisk Program, 2001–2005). Eighteen lithium cases from each service, as well as 70 and 72 nonteratogen-exposed pregnancies from the MotherSafe and Motherisk centers, respectively, were added (Table 4). In this multicenter part of the study, the overall rate of major anomalies among those exposed to lithium during the first trimester after exclusion of genetic or cytogenetic anomalies was higher than that in the nonteratogenic exposure group. Cardiovascular anomalies were more common in the lithium (first trimester) group, even after excluding those cases that resolved. Additionally, the rate of noncardiovascular anomalies was higher in the lithium-exposed group. To assess the contribution of potential confounding variables to the increase in the overall rate of major anomalies among those exposed to lithium during the first trimester after exclusion of genetic or cytogenetic anomalies, logistic regression was carried out. The regression analysis was repeated for cardiovascular anomalies, cardiovascular anomalies that did not spontaneously resolve, and noncardiovascular anomalies. None of the predictors (i.e., additional psychiatric drugs, lithium dosage, pregnancy order, and Canada's Motherisk center) significantly contributed to the model, except for MotherSafe (Australia) as the service center, which was associated with a higher risk of major anomalies (overall anomalies: adjusted odds ratio=5.37, 95% CI=1.01–28.56, $p<0.05$; noncardiovascular anomalies: adjusted odds ratio=9.22, 95% CI=1.55–54.77, p=0.02).

Major congenital anomalies in the lithium and bipolar groups are listed in Table 5. Cardiovascular anomalies were diagnosed in five fetuses or neonates in the Israeli lithium group. Three of these five cardiovascular anomalies were either complex or a part of multiple anomalies. An additional complex cardiovascular anomaly was reported among the Canadian lithium cases. Two cases of ventricular septal defects spontaneously resolved. Ebstein's anomaly was diagnosed in one prospective case in the lithium group, which was included in the analysis. The woman in this case was treated with lithium (1,200 mg/day) and citalopram throughout pregnancy. She chose to terminate her pregnancy at 21 weeks after the diagnosis. In addition, Ebstein's anomaly was diagnosed in two retrospective cases in the lithium group that were not included in the analysis because the contact with the information service

TABLE 1. Maternal Characteristics and Obstetrical History of Study Participants

Characteristic	Lithium-Exposed Group (N=183)			Bipolar Disorder Comparison Group (N=72)			Nonteratogenic Exposure Comparison Group (N=748)			Analysis[a]		
	N	Total N	%	N	Total N	%	N	Total N	%	χ^2	df	p
Pregnancy order		171			71			716				
1st	48		28.1	26		36.6	191		26.7	3.2	2	0.20
2nd–4th	86		50.3[b]	39		54.9	438		61.2	7.2	2	**0.03**
≥5th	37		21.6[b,c]	5		7.0	87		12.2	13.4	2	**0.001**
Parity		172			71			717				
0	68		39.5	36		50.7[b]	227		31.7	12.7	2	**0.002**
1–3	82		47.7[b]	32		45.1[b]	458		63.9	21.8	2	**<0.001**
≥4	22		12.8[b]	3		4.2	32		4.5	17.6	2	**<0.001**
Previous miscarriage		170			71			712				
0	132		77.6	62		87.3	575		80.8	3.0	2	0.22
1	27		15.9	4		5.6	102		14.3	4.7	2	0.10
≥2	11		6.5	5		7.0	35		4.9	1.1	2	0.58
Previous elective termination of pregnancy	33	171	19.3[b]	9	71	12.7	60	712	8.4	17.4	2	**<0.001**
Cigarette smoking		170			62			704				
None	138		81.2[b]	48		77.4[b]	667		94.7	46.6	2	**<0.001**
<10 cigarettes per day	9		5.3	3		4.8	17		2.4	4.5	2	0.11
≥10 cigarettes per day	23		13.5[b]	11		17.7[b]	20		2.8	46.3	2	**<0.001**
	Median		Interquartile Range	Median		Interquartile Range	Median		Interquartile Range	K[d]	df	p
Gestational age (weeks) at initial contact with information service center	7		5–12[b]	6		5–9[b]	11		7–18	77.2	2	**<0.001**
	Mean		SD	Mean		SD	Mean		SD	F[e]	df	p
Maternal age (years)	32		6[b]	31		6	30		5	8.2	2	**<0.001**

[a] Values in bold indicate statistical significance ($p<0.05$).
[b] There were statistically significant differences in comparison with the nonteratogenic exposure group ($p<0.017$).
[c] There were statistically significant differences in comparison with the bipolar group ($p<0.017$).
[d] Data were compared using Kruskal-Wallis test.
[e] Data were compared using analysis of variance.

center was made after the prenatal diagnosis by ultrasound. In the first case, the woman was treated with lithium (1,200 mg/day) throughout pregnancy and chose to continue the pregnancy despite the prenatal diagnosis. She delivered a male infant at 38 weeks, with a birth weight of 2,900 g, who died at 6 months perioperatively. In the other case, the woman was treated with lithium (1,800 mg/day) and haloperidol throughout pregnancy. She chose to terminate her pregnancy at week 26 after diagnoses of Ebstein's anomaly, edema, and multiple anomalies. Thus, the absolute risk of Ebstein's anomaly among prospective cases from the Israeli Teratology Information Service was 1/123 (0.8%). However, taking into account the retrospective cases, the risk is increased to 2.4%. There were no cases of Ebstein's anomaly in the two comparison groups. It is worth noting that there was one fetus from the MotherSafe center prenatally diagnosed with anencephaly and multiple anomalies with exposure to lithium (1,500 mg/day), valproic acid (1,500 mg/day), venlafaxine, and olanzapine. In this case, the woman chose to terminate her pregnancy. The median age at follow-up was 15 months (interquartile range: 6–28) in the lithium group, 13 months (interquartile range: 6–27) in the bipolar group, and 12 months (interquartile range: 7–19) in the nonteratogenic exposure group (K=7.0, df=2, p=0.03). However, all the anomalies in the lithium group were diagnosed during pregnancy or in the first year of life, most perinatally.

To assess the association of potential confounding variables with the increase in the miscarriage rate in the lithium group, logistic regression was performed (for results of the logistic regression analysis, see Table 6). The significant predictors in the model were gestational age at initial contact with the information center, maternal age, previous miscarriages, and intrauterine exposure to lithium. Bipolar disorder and smoking during pregnancy were not significant predictors in this model.

To assess the association of potential confounding variables with the increase in cardiovascular anomalies in the

TABLE 2. Pregnancy Outcome in Lithium-Exposed Pregnancies and in Bipolar and Nonteratogenic Exposure Comparison Groups

Outcome	Lithium-Exposed Group			Bipolar Disorder Comparison Group			Nonteratogenic Exposure Comparison Group			Analysis[a]		
	N	Total N	%	N	Total N	%	N	Total N	%	χ^2	df	p
Delivery resulting in live birth	133	183	72.2[b,c]	59	72	81.9[b,d]	685[e]	748	91.6	49.9	2	**<0.001**
Miscarriage	30	183	16.4[b]	6	72	8.3	43	748	5.7	23.0	2	**<0.001**
Elective termination of pregnancy	17	183	9.3[a]	6	72	8.3[b]	15	748	2.0	25.8	2	**<0.001**
Stillbirth	3	183	1.6	0	72	0.0	5	748	0.7		[f]	[f]
Ectopic pregnancy	0	183	0.0	1	72	1.4	0	748	0.0		[f]	[f]
Preterm delivery (<37 weeks)	18	131	13.7[b]	6	59	10.2	41	683	6.0	10.2	2	**0.006**
	Median		Interquartile Range	Median		Interquartile Range	Median		Interquartile Range	K[g]	df	p
Gestational age at delivery (weeks)	40		38–40	39		38–40	40		38–41	4.0	2	0.14
Birth weight (grams)	3,200		2,775–3,500	3,100		2,600–3,550	3,240		2,900–3,600	5.2	2	0.07
	Mean		SD	Mean		SD	Mean		SD	F[h]	df	p
Birth weight, full-term (grams)	3,256		482	3,257		519	3,287		478	0.3	2	0.78

[a] Values in bold indicate statistical significance ($p<0.05$).
[b] Differences that reached statistical significance ($p<0.017$) were found when compared with the nonteratogenic exposure group.
[c] The cohort included four sets of twins.
[d] The cohort included two sets of twins.
[e] The cohort included 16 twin sets and two sets of triplets.
[f] Data are not applicable because more than 20% of the cells had an expected count less than 5.
[g] Data were compared using Kruskal-Wallis test.
[h] Data were compared using analysis of variance.

TABLE 3. Comparison of the Rate of Major Anomalies From the Israeli Teratology Information Service

Anomaly	Lithium-Exposed Group			Bipolar Disorder Comparison Group			Nonteratogenic Exposure Comparison Group		
	N	Total N	%	N	Total N	%	N	Total N	%
Major anomalies	8	140	5.7	3	61	4.9	24	711	3.4
Major anomalies without chromosomal or genetic conditions	8	123[a]	6.5	2	61	3.3	19	711	2.7
Cardiovascular anomalies	5[b]	123[a]	4.1[c]	2[b]	61	3.3	4	711	0.6
Cardiovascular anomalies excluding resolved cases	3[b]	123[a]	2.4	1[b]	61	1.6	2	711	0.3
Noncardiovascular anomalies	5[b]	123[a]	4.1	1[b]	61	1.6	15	711	2.1

[a] Data do not include non-first-trimester lithium exposures.
[b] Two cases of multiple anomalies in the lithium group and one case in the bipolar group counted twice, both as a cardiovascular and a noncardiovascular anomaly.
[c] Differences that reached statistical significance ($p<0.017$) were found when compared with the nonteratogenic group.

lithium group, logistic regression was performed (Table 7). The only significant predictor in the model was exposure to lithium (adjusted odds ratio=4.75, 95% CI=1.11–20.36). Pregnancy order, smoking 10 or more cigarettes per day, and bipolar disorder were not significant predictors of cardiovascular anomalies in this model.

In the lithium group, pregnancy complications were reported in 23.5% of cases. The most common of these complications were gestational diabetes, polyhydramnios, hypertension, toxemia, oligohydramnios, and polyuria/polydypsia. Neonatal complications were reported in 19.3% of offspring in the lithium group exposed close to term; these complications included respiratory problems, jaundice, tachycardia, tremor, sleepiness, and hypoglycemia.

Discussion

In this prospective, observational comparative cohort study, 183 lithium-exposed pregnancies were followed up by the Israeli Teratology Information Service. First-trimester

TABLE 4. Comparison of the Rate of Major Anomalies From Multicenter Data

	Group						Analysis[b]		
	Lithium-Exposed[a]			Nonteratogenic Exposure Comparison					
Center and Anomaly	N	Total N	%	N	Total N	%	χ^2	df	p
Australia		16			65				
Major anomalies without chromosomal or genetic conditions	4		25.0	0		0.0	17.094	1	**0.001**
Cardiovascular anomalies	0		0.0	0		0.0			
Cardiovascular anomalies excluding resolved cases	0		0.0	0		0.0			
Noncardiovascular anomalies	4		25.0	0		0.0	17.094	1	**0.001**
Canada		13			66				
Major anomalies without chromosomal or genetic conditions	1		7.7	2		3.0	0.646	1	0.421
Cardiovascular anomalies	1		7.7	0		0.0	5.142	1	0.165
Cardiovascular anomalies excluding resolved cases	1		7.7	0		0.0	5.142	1	0.165
Noncardiovascular anomalies	0		0.0	2		3.0	0.404	1	1.000
Combined multicenter data		152			842				
Major anomalies without chromosomal or genetic conditions	13		8.6	21		2.5	14.306	1	**0.001**
Cardiovascular anomalies	6		3.9	4		0.5	15.588	1	**0.001**
Cardiovascular anomalies excluding resolved cases	4		2.6	2		0.2	12.300	1	**0.006**
Noncardiovascular anomalies	9		5.9	17		2.0	7.696	1	**0.011**

[a] Data represent first-trimester exposure.
[b] Differences that reached statistical significance ($p<0.05$) are indicated in bold.

lithium exposure was associated with an increased risk (adjusted odds ratio=4.75 [95% CI=1.11–20.36]) of cardiovascular anomalies compared with nonteratogenic exposure. However, there were results that fell short of statistical significance for higher overall risk of major anomalies, higher risk of noncardiovascular anomalies, and higher risk of cardiovascular anomalies after excluding those anomalies that spontaneously resolved.

In the multicenter part of the study, 219 lithium-exposed pregnancies were followed up. Based on this multicenter analysis, first-trimester lithium treatment seems to be associated with an increased risk of major anomalies. The relative contribution of the three centers participating in the multicenter analysis (from Israel, Canada, and Australia) was not proportional to the country's population. Both Canada and Australia have much larger populations than Israel. However, the time frame of data collection differed among the three centers, with the Israeli Teratology Information Service covering 16 years, the Australian MotherSafe service covering 11 years, and the Canadian Motherisk service covering 4 years. These countries also differ in birth rate, with Canada and Australia having lower annual birth rates compared with Israel. Additionally, there may be differences between the three countries in the prevalence of bipolar disorder, prescription practices, and the medico-legal environment, as well as cultural differences in taking medications, partially explaining the different input. The regression analysis of the multicenter part of the study showed that the Australian service was associated with a higher risk of major anomalies. This finding raises concern regarding the possibility of selection bias. The relative contribution of abnormal findings in a small group may result in overestimation of risk.

The risk of cardiovascular anomalies appears to be higher than reported in previous prospective studies (20–22) but still lower than reported in the retrospective Lithium Baby Register (16–18). The association between lithium exposure during pregnancy and Ebstein's anomaly, previously reported in the literature, is supported by one prospective case and two retrospective cases in the present cohort. In the single-center part of the study, the absolute risk of overall major anomalies after lithium exposure during the first trimester of pregnancy was 6.5%, and the risk was 2.4% for cardiovascular anomalies that did not resolve spontaneously.

In the multicenter analysis, one fetus in the lithium-exposed group who was prenatally diagnosed with anencephaly and multiple anomalies also had been exposed to valproic acid (1,500 mg/day) during the first trimester, as well as venlafaxine and olanzapine. The anencephaly could potentially be explained by the exposure to valproic acid, although in human studies valproic acid has been associated mainly with lumbosacral neural tube defects (30–32). However, it is noteworthy that in a previous prospective study (21), two children in the lithium group had neural tube defects, one had hydrocephalus and meningomyelocele and also had been exposed to carbamazepine during the first trimester, and the other had spina bifida and tethered cord and had no additional drug exposures. A child with lumbar myelomeningocele after lithium exposure was reported in another prospective cohort study (20). Furthermore, there is a reported case of spina bifida

TABLE 5. Major Congenital Anomalies in the Lithium-Exposed and Bipolar Groups

Anomaly	Teratology Information Service	Lithium Exposure	Additional Exposure	Outcome, Sex, Birth Weight (Grams), and Gestational Age (Weeks)
Undescended testis, with surgery performed at 1 year	Israeli	900 mg/day decreased to 600 mg/day throughout pregnancy	None	Live birth; male; 3,500 g; 40 weeks
Muscular ventricular septal defect, spontaneously closed	Israeli	150 mg/day until week 12	Olanzapine	Live birth; female; 3,025 g; 39 weeks
Septal defect (two), single ventricle, skeletal dysplasia[a]	Israeli	900 mg/day throughout pregnancy	None	Elective termination of pregnancy; 700 g; 34 weeks
Bilateral hydronephrosis, right ureteropelvic junction obstruction, suspected pervasive developmental disorder	Israeli	750 mg/day throughout pregnancy	Topical neomycin methylprednisolone	Live birth; female; 3,025 g; 41 weeks
Multiple anomalies (heart, lungs)[a]	Israeli	900 mg/day throughout pregnancy	Perphenazine	Stillbirth (21 weeks)
Microtia operation planned at 7 years old, mild tricuspid regurgitation, twin	Israeli	1,200 mg/day throughout pregnancy	Olanzapine	Live birth; male; 2,090 g; 34 weeks
Ventricular septal defect closing	Israeli	900 mg/day decreased to 600 mg/day throughout pregnancy	None	Live birth; female; 3,240 g; 41 weeks
Ebstein's anomaly	Israeli	1,200 mg/day throughout pregnancy	Citalopram	Elective termination of pregnancy (21 weeks)
Diaphragmatic hernia, with surgery performed at 2 days old	MotherSafe (Australian)	NA (first trimester)	None	Live birth; female; 3,290 g; 36 weeks
Anencephaly, multiple anomalies[b]	MotherSafe (Australian)	1,500 mg/day throughout pregnancy	Valproic acid (1,500 mg/day), venlafaxine, olanzapine	Elective termination of pregnancy (12 weeks)
Left kidney agenesis, right enlarged, massive reflux	MotherSafe (Australian)	500 mg/day throughout pregnancy	None	Live birth; male; 2,840 g; 40 weeks
Talipes splints, with no family history	MotherSafe (Australian)	500 mg/day throughout pregnancy	None	Live birth; male; 3,300 g; 37 weeks
Atrial septal defect, ventricular septal defect transposition of great arteries, dilated pulmonary artery	Motherisk (Canadian)	300 mg/day until week 12	Doxylamine, vitamin B_6	Live birth; 3,555 g
Atrioventricular canal (normal karyotype), unilateral clubfoot, with surgery for both at 5 months old[a,b]	Israeli	None	Valproic acid (800 mg/day) until week 5, olanzapine (15 mg/day) throughout pregnancy	Live birth; male; 3,680 g; 40 weeks
Patent ductus arteriosus atrial septal defect, spontaneously resolved at 1 year, short frenulum, bilateral syndactyly of toes 2 and 3	Israeli	None	Lamotrigine (100 mg/day) until week 8	Live birth; male; 2,800 g; 41 weeks
45,X/46,XY mosaicism[c]	Israeli	None	Carbamazepine (200 mg/day), duloxetine (60 mg/day) until week 5	Live birth; male; 4,350 g; 39 weeks

[a] Counted as both a cardiovascular and a noncardiovascular anomaly.
[b] Potentially explained by other teratogens.
[c] Cytogenetic condition.

with meningoyelocele published in the 1970s (16, 32, 33). Some animal studies in rodents suggest that lithium salts are teratogenic and result in neural tube defects (9–11). Thus, five cases of neural tube defects (from the literature and the present study) in a relatively small group, although two with concurrent administration of other known

TABLE 6. Logistic Regression Analysis of Miscarriages[a]

Independent Variable	B	SE	Wald	df	p[b]	Adjusted Odds Ratio	95% CI
Maternal age (years)	0.078	0.028	7.854	1	**0.005**	1.08	1.02–1.14
Previous miscarriage	0.343	0.135	6.476	1	**0.01**	1.41	1.08–1.84
Exposure group			5.477	2	0.07		
Lithium	0.662	0.298	4.944	1	**0.03**	1.94	1.08–3.48
Bipolar disorder	–0.039	0.497	0.006	1	0.94	0.96	0.36–2.55
Smoking status			0.131	2	0.94		
<10 cigarettes per day	–0.138	0.792	0.030	1	0.86	0.87	0.19–4.11
≥10 cigarettes per day	–0.463	0.492	0.110	1	0.74	0.85	0.32–2.23
Gestational age (weeks) at initial contact with information service center	–0.215	0.042	25.913	1	<**0.001**	0.81	0.74–0.88
Constant	–3.398	0.943	12.991	1	<**0.001**	0.03	

[a] The dependent variable in this analysis is miscarriage, i.e., 0=no miscarriage and 1=miscarriage (model: χ^2=90.180, df=7, p<0.001; pseudo R^2=0.225; total number of cases included in the analysis, N=911).
[b] Differences that reached statistical significance (p<0.05) are indicated in bold.

TABLE 7. Logistic Regression Analysis of Cardiovascular Anomalies[a]

Independent Variable	B	SE	Wald	df	p[b]	Adjusted Odds Ratio	95% CI
Pregnancy order	0.190	0.146	1.675	1	0.20	1.21	0.91–1.61
Smoking ≥10 cigarettes per day	1.139	0.846	1.813	1	0.18	3.12	0.60–16.40
Exposure group			5.626	2	0.06		
Lithium	1.558	0.743	4.401	1	**0.04**	4.75	1.11–20.36
Bipolar disorder	1.692	0.903	3.509	1	0.06	5.43	0.93–31.90
Constant	–5.685	0.683	69.342	1	<**0.001**	0.003	

[a] The dependent variable in this analysis is cardiovascular anomalies, i.e., 0=no cardiovascular anomaly and 1=cardiovascular anomaly (model: χ^2=10.676, df=4, p=0.03; pseudo R^2=0.105; total number of cases included in the analysis, N=822).
[b] Differences that reached statistical significance (p<0.05) are indicated in bold.

teratogens associated with neural tube defects, raise the question of whether lithium exposure is also associated with neural tube defects or whether it potentiates the teratogenic effect induced by coadministration of valproic acid or carbamazepine.

The finding of a higher rate of cardiovascular anomalies in the bipolar group, relative to the lithium and nonteratogenic groups, that fell short of statistical significance may be a result of insufficient power of the relatively small sample size of the bipolar group or may be related to exposure to potential teratogens, such as valproic acid, as in the case of atrioventricular canal and clubfoot. Alternatively, this suggests that the risk might partly be attributed to the underlying bipolar disorder.

Further studies are needed to determine whether lithium is also associated with an increased risk for noncardiovascular anomalies. According to the logistic regressions, gestational age at initial contact with the information service center, maternal age, previous miscarriage, and exposure to lithium significantly predicted the risk of miscarriage. However, lithium exposure was the only significant predictor of cardiovascular anomalies.

Increased risk of preterm delivery among infants of women treated with lithium during pregnancy has been previously reported (34). The increased risk of preterm deliveries in lithium-exposed offspring may be associated with the underlying disorder. In another study, pregnant women with bipolar disorder had a twofold increase in the rate of preterm delivery compared with pregnant women with no history of mental illness (35). In the present study, birth weight was not higher in the lithium group, as suggested in a previous prospective study (21).

Our study has certain limitations and advantages. The study is based primarily on pregnancies of women who made contact with the Israeli Teratology Information Service, which may not represent the general population. However, we included two comparison groups, one unexposed to lithium but with psychiatric illness similar to that of the lithium group (although this comparison group was relatively small and occasionally exposed to potential teratogens) and also counseled by the Israeli Teratology Information Service and a second group counseled by the same service for nonteratogenic exposure using the same methodology of data collection. Detection bias is especially common when a concern about drug safety has been previously reported, as in our study. For example, offspring exposed in utero to lithium are more likely to be assessed for cardiovascular anomalies than unexposed offspring. To minimize this bias, standardized questionnaires were used in all groups; medical records were used for cases with congenital anomalies, when available; and the classification of anomalies was done by a pediatrician who was blinded to the exposure group. In addition, routine prenatal diagnosis is performed in Israel,

Australia, and Canada. Detection bias is probably a more significant problem with congenital anomalies of lesser clinical significance than with severe anomalies resulting in serious clinical consequences. Unfortunately, the rate of general incidence of major anomalies by country statistics was not available for comparison. The study relies on maternal interview as the primary source for outcome data and lacks medical records in most cases. Physical examinations of neonates are routinely performed in the participating countries; however, the study lacks direct physical examination by an investigator as part of the protocol. Additionally, there is variation in timing of follow-up. Data are primarily from a single center. There is a multicenter part in which data were combined from three services, one in Israel, one in Australia, and one in Canada. The study design is nonrandomized, and it has limited power to detect specific rare defects. Randomized controlled trials are often not feasible in pregnancy because of ethical considerations. However, applying the same procedure to all arms of the study and its prospective nature minimizes these potential biases. Another advantage of the study is that data were available on elective terminations of pregnancies and stillbirths and were included in the analysis. Finally, the relatively large number of lithium-exposed cases gives reasonable power.

The conclusions drawn from observational epidemiological studies are often hampered by the problem of confounding. Such confounders can be found in maternal characteristics, such as age, parity, smoking, alcohol use, body mass index, ethnic background, concomitant drug exposure, and the underlying disorder (36). Selection and reporting biases, along with cognitive biases, are additional potential problems. In our study, logistic regression analysis was performed to assess the relative contribution of various available predictors to the differences in the rate of miscarriages and major anomalies. Maternal body mass index was only partially available and therefore not included as a predictor. In an attempt to address the problem of confounding by indication, comparison including a group of pregnant women with bipolar disorder and no exposure to lithium was conducted. Further studies are needed to accurately assess the risk associated with lithium treatment in pregnancy, as well as the risks associated with the underlying bipolar disorder.

When evaluating the risk-benefit ratio of lithium treatment in pregnancy, the risks associated with treatment discontinuation, as well as with alternative mood stabilizers, should also be considered. Discontinuation of mood stabilizer treatment, particularly abruptly, during pregnancy carries a high risk of morbidity in women with bipolar disorder (1, 37). Untreated or undertreated bipolar disorder during pregnancy may also increase the risk of poor pregnancy outcome and perinatal complications (38). In a prospective observational clinical study, the overall risk of at least one relapse of bipolar disorder in pregnancy was 71% (1). Women who discontinued mood stabilizer treatment, compared with those who continued treatment, had a twofold increased risk of recurrence, shorter time to first recurrence, and longer duration of recurrence. In a Swedish population-based cohort study, women with bipolar disorder, regardless of treatment with mood stabilizers, had increased risk of adverse pregnancy outcome, such as delivering a preterm infant (36). Infants of women with untreated bipolar disorder had increased risk of microcephaly and neonatal hypoglycemia. The risk of any congenital malformation in offspring of women with bipolar disorder in pregnancy in the Swedish study was 3.4% among treated women, compared with 1.9% among untreated women.

Lithium remains one of the mainstays for treatment of bipolar disorder, even during pregnancy. A clinical alternative, valproic acid, is both a human teratogen and a neurobehavioral teratogen and therefore is not recommended during pregnancy. Carbamazepine, another optional mood stabilizer, also carries a teratogenic risk. Human pregnancy experience with lamotrigine is generally reassuring; however, its effectiveness, especially in the treatment of mania, is questionable. In conclusion, the decision whether to continue lithium therapy during pregnancy should be made on an individual basis. The risks of lithium exposure in pregnancy need to be weighed against the risks of untreated bipolar disorder. Folate supplementation, with 5 mg daily before and during pregnancy, may be advisable for women who continue lithium during pregnancy to prevent neural tube and cardiovascular defects. Women who are treated with lithium during organogenesis should undergo fetal echocardiography in addition to level-2 ultrasound.

Previously presented in part at the 19th International Conference of the Organization of Teratology Information Specialists, June 24–27, 2006, Tucson, Ariz., and the 25th International Conference of the Organization of Teratology Information Specialists, June 22–26, 2012, Baltimore. Received Nov. 8, 2012; revisions received Aug. 7 and Nov. 21, 2013; accepted Feb. 10, 2014 (doi: 10.1176/appi.ajp.2014.12111402). From the Israeli Teratology Information Service, Israel Ministry of Health, Jerusalem; the Hebrew University Hadassah Medical School, Jerusalem; MotherSafe, Royal Hospital for Women, Sydney, Australia; and the Motherisk Program, Hospital for Sick Children, Toronto. Address correspondence to Dr. Diav-Citrin (orna.diav-citrin@moh.health.gov.il).

Adrienne Einarson has received consulting fees from Eli Lilly for a duloxetine pregnancy registry. All other authors report no financial relationships with commercial interests.

The Motherisk Program has received an unrestricted educational grant from Eli Lilly to study the safety of duloxetine in pregnancy.

The authors thank Yael Glazer and Dr. Isabella Karakis from the Division of Epidemiology, Israel Ministry of Health, Jerusalem, for their valuable advice and contribution to the statistical analysis and presentation of data.

References

1. Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Reminick A, Zurick A, Cohen LS: Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. Am J Psychiatry 2007; 164: 1817–1824, quiz 1923

2. Schou M, Amdisen A: (letter): Lithium and the placenta. Am J Obstet Gynecol 1975; 122:541
3. Mizrahi EM, Hobbs JF, Goldsmith DI: Nephrogenic diabetes insipidus in transplacental lithium intoxication. J Pediatr 1979; 94:493–495
4. Johansen KT: Lithium teratogenicity. Lancet 1971; 1:1026–1027
5. Gralla EJ, McIlhenny HM: Studies in pregnant rats, rabbits and monkeys with lithium carbonate. Toxicol Appl Pharmacol 1972; 21:428–433
6. Szabo KT: Teratogenic effect of lithium carbonate in the foetal mouse. Nature 1970; 225:73–75
7. Marathe MR, Thomas GP: Embryotoxicity and teratogenicity of lithium carbonate in Wistar rat. Toxicol Lett 1986; 34:115–120
8. Wilby OK, Tesh SA, Ross FW, Tesh JM: (abstract): Effects of lithium on development in vitro and in vivo in the rat. Teratology 1987; 35:69
9. Jurand A: Teratogenic activity of lithium carbonate: an experimental update. Teratology 1988; 38:101–111
10. Hansen DK, Walker RC, Grafton TF: Effect of lithium carbonate on mouse and rat embryos in vitro. Teratology 1990; 41:155–160
11. Giles JJ, Bannigan JG: The effects of lithium on neurulation stage mouse embryos. Arch Toxicol 1997; 71:519–528
12. Nora JJ, Nora AH, Toews WH: (letter): Lithium, Ebstein's anomaly, and other congenital heart defects. Lancet 1974; 2:594–595
13. Park JM, Sridaromont S, Ledbetter EO, Terry WM: Ebstein's anomaly of the tricuspid valve associated with prenatal exposure to lithium carbonate. Am J Dis Child 1980; 134:703–704
14. Allan LD, Desai G, Tynan MJ: Prenatal echocardiographic screening for Ebstein's anomaly for mothers on lithium therapy. Lancet 1982; 2:875–876
15. Long WA, Willis PW 4th: Maternal lithium and neonatal Ebstein's anomaly: evaluation with cross-sectional echocardiography. Am J Perinatol 1984; 1:182–184
16. Schou M, Goldfield MD, Weinstein MR, Villeneuve A: Lithium and pregnancy, I: report from the Register of Lithium Babies. BMJ 1973; 2:135–136
17. Weinstein MR, Goldfield M: Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry 1975; 132:529–531
18. Frankenberg FR, Lipinski JF: Congenital malformations. N Engl J Med 1983; 309:311–312
19. Källén B, Tandberg A: Lithium and pregnancy: a cohort study on manic-depressive women. Acta Psychiatr Scand 1983; 68:134–139
20. Cunniff CM, Sahn DJ, Reed KL, Chambers CC, Johnson KA, Jones KL: (abstract): Pregnancy outcome in women treated with lithium. Teratology 1989; 39:447–448
21. Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, Donnenfeld AE, Rieder M, Santelli R, Smythe J, Pastuszak A, Einarson T, Koren G: Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet 1992; 339:530–533
22. Briggs GG, Freeman RK, Yaffe SJ (eds): Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 8th ed. Philadelphia, Lippincott Williams and Wilkins, 2008, p 1064
23. Warkany J: Teratogen update: lithium. Teratology 1988; 38: 593–597
24. Källén B: Comments on teratogen update: lithium. Teratology 1988; 38:597
25. Sípek A: Lithium and Ebstein's anomaly. Cor Vasa 1989; 31: 149–156
26. Zalzstein E, Koren G, Einarson T, Freedom RM: A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol 1990; 65:817–818
27. Edmonds LD, Oakley GP: (abstract): Ebstein's anomaly and maternal lithium exposure during pregnancy. Teratology 1990; 41:551–552
28. Schou M: What happened later to the lithium babies?: a follow-up study of children born without malformations. Acta Psychiatr Scand 1976; 54:193–197
29. Yacobi S, Ornoy A: Is lithium a real teratogen? What can we conclude from the prospective versus retrospective studies?: a review. Isr J Psychiatry Relat Sci 2008; 45:95–106
30. Bjerkedal T, Czeizel A, Goujard J, Kallen B, Mastroiacova P, Nevin N, Oakley G Jr, Robert E: Valproic acid and spina bifida. Lancet 1982; 2:1096
31. Omtzigt JG, Los FJ, Grobbee DE, Pijpers L, Jahoda MG, Brandenburg H, Stewart PA, Gaillard HL, Sachs ES, Wladimiroff JW, Lindhout D: The risk of spina bifida aperta after first-trimester exposure to valproate in a prenatal cohort. Neurology 1992; 42(suppl 5): 119–125
32. Vacaflor L, Lehmann HE, Ban TA: Side effects and teratogenicity of lithium carbonate treatment. J Clin Pharmacol J New Drugs 1970; 10:387–389
33. Aoki FY, Ruedy J: Severe lithium intoxication: management without dialysis and report of a possible teratogenic effect of lithium. Can Med Assoc J 1971; 105:847–848
34. Troyer WA, Pereira GR, Lannon RA, Belik J, Yoder MC: Association of maternal lithium exposure and premature delivery. J Perinatol 1993; 13:123–127
35. Lee HC, Lin HC: Maternal bipolar disorder increased low birth weight and preterm births: a nationwide population-based study. J Affect Disord 2010; 121:100–105
36. Bodén R, Lundgren M, Brandt L, Reutfors J, Andersen M, Kieler H: Risks of adverse pregnancy and birth outcomes in women treated or not treated with mood stabilisers for bipolar disorder: population based cohort study. BMJ 2012; 345:e7085
37. Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ: Risk of recurrence of bipolar disorder in pregnant and nonpregnant women after discontinuing lithium maintenance. Am J Psychiatry 2000; 157:179–184
38. Jablensky AV, Morgan V, Zubrick SR, Bower C, Yellachich LA: Pregnancy, delivery, and neonatal complications in a population cohort of women with schizophrenia and major affective disorders. Am J Psychiatry 2005; 162:79–91

Clinical Guidance: Lithium in Pregnancy

Lithium taken during the first trimester of pregnancy appears to increase the risk of cardiovascular anomalies in infants, although some of these anomalies resolve spontaneously. Lithium also raises the likelihood of miscarriage. On the other hand, the risk of illness recurrence is high for women who discontinue taking medication during pregnancy, and so the decision should be made on an individual basis. Diav-Citrin et al. recommend that women treated with lithium during organogenesis receive fetal echocardiography and level-2 ultrasound. Bergink and Kushner add in an editorial (p. 712) that guidelines favor using a single medication during pregnancy and that twice-a-day dosing helps avoid high peak lithium serum levels.