Is Lithium a Real Teratogen? What Can We Conclude from the Prospective Versus Retrospective Studies? A Review

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Abstract: Background: Lithium is a drug used mainly for the treatment of Bipolar Disorder (BD). Case reports and several retrospective studies have demonstrated possible teratogenicity, but the data in the different studies was inconclusive. *Methods*: We summarized all published studies in English, including case reports. *Results*: We found 24 case reports, of which six infants had congenital anomalies, five having cardiac anomalies, one of them being Ebstein's anomaly. In the retrospective studies there were, in the Lithium Baby Registry, 225 registered cases with 25 anomalies, 18 of them being cardiac, of which six had Ebstein's anomaly. An additional retrospective study on 59 cases found seven anomalies, four of them being cardiac. On the other hand, none of the prospective studies (296 liveborn infants) demonstrated any increase in the rate of congenital anomalies, although two had Ebstein's anomaly. All case control studies regarding Ebstein's anomaly were negative, and among 222 infants with Ebstein's anomaly and 44 with tricuspid atresia none of the mothers had taken lithium during pregnancy. *Conclusions*: Considering the serious limitations of the retrospective and case control studies that are also retrospective, lithium does not seem to be a significant teratogen, and hence should be given, if indicated, in pregnancy. It is, however, advisable to perform a fetal echocardiography to exclude the possibility of cardiac anomalies. Lamotrigine seems to be a possible alternative.

Introduction

The teratogenicity of lithium following administration during the first trimester, or throughout pregnancy, has been demonstrated by several authors, exhibiting high rates of cardiovascular defects, in particular Ebstein's anomaly.

Following these reports, the Lithium Baby Register was founded in 1968 (1). Ever since, case reports, case control, retrospective and prospective studies have been performed, along with animal studies, in order to evaluate the real embryotoxic effect of lithium on the human embryo.

Lithium ions equilibrate across the placenta, and therefore the concentrations in the maternal and fetal plasma are almost equal. As a result, lithium intoxication among mothers and neonates has been reported, the prevalent post-natal symptoms being: low Apgar score, heart failure, hypotonicity and nephrogenic diabetes insipidus (2).

In this review we survey and summarize all human data published in the English literature and draw conclusions regarding fetal effects of lithium therapy during pregnancy. These conclusions could lead to establishing a policy for both psychiatrists and gynecologists while treating women with bipolar disorders (BD) during pregnancy.

Methodology

We reviewed all studies that discussed the teratogenic and embryotoxic effect of Li intake during pregnancy on infants born to mothers with BD. For this purpose data were obtained from all published studies and case reports in English, referenced in Medline between the years 1969 and 2005 that included the key words: lithium and pregnancy, with related phrases such as lithium and embryotoxicity, lithium and teratogenicity, lithium and Ebstein's anomaly, lithium, pregnancy and Ebstein's anomaly and lithium and cardiac anomalies. This review surveys case report studies (including 24 separate cases) between the years 1969–2005; retrospective studies; a follow-up study and controlled prospective studies.

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Results

Case Report Studies

We found 24 studies (3–26) each reporting one case. Nine of these infants (one of which was stillborn) were born to mothers with BD, who were treated some time during pregnancy with lithium only. The remaining 15 women were also treated with antidepressants and/or anti-psychotics or other drugs.

Pregnancy outcome: Generally, gestational age at delivery was lower because of a higher rate of prematurity (6/23) in liveborn infants. Birth weight was higher in the eight infants born to mothers on lithium monotherapy in comparison to the polytherapy, with two being Large for Gestational Age (LGA). In the polytherapy group there was only one LGA infant (Table1a).

Perinatal toxicity: Lithium had the potential for perinatal toxicity as reported in 78% (19/23) of the liveborn infants (Table 1b). Most of these effects were transitory and self limiting, lasting between hours and a few weeks, partly because of the prolonged half life of the lithium in the newborn's serum. The complications included: goiter, respiratory distress, apnea, cyanosis and asphyxia, cardiomegaly, A-V block, atrial flutter supra-ventricular tachycardia, poor reflexes and hypotonicity. In the polydrug therapy, similar complications were observed, but the rate of goiter was higher (three cases, of which one had also transient hypothyroidism). Further subdivision of the complications is as follows (Table 1b).

Neuromuscular: The occurrence of cyanosis, hyporeflexia and flaccid muscle tone in an infant of a mother treated with lithium was first recorded by Wilbanks et al. in 1970 (6). Although serum lithium levels in the mothers were within normal limits, those of the infants were much higher (2.4 and 2.2 mEq/L), dropping gradually within 13 days (27). Neuromuscular effects were described in eight of the case reports (6, 8, 9, 11, 16, 21, 25, 28).

Neonatal goiter: Maternal lithium ingestion during pregnancy is known to occasionally cause goiter in the infants, as well as in the mother. We found four cases of goiter from the 23 reported cases (10, 12, 15, 23). Goiter was accompanied in one case by transient neonatal hypothyroidism. Neonatal goiter was described in these infants in addition to other complications such as respiratory, neurological and hematological complications.

Urinary — Polyhydramnios and nephrogenic diabetes insipidus (NDI): The most common side effect of lithium is polyuria, a form of NDI. Since lithium crosses the placenta, Ang et al. (20) postulated that fetal polyuria resulting in polyhydramnios emerges by the same mechanism as the maternal. Among the case reports, five cases of polyhydramnios were reported (12, 14, 16, 20, 21) and two cases of NDI (21, 24).

Relation between lithium blood levels and perinatal complications: Four of the 23 reported liveborn infants did not show after birth any remarkable findings on examination. Their serum Li levels were 0.37, 0.57 0.9 and 1.0 mEq/L, within normal therapeutic range. Both maternal and newborn's serum levels were similar (4, 5, 7, 18). The lithium serum levels of the newborns that exhibited neonatal toxicity were, in several cases, below 1.0 mEq/L, but in many it was much higher, the highest level being 46 mEq/L (29). In view of these results, it seems possible to link maternal and/or fetal blood Li levels with postnatal complications.

Congenital Malformations

Of the eight Li-only exposed infants, two had cardiac anomalies; one of them was Ebstein's anomaly and the second patent ductus arteriosus (PDA). A third case had delayed motor development (Table1c).

In the 15 cases of multi-drug therapy, there were three infants with cardiovascular anomalies; one had dextrocardia, PDA and Juxta ductal aortic coarctation; another had PDA and the third tricuspid regurgitation, which spontaneously resolved. Two had developmental delay. No Ebstein's anomaly was reported (Table1c).

Of the total 23 reported liveborn infants, only six had congenital anomalies. Another three had developmental retardation while the others had various complications of pregnancy. An additional case was of a macerated stillborn infant. It is clear that there was no specific pattern of anomalies, although most (5/6) had cardiac anomalies.

Table 1a. *The effect of in-utero exposure to lithium on birth weight and prematurity rate among infants born to women with bipolar disorder in 23 * separate case reports*

Medication used in pregnancy	Gestational age (wks)** / range	Median birth weight gr / range	Term born / premature (<36) / LGA
Lithium only		3,305	4 /
	36.66±3.98		2 /
	30–40	1,550–4,430	2 /
Lithium and other drugs		2,873	10 /
	37.1±2.97		4 /
	32–42	1526–4593	/ 1
Both groups		3,030	14 /
	36.73±36.97		6 /
	30–42	1526–4593	3 /

* one additional stillborn infant from lithium was macerated and excluded.

** Mean ± SD

Table 1b. *The effect of in-utero exposure to lithium on perinatal complications among infants born to women with bipolar disorder — results of 23* separate case reports*

Medications used in pregnancy /n	Perinatal complications									
	RDS no.	Apnea no.	Cyanosis no.	Asphyxia no.	Atrial flutter /cardiomeg.	Syst. murm / A-V block	Goiter / Hypothyr.	Hepatomeg.	Poor refllexes / Hypotonia	Polyhydra. / NDI
Lithium only / 8	3	1	2	1	2 / 2	1 / 1	1 / 0	0	1 / 1	2 / 0
Lithium and other drugs /15	2	3	4	0	0 / 3	3 / 0	3 / 1**	3	6 / 7	5 / 2
Both groups / 23	5	4	6	1	2 / 5	4 / 1	4 / 1**	3	7 / 8	7 / 2

* one additional stillborn infant from lithium was macerated and excluded.

** One out of three mentioned

RDS — Respiratory distress syndrome

NDI — nephrogenic diabetes insipidus

Table 1c. *The effect of in-utero exposure to lithium on malformations rate, developmental retardation, maternal lithium levels and cord lithium levels among infants born to women with bipolar disorder — results of 23 separate case reports*

Medications used in pregnancy /n	Major malformations				Other malformations		Maternal lithium levels mEq /L (range)	Cord lithium levels mEq /L (range)
	Ebstein's anomaly	Tricuspid regurgit.	PDA	Skeletal malform.	Total no. / malformat.	Psychomotor retardation		
Lithium only / 8	1	0	1	0	2	1 n =6	0.55–1.8 n=2	0.37–0.9
Lithium and other drugs /15	0	1	2ᵃ	1	4	2 n=11	0.6–4.0 n=6	0.7–4.6
Both groups / 23	1	1	3	1	6	3 (1 year) n=15	0.55–4.0 n=5	0.7–4.0

a — one case had also dextrocardia and aortic coarctation; one malformation was skeletal: errors of segmentation of upper thoracic spine

n — number of live infants

Table 2. *The effect of in-utero exposure to lithium on malformations rate, among 225 infants born to women with bipolar disorder (of the Lithium Registry) (29)*

Treatment group no. of cases	Malformed infants (no.) / %	Birth weight range	Ebstein's anomaly (no.)	Other card-vasc. defects	CNS defects (no.)	Other malform. (no.)	Postnatal death / stillbirth
225	25 11.1	1880–4100	6	12	3	4	10^a / 7^b

CNS — central nervous system

Another two Down's syndrome and one case of congenital toxoplasmosis were documented

a — number of postnatal death out of the 25 malformed infants

b — number of stillbirth out of 225 cases of lithium registry

Table 3. *The effect of lithium therapy in 84 * women with bipolar disorder on birth weight and gestational age at birth (32)*

Gestational age / no. of cases	Mean lithium intake mg/d	Gestational age (week) mean ± SD	birth weight / grams mean ± SD	LGA no. (%)
Term deliver. >36wk / 54	984; 680; 726 (1st, 2nd, 3rd,tr.)	38.9 ±1.4 64.3%	3490 ± 0.52	8 (15.0%)
Premat.deliv. < 36 wks. / 30	1270, 1090, 998 (1st, 2nd, 3rd,tr.)	34.2 ± 2.9 30 (35.7%)	2990 ± 0.78 a	11 (37.0 %)

* 84 complete maternal-infant records of 252 records from the international lithium register (1968–1983)

a — prematures compared to term infants p < 0.01

LGA — Large for gestational age

Although in the reported cases most anomalies were of the cardiovascular system, we must keep in mind that we do not know the number of the unreported lithium-treated women with normal children, a fact that we have to consider when evaluating case reports.

Retrospective studies

Lithium babies registry

In a retrospective study published in its final form in 1980, including all 225 cases of the registry, Weinstein (29) reported 25 malformed infants from a total of 225 reported lithium babies (11.1%). This rate consisted of 18 (8%) cardiovascular defects — six of which were Ebstein's anomaly. The other seven defects involved different systems. Ten of the 25 malformed infants died during the first postnatal week (Table 2). In addition to the 25 malformed infants, there were seven stillborn infants, two children had Down syndrome and one had congenital toxoplasmosis. This registry was published partly in

several other studies, by Weinstein and Goldfield (30), Weinstein (1, 31), and by Schou et al. (28).

Troyer et al. (32) reviewed the records of these 225 infants from the International Registry of Lithium Babies and found 84 complete maternal-infant data that included gestational age at delivery and birth weight. They found that lithium therapy during pregnancy increased the incidence of premature birth, as over one-third (35.7%) were prematurely born. They also demonstrated more than two-fold increase in large for gestational age infants (LGA) among prematures compared to the term born infants (37% vs15.0%, Table 3).

Retrospective cohort study

From a total of 350 infants born to manic-depressive women, information was obtained by Kallen and Tandberg (33) for 287 cases (82%). In this group, a sub-group of 59 infants exposed to either lithium alone or lithium in combination with other psychotropic agents was compared to 190 untreated women and to 38 women treated with antidepressants other

than lithium. In the 59 Li-exposed group, a 10.2% neonatal death rate was reported, as well as a 11.9% malformation rate (seven infants) and 6.8% (four infants) rate of heart defect (Table 4). Although the rate of anomalies among the lithium-treated newborns was higher as compared to control untreated manic-depressive women, the difference was not statistically significant and, due to the small sample size, could still be random. Ebstein's anomaly was not demonstrated.

Nested case-control study: Kallen (34) evaluated all infants with cardiac defects born to 716 women hospitalized for BD and compared two matched controls for each malformed infant. Fourteen cardiac defects were identified, more than twice the expected rate. One infant had a chromosomal anomaly and was therefore excluded. Among the 13 left, seven had Ventricular Septal Defect and two had a systolic murmur — all considered to be relatively mild cardiac anomalies. The others had other cardiac anomalies, including one case of Ebstein's anomaly that was not exposed in utero to lithium or other antidepressants. There was no significant difference in the rate of exposure to lithium between the malformed (3/13) and the control infants (4/20). Thus, lithium could not be associated with the increase in the rate of cardiac anomalies. One possible explanation for the lack of this association, given by the author, was the fact that most women stopped lithium once pregnancy was diagnosed.

Retrospective case control study: Czeizel and Racz (35) studied 10,698 children with congenital anomalies between the years 1980–1987. Their study included all malformed still-born and live-born cases diagnosed from birth till the age of one year, as well as prenatally diagnosed and electively terminated malformed fetuses. They observed no association with maternal lithium use during pregnancy; however, only six infants were exposed to lithium.

Studies on cardiac anomalies, especially Ebstein's anomaly

In a joint case-control study Kallen (36) collected 25 cases of Ebstein's anomaly and 44 cases of tricuspid atresia. In addition, he added 15 cases of Ebstein's anomaly that were reported in France. None of these infants with Ebstein's anomaly or with tricuspid atresia were exposed in-utero to lithium (Table 5).

Sipek (37) reported 89 cases of infants with Ebstein's anomaly in a Czech study, conducted between 1960–1985. None of their mothers were treated with lithium during pregnancy. The author, however, could not rule out possible occupational exposure to lithium. No statistical differences were found in exposure to lithium between these mothers and a control group of women with children without anomalies (7.1% vs. 11.4%).

Table 4. *The effect of treatment with lithium taken by 59 women with bipolar disorder on neonatal death and malformation rate — a retrospective cohort study (33)*

Treatment group no. / %	Total no. of infants no. / %	neonatal death no. / %	malformed infants no. / %	dead & malformed	heart defects
B-D untreated women	190	3	8	2	2**
		1.6	4.2	1.0	1.05
Psychotrophic drugs — not lithium	38	1	1	0	0
		2.6	2.6		
Lithium ± other psychotr. drugs	59	6	7	4	4*
		10.2	11.9	6.8	6.8

* out of the four malformed infants: three died and one with transposition of great vessels survived the neonatal period
** one infant also had Down syndrome

Table 5. *The link between lithium therapy during pregnancy and the rate of Ebstein's anomaly among infants of women with B–D performed by four different researchers and analyzed by Cohen et al. (44)*

Authors	year	Lithium Exposure among		
		Ebstein's Infants	tricuspid atresia	Control
Kallen	1988	0 / 40	0 / 44	0 / 138
Sipek	1989	0 / 89	none	0 / 178
Zalzstein et al.	1990	0 / 59	none	1 / 168
Edmonds & Oakley	1990	0 / 34	unknown	0 / 34
Total no.of cases		0 / 222	0 / 44	1 / 518

Zalzstein et al. (38) analyzed data from 59 patients diagnosed as having Ebstein's anomaly, using 168 children with neuroblastoma as a control group. They found that none of the mothers of the 59 children had lithium therapy during pregnancy. These results led them to the conclusion that lithium does not increase the rate of cardiac anomalies, especially of Ebstein's anomaly.

In a case-control study, Edmonds and Oakley (39) compared 76 infants who were "possibly" born with Ebstein's anomaly with the same number of control infants. Of the 76 infants, 34 were confirmed as Ebstein's anomaly. However, none of them or of the control group were born to women with BD or were exposed to Li during pregnancy.

Ebstein's anomaly and lithium: A direct link?

Ebstein's anomaly is defined as downward displacement and malformation of the tricuspid valve, often together with atrial septal defect (ASD) and right ventricular hypoplasia. The basal risk rate of Ebstein's anomaly is about 1:20,000 live births in the general population (40, 41). Once exposed to lithium during the first trimester of pregnancy, the risk for Ebstein's anomaly apparently mounts to 1:1,500 births. The cardiac teratogenic effects of early exposure to lithium had been proven to be less ominous than originally thought (41–43).

Confirmation for the doubts as to the possible link between lithium and the rare Ebstein's anomaly came from two studies summarizing data regarding lithium exposure during pregnancy and Ebstein's anomaly. Cohen et al. (44) analyzed 207 infants iden-

tified as having Ebstein's anomaly from four different case-control studies mentioned above (36–39) None of the 207 children with Ebstein's anomaly was found to be exposed to lithium during pregnancy, whereas two children of the 398 controls were exposed to lithium in-utero. Following this analysis, the risk for Ebstein's anomaly, estimated by Cohen et al. (44) ranged between 0.1% (1:1000) and 0.05% (1:2000) births. The risk of other cardiovascular defects among infants born to mothers who consumed lithium in pregnancy ranged between 0.9% (similar to controls) in prospective studies to 12% in retrospective studies. Another support comes from Shepard et al. (45) who analyzed 180 cases of Ebstein's anomalies from the same case-control studies and found that none of the malformed infants was exposed in utero to lithium. Kallen (34) supposed that, in spite of all the results that link Li-therapy during pregnancy to high rates of severe cardio-vascular malformation, there is a possibility that the psychiatric disease itself or genetic dispositions for the disease may link lithium and consequent cardiac malformations. Therefore, in order to verify or disprove the real correlation between Li-therapy in pregnancy and teratogenicity, much larger prospective studies should be performed. The results of an American Expert Scientific Committee on lithium in pregnancy were published by Moore in 1995 (46).

In summary: While two retrospective studies show a significant association between Li intake by the pregnant mother and cardiac anomalies and one did not, the studies mentioned above regarding 222 cases of Ebstein's anomaly and 44 cases of other cardiac anomalies are entirely negative. Thus, if a corre-

lation between in utero lithium exposure and Ebstein's anomaly exists, it is weak.

Prospective studies

We found only one record linkage study and two published prospective studies regarding lithium use in pregnancy, and they were all negative regarding major anomalies.

In a record linkage study of Michigan Medicaid recipients (Rosa, personal communication (47) cited by Briggs et al. (48), only two (3.2 %) of 62 infants of women treated with lithium during the first trimester of pregnancy were reported to have major congenital anomalies, and none of them was cardiac.

In an uncontrolled prospective study Cunniff et al. (49) identified 72 lithium-treated women with BD. Of these, six had pregnancy termination, four resulted in first trimester spontaneous abortions and 12 were lost to follow-up. Only 50 were known as live-born infants, two of them reported as having major malformations: one lumbar myelomeningocele and the other unilateral inguinal hernia. The rate of anomalies was not different from that generally observed in controls. There were no cases of cardiac anomalies.

In another controlled prospective study, Jacobson et al. (50) studied the pregnancy outcome of 138 Li-exposed pregnant women (who gave birth to 105 liveborn infants), and 148 controls. They observed

one case of Ebstein's anomaly, but failed to show any differences with respect to major congenital anomalies and number of livebirths between controls and lithium exposed group (Table 6).

In the lithium-exposed group, four malformations were observed: two neural tube defects, one of which was exposed also to carbamazepine. The third infant had meromelia and died because of prematurity, and one fetus was diagnosed as severe Ebstein's anomaly at 16 week gestation and pregnancy was terminated. In the control group the three anomalies observed were: ventricular septal defect (VSD); congenital hip dislocation (CDH) and cerebral palsy (CP) with torticolis. Birth weight was higher in the lithium group (Table 6).

In the controlled prospective study from our Israeli Teratogen Information Service, yet unpublished, Diav-Citrin et al. (51) observed, among 105 pregnant women exposed in pregnancy to lithium (86% were exposed from the first trimester), 79 liveborn infants. Two infants were malformed (2.9%). One infant had cryptorchidism that was operated and the other had Ebstein's anomaly. This was compared to 1,234 control infants with 39 cases of major malformations (3.2%), none of which had Ebstein's anomaly. In addition, there was an 8.7% rate of pregnancy interruptions (vs. 2.9 in the controls) and 14.3% of spontaneous abortions (vs. 5.9% in the controls).

In summary: Of a total of at least 377 lithium treated

Table 6. *The effect of lithium therapy given to women with B-D on pregnancy outcome and malformation rate among their infants — a controlled prospective study (50)*

Treatment group / no. of cases	Lithium intake 1st trimester mean / range	normal livebirth / stillbirth no. (%)	term delivery / premat. no. (%)	birth weight* / range gestational age* / range	spontan. abortions / therapeut. no. (%)	maternal age* / range	congenital malformat.	Types of malformations
Li-exposed / 138	927mg/d 50-2400mg/d	105 (76%) / 1	99 (72%) / 6 (4%)	3475±660** / 539-5024 39.1±3.0 / 23-42.5	13 (9%) / 15 (10%)	30.0±5.3 15-40	3 (3%)	1. meningomyelocele, hydrocephalus (treated: Li + carbamazepine 2.spina bifida + tethered cord 3. meromelia,born& died 23wk,1/twins 1 severe form of Ebstein's anomaly diagnosed wk.16, pregnan. terminated (treated:fluoxetine,trazodone+L-thyoxin)
control / 148	drugs other than Lithium	123 (83%) / 0	116 (78%) / 7 (5%)	3383±566 / 950-4896 39.2±2.5 / 26-43	12 (8%) / 9 (6%)	29.8±5.3 16-40	3 (2%)	1. Ventricular septal defect 2 Congenital hip dislocation 3. Cerebral palsy & torticolis

Four sets of twins were born in the Li group: one pair died from complications of prematurity at 23 weeks.
One set of twins was born in the control group.
* Mean ± SD
** significantly higher than controls

pregnancies (in one study the number of pregnancies was unknown) with 296 liveborn infants, there were eight malformed (2.7%), not different from controls. However, two of the malformed infants had Ebstein's anomaly while none of the 43 malformed infants among 1,354 controls (3.2%) had this cardiac anomaly.

A sample size of 296 liveborn infants exposed to lithium with a ratio of 1:4.6 (lithium/control) and a power of 80%, assuming a baseline risk of 3% for major anomalies, enables detection of a 2.27-fold increase in the overall rate of major anomalies (with 95% CI).

It is interesting that only few perinatal complications were described in the retrospective or prospective studies, apparently due to the fact that this was not the main purpose of these investigations.

Developmental Follow-up studies

While experimental studies in animals have shown long-term developmental effects of psychotropic drugs, including altered emotional behavior in adult mice exposed in-utero to fluoxetine (52), most developmental studies in children exposed in-utero to such drugs are negative (53). Several human case reports have demonstrated transient neuro-developmental deficits in infants born to lithium exposed mothers (26). However, long-term developmental studies on lithium-exposed children are generally lacking. In a single prospective follow-up study, Schou (54) compared the motor and mental development of 60 non-malformed lithium babies to their own 57 siblings, who were not exposed to lithium in-utero. The data were calculated based on the information obtained from questionnaires and letters sent to doctors (psychiatrists/general practitio-

ners) who primarily reported the children. Out of 60 lithium-exposed children, 10 were abnormally developed, in six developmental delay was transitory and in four it was permanent (Table 7). In this group, three children were exposed to lithium only in the first trimester and the seven others throughout pregnancy. In the 57 control siblings, six children were identified with persistent abnormal development. The data shown by Schou indicates that in-utero exposure to lithium does not increase the risk of developmental (both motor and mental) disorders.

Discussion

This review deals with the effects of lithium intake in pregnancy by women with BD on their offspring, with special emphasis on major anomalies. Concerns about the correlation between lithium and severe congenital cardiac defects encouraged retrospective and prospective studies. The two retrospective studies (29, 33) described a total number of 284 infants born to mothers with BD who took lithium in pregnancy, of them 22 (7.7%) had cardiac anomalies, six (2.1%) having Ebstein's anomaly. These studies demonstrated high rates of cardiovascular malformations, notably Ebstein's anomaly.

Since these reports were voluntary, it was only natural that over-reporting of malformed infants would be expected, as is the main weakness of most retrospective studies. Hence, several prospective studies were published, and all (controlled or uncontrolled) were negative. Similarly, all case control studies regarding cardiac anomalies also failed to show an association between in-utero lithium exposure and cardiac anomalies, including Ebstein's anomaly.

Table 7. *The effect of in-utero exposure to lithium on psychomotor development among infants born to women with bipolar disorders (54)*

Treatment Group	Duration / treatment	Normal develop.	Abnormal develop.	Age of children*	Male / female
Lithium 60	20 — 1st tri. 40 — entire pregnancy	50	10	7.3 ± 0.2 years	26 / 34
Control Siblings 57	None	51	6	12.2 ± 0.8 years	25 / 32

* Mean +SD

The strong impact of the high rate of cardiac anomalies from the lithium registry seems to stem from the fact that the same cases were published in several publications (1, 28, 30–32) before the registry was completed, and it was not always clear from the publications that they refer to the same cases. Kallen and Tandberg's study (33) is only on 59 cases, and the results, although not statistically significant, point to the same possibility of increased cardiac anomalies in association with lithium therapy in pregnancy.

Of the 24 separate case reports we surveyed, there were six infants with major congenital anomalies and three with developmental delay. Of the malformed infants, five had cardiovascular defects, one of them had Ebstein's anomaly. As high as it may be seen, these results do not reflect the real malformation rate, since we do not know how many women took lithium without having malformed infants. It is also clear that there is no specific pattern of anomalies following lithium intake, except for, possibly, Ebstein's anomaly.

Reviewing the data accumulated until today regarding lithium exposure and cardiovascular anomalies, including Ebstein's anomaly, it is to be concluded that the risk is much lower than previously thought, and that whenever lithium is given to pregnant women with BD, treatment should continue. It is however advisable to perform a fetal echocardiography to exclude the possibility of cardiac anomalies.

Warner (40) suggested that the real impact of lithium is under-represented since many women who become pregnant while being treated with lithium may prefer to abort the malformed fetuses. Indeed, Jacobson et al. (50) reported a higher rate (though not statistically significant) of therapeutic abortions in the lithium exposed group (10%) compared to 6% in the control. This was also corroborated in our findings: 8.6% in the lithium group vs. 2.9% in the controls (51).

Since not all women with BD can be stabilized with lithium, a comparably safe alternative is needed. Other mood stabilizers such as carbamazepine and valproic acid, used for the same indications in BD patients, are certainly more teratogenic and, whenever possible, should be replaced by lithium. An apparently effective and relatively safe alternative in pregnancy seems to be lamotrigine, as demonstrated in both human and animal studies.

The largest pregnancy registry regarding the possible effects of lamotrigine in pregnancy was initiated by the manufacturer: GlaxoSmithKline, Research Triangle Park NC (55). Among 707 women from the international registry reported with first trimester monotherapy of lamotrigine, they found no increase in the rate of major anomalies (2.8%). No dose-related effect was detected in daily doses lower than 400 mg, while the regular daily doses are about 200 mg. Most of the cases in this registry were recently published by Cunnington et al (56).

Another recent prospective study of the U.K. epilepsy and pregnancy register (57) reported 647 cases of exposure to lamotrigine monotherapy during pregnancy. Of these, 21 infants (3.2%) demonstrated major congenital anomalies, compared to 6.2% major anomalies found among 715 valproate-exposed infants. Daily lamotrigine doses above 200 mg. induced higher risk of anomalies, as 15 malformed infants (5.4%) were reported from 279 such exposures. No studies were found regarding the long-term developmental effects of lamotrigine in pregnancy on the offspring. Hence, lamotrigine can apparently safely replace lithium therapy in pregnant women with BD.

Lithium discontinuation

In a retrospective study, Viguera et al. (58) studied the recurrence rate of bipolar disorders following disruption of lithium treatment among pregnant women as compared to non-pregnant women. No differences were found between the groups during the first 40 weeks (52% and 58% appropriately), yet these rates were over two fold the recurrence rate of bipolar disorders of both groups in the precedent year (21%) (58).

These findings suggest a limited protective effect of pregnancy itself in regards to risk of BD recurrences and brought Viguera et al. (43) to the conclusion that of all the mood stabilizers, lithium should be considered the first-line treatment option in pregnancy since reproductive safety data concerning new mood stabilizers are yet limited.

Conclusions

Evaluation of the studies on lithium in pregnancy shows that lithium therapy throughout pregnancy does not seem to increase the general rate of major anomalies, and apparently adds only a small risk for cardiovascular defects, notably Ebstein's anomaly.

We can therefore conclude that whenever lithium is the drug of choice in women with BD, it may be continued even in pregnancy. Moreover, it is advisable not to discontinue lithium in pregnancy as it may subsequently lead to relapse of the disorder. This is in spite of the fact that treatment of BD patients with lamotrigine was recently proven quite effective, and that prospective studies regarding its use in pregnancy are so far reassuring. In addition, pregnancy of lithium-treated women should be considered high risk, and therefore monitoring during pregnancy has to include fetal echocardiography, and studies of serum Li levels throughout pregnancy. Pregnancy interruption in lithium-treated mothers can probably be considered only if a severe cardiac (or other) anomaly is diagnosed.

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