Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.

by S.J. Jacobson, K. Jones, K. Johnson, L. Ceolin, P. Kaur, D. Sahn, A.E. Donnenfeld, M. Rieder, R. Santelli, J. Smythe, A. Pastuszak, T. Einarson and G. Koren

Lithium carbonate is an effective drug for prophylaxis and treatment of major affective disorders. In-utero exposure to lithium during the first trimester of pregnancy might be associated with an increased risk of cardiac malformation, especially the rare Ebstein's anomaly.

We prospectively recruited and followed 148 women (mean age 30 years, SD 5 range 15-40) using lithium during the first trimester of pregnancy, who consulted four teratogen information centres in the USA and Canada. Pregnancy outcome was compared with that of controls matched for maternal age. We had complete follow-up of pregnancy outcome in 138 of 148 patients recruited. In the other 10, fetal echocardiograms were available but postnatal follow-up was not done. Mean daily dose of lithium was 927 mg (SD 340). Rates of major congenital malformations did not differ between the lithium (2.8%) and control (2.4%) groups. 1 patient in the lithium group chose to terminate pregnancy afer Ebstein's anomally was detected by a prenatal echocardiogram. There was 1 ventricular septal defect in the controls. Birthweight was significantly higher in the lithium-exposed infants than in the controls despite identical gestational ages (3475 [660] g vs 3383 [566] g, p=0.02). The true difference in birthweight might have been even larger, since significantly more women using lithium than controls were cigarette smokers (31.8% vs 15.5%, p=0.002).

These results indicate that lithium is not an important human teratogen. Women with major affective disorders who wish to have childen may continue lithium therapy, provided that adequate screening tests, including level II ultrasound and fetal echocardiography, are done.

Mood disorders are often effectively treated with lithium carbonate. Lithium was suspected of causing heart defects in the human embryo. A study of the infants of 148 women taking lithium carbonate during the crucial first trimester of pregnancy revealed no statistical difference in heart anomalies between the lithium-exposed fetuses and a control group matched for the age of the mothers. Tests included fetal echocardiograms. Post-natal follow-up revealed that the birth weight of babies exposed to lithium was higher than those in the control group. Women can therefore continue lithium therapy during pregnancy without risking the health of their infants, although echocardiograms and ultrasound screening are recommended.

© COPYRIGHT 1992 The Lancet Ltd.

Introduction

0.1% of pregnant women are estimated to use lithium. [1] This drug crosses the placenta, and concentrations are much the same in maternal and cord serum. Therapeutic and supratherapeutic doses of lithium have caused craniofacial defects in rodents, [2] but malformations have not been demonstrated in primates. [3] Since 1970, isolated instances of congenital anomalies (specifically Ebstein's anomaly) as well as normal outcomes have been reported in association with lithium exposure during pregnancy. [4-6]

In 1968, the Danish Register of Lithium Babies was established to obtain further information about infants and children who had been exposed to lithium during the first trimester of pregnancy. Data were collected by a voluntary retrospective reporting system, and included cases from Scandinavia, Canada, and the USA. Of a total of 225 cases reported by 1983, 25 (11%) had major congenital malformations. [7] 18 (72%) of these patients had cardiac anomalies; of these, a third were Ebstein's anomaly, which is a rare congenital heart defect with an incidence of 1 in 20 000 in the general population. On the basis of this information, lithium has become widely regarded as a human teratogen.

Voluntary, retrospective reports of reproductive outcome have many serious methodological shortcomings. In particular, there is evidence that bias towards reporting of adverse outcomes is common. [8] With an unknown denominator (total number of exposures), an increased risk cannot be defined. Furthermore, two case-control studies [1,9] have not demonstrated increased use of lithium in mothers giving birth to children with Ebstein's anomaly (although one of them reported Ebstein's

- Reprinted with permission. Additional copying is prohibited. -

GALE GROUP

Information Integrity

Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.

anomaly after exposure to lithium [9]), and a retrospective study [10] of 350 women with major effective disorders showed no difference in outcome between infants exposed to lithium and those who had been exposed to other psychotropic drugs, although 4 cardiac defects were seen in 59 lithium-exposed infants, and none in the 38 controls. [10]

To evaluate the teratogenic potential of lithium in pregnancy, we have conducted a controlled, prospective study of women using lithium, who contacted teratogen information services in two American and two Canadian university programmes.

Patiens and methods

We enrolled 148 women who called one of four teratogen information services to obtain information about the potential risks of therapeutic drugs during pregnancy: these centres were Motherisk (Toronto), the California Teratogen Information Service (CTIS) (San Diego), the Philadelphia Pregnancy Healthline, and Foetal Risk Assessment from Material Exposure (FRAME) (London, Ontario).

The prospective collection of the study and follow-up data were consistent between centres. Motherisk and FRAME referred patients to a weekly clinic, where at interview a doctor obtained information about drugs or other chemicals taken during or before pregnancy, including indication, dose, toxicity of the drug and its toxic effects, and monitoring. A medical and obstetric history was also elicited, as well as occupational exposures and family history. At this visit adivce was offered and appropriate referrals were made. After the expected date of delivery, each woman was telephoned and a follow-u history of the pregnancy was obtained. The mother was asked for details about pregnancy outcome, perinatal complications, birthweight, physical findings, and developmental milestones. In addition, the physician caring for the baby was contacted to confirm this information and to provide a written report of the delivery and health status of the child. The CTIS and the Philadelphia Pregnancy Healthline obtained all initial information by telephone interview. In San Diego, postnatal follow-up was done by one of the investigators in the clinic; details of delivery and postnatal course were collected. The Philadelphia Pregnancy Healthline obtained all follow-up data by telephone; detailed records from physicians caring for the babies were also obatined. Patient enrolment into the study began with the initiation of each programme--ie, CTIS 1979, Philadelphia Pregnancy Healthline 1984, Motherisk 1985, FRAME 1989, until February, 1991.

All pregrant women who called during these dates and who reported lithium ingestion during part or all of their first trimester were prospectively enrolled. Lithium exposres as early as 3 weeks' gestion were included since the half-life of lithium is long (2-4 days) in patients receiving long-term therapy. [11] Thus detectable

[TABULAR DATA FOLLOWS REFERENCES]

serum concentrations can still be present 2 weeks after cessation of treatment. All patients were offered fetal echocardiography at 18 weeks' gestation, to rule out cardiac anomalies. If prenatal echocardiography had not been done, infants were referred for postnatal echocardiographs. 101 patients were enrolled by CTIS, 25 by Motherisk, 19 by Phiadelphia Pregnancy Healthline, and 3 by FRAME.

Controls were women who were seen at the Motherisk clinic for counselling about drugs that are not known or suspected to be teratogenic. Each study patient was matched with a woman of similar age (to within 2 years). Prenatal and postnatal evaluation was the same as described for the Motherisk programme. Echocardiography was not done in this group, since this was not deemed to be medically or ethically justifable.

We used Marden's definition of major anomaly--ie, one that has an adverse effect on either the function or social acceptability of the individual. [12]

We used chi-square analysis to compare the frequency of malformations in study and control groups and the frequency of smoking in the two groups. We calculated risk ratios and 95% confidence intervals (Taylor series) to establish the relation between lithium exposure and malformations. These statistics were obtained first for all congential malformations, then for cardiac malformations and Ebstein's anomaly. Birthweight, gestational age, and development milestones were compared with Student's t-test for paired data. Correlations between values were studied by least-square regression analysis.

Results

10 of the 148 patients were lost to follow-up postnatally; however, they were included in part of the analysis because all had had prenatal echocardiography. A total of 68 patients had echocardiographs (46%). Maternal age ranged from 15 to 40 years (mean 30, SD 5 years). All patients were receiving lithium for major effective disorders. The mean daily lithium dose was 927 (SD 340) mg, range 50-2400 mg.

- Reprinted with permission. Additional copying is prohibited. -

GALE GROUP

Information Integrity

Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.

Pregrancy outcome did not differ between patients and controls with respect to the total number of livebirths, frequency of major anomalies, spontaneous or therapeutic abortions, ectopic pregnancy, and prematurity (table I). Three major congenital malformations occurred in each group--2.8% of livebirths in the lithium group and 2.4% in controls. The 10 pregnancies for which final outcome was not known were not included in this part of the analysis. There were four sets of twins in the lithium group; one pair was born at 23 weeks' gestation and both infants died shortly after birth due to complications of prematurity. There was one set of twins in the control groups.

2 children in the lithium group had neural-tube defects: 1 of these had hydrocephalus and meningomyelocle and had also been exposed to carbamazepine during the first trimester; the other had spina bifida and tethered cord. A 3rd infant (one of a twin) had meromelia, and was born at 23 weeks', dying shortly after birth. 1 fetus in the lithium group had a severe form of Ebstein's anomaly, which was diagnosed at 16 weeks' gestation, and this pregnancy was terminated. This fetus had also been exposed to fluoxetine, trazodone, and L-thyroxine in the first trimester. In the

[TABULAR DATA FOLLOWS REFERENCES]

controls, 1 child had a ventricular septal defect, 1 had congential hip dislocation, and 1 had cerebral palsy and torticollis.

The risk ratio for all congential defects was 1.2 (95% confidence interval 0.2-5.7) when only livebirths were compared. When the case of Ebstein's anomaly was included (since this pregnancy would probably have gone to term if the anomaly had not been detected) the risk ratio became 1.5 (0.4-6.7). The risk ratio for cardiac anomalies was 1.1 (0.1-16.6), and for Ebstein's anomaly was 3.5 (0.1-84.9).

The mean age at which postnatal follow-up was done in the lithium-exposed group was 61 (SD 87.5) weeks (range 1 week to 9 years). Lithium-exposed infants weighed a mean of 92 g more than controls ($p = 0.01$) at birth (table II). Gestational age and frequency of prematurity did not differ between the groups. Because all controls were enrolled in Toronto, we examined whether the difference in birthweight was related to geographic factors in the various study groups. However, when the Motherisk data were analysed separately, the difference in birthweight persisted and remained significant ($p = 0.018$). There was no correlation between maternal lithium dose and birthweight. More women using lithium than controls were cigarette smokers (31.8% vs 15.5%; $p = 0.002$).

Data on attainment of major developmental milestones (smiling, lifting head, sitting, crawling, standing, talking, and walking) were available for 21 lithium-exposed patients enrolled by Motherisk and 1 patient enrolled by FRAME. Study and control groups did not differ in age of attainment of any of the milestone (data not shown).

Discussion

Discontinuation of lithium therapy can have devastating results for the mental and physical health of young women with major effective disorders. On the other hand, many women who inadvertently conceive while on lithium therapy choose to terminate pregnancy because of a perception of teratogenic risk, on the basis of retrospective reports. As far as we are aware, this is the first prospective study of infants exposed to lithium during the first trimester of pregnancy. The recent establishment of teratogen information services has provided a very good opportunity to investigate large numbers of patients exposed to substances of interest within short periods. Our service is uniquely designed to counsel pregnant women, and we are contacted directly by those exposed to lithium, almost invariably at the time of exposure. Accurate information about time of exposure and drug dosage are crucial to assess any causal relation between any zenobiotic and outcome. Moreover, information about other risk factors such as illicit drugs and smoking is obtained prospectively.

Case-control studies rely on maternal recall, which can be poor and is subject to bias. [13] Our results accord with those of previous prospective cohort and case-control studies [1,9,10] suggesting that the risk of congenital defects in babies after lithium exposure is lower than that reported by the Danish Registry of Lithium Babies. The registry investigators claim that lithium is associated with a 10% incidence of cardia malformations, and a 3% incidence of Ebstein's anomaly; they believe that the drug is a major teratogen. Because the registry is a voluntary, retrospective database, the number of cases not reported is unknown, as is the number of unreported normal outcomes of lithium exposure.

Our results cannot rule our an association between lithium and major anomalies, even though there was no difference in the number of anomalies between the study and control groups. Since Ebstein's anomaly is very rare a much larger sample size would be needed to define the real risk of this abnormality. That the single cardiac malformation in our study group was Ebstein's anomaly indicates that lithium as a cause of this disorder is rare.

Since under half our patients had echocariographs, some cardiac malformations might have been missed, including

- Reprinted with permission. Additional copying is prohibited. -
GALE GROUP
Information Integrity

Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.

milder forms of Ebstein's anomaly. This might also be true for the control group, in which no echocardiographs were done. Moreover, since all patients were examined by a doctor clinically significant lesions were probably not missed.

The infant with hydrocephalus and meningomyelocoele who was exposed to lithium in utero had also been exposed to carbamazepine during the first trimester; that drug has been associated with an increased incidence of neural-tube defects. [14] The fetus that had Ebstein's anomaly was also exposed in the first trimester to several other drugs, none of which has been associated with cardiac anomalities; lithium remains the most likely causative factor.

The teratogenicity of lihium might be dose-related, as has been shown in animals. [2] The doses used at the time the Danish Registry data were obained could have been higher than present recommended doses. This could explain the discrepancy between their results and ours. However, there is no evidence that lithium doses have changed during this time. [15] In addition, lithium has a very narrow therapeutic window, above which toxic effects are common. Most patients are prescribed the highest dose that they can tolerate and that will maintain serum concentrations in the therapeutic range. [15] We therefore believe that a dose-relation does not account for the different findings of the two studies. The probable reason is the different methods of data collection used by the two groups.

Although the difference in the number of elective abortions was not statistically significant between the groups, the rate was higher in the lithium group than in the controls (10% vs 6%). The increased trend to voluntary termination might have been due to the perceived teratogenic risk of lithium, since women who belive that they are at such risk are more likely to terminat etheir pregnancies. [16] counselling provided by the teratogen information services and referral for appropriate screening tests such as echocardiography might have reduced the perception of teratogenic risk of lithium. As a result, the number of terminations in our study was probably lower than it would have been, and thus the figures for elective abortion are higher than ours in centres where no such counselling is provided; American Medicaid data indicate termination rates of over 50% in women exposed to lithium during pregnancy (Rosa F, personal communication).

The babies exposed to lithium were heavier than controls, and fetal macrosomia has been associated with lithium therapy. [17,18] Yoder [18] proposed that lithium may have an insulin-like effect on carbohydrate metabolism. We did not find that demographic variations contributed to the difference in weight between the groups, and the proportion of diabetic patients did not differ. In additon,the proportion of cigarette smokers in the lithium group was twice that in the controls. One would therefore expect that the babies in the lithium group would be smaller than the controls. Hence, the effect of the drug on birthweight might be even larger than is evident in this study. Although only a few babies were assessed for development milestones, no differences were seen, which is consistent with findings of previous reports. [19]

We conclude on the basis of our results and those of others [1,9,10] that lithium is not a major human teratogen. We believe that women with major effective disorders who wish to have children may continue lithium during pregnancy, and do not need to terminate pregnancy provided that level II ultrasound and fetal echocardiography are done.

REFERENCES

[1] Zalstein E, Koren G, Einarson T, et al. A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol 1990; 65: 817-18.

[2] Smithberg M, Dixet PK. Teratogenic effects of lithium in mice. Teratology 1982; 26: 239-46.

[3] Gralla EJ, McIlhenny HM. Studies in pregnant rats, rabbits and monkey with lithium carbonate. Toxicol Appl Pharmacol 1972; 21: 428-33.

[4] Nora Jj, Nora AH, Toews WH. Lithium, Ebstein's anomaly, and other congenital heart defects. Lancer 1974; ii: 594-95.

[5] Long WA, Park WW. Maternal lithium and neonatal Ebstein's anomaly: evaluation with cross-sectional echocardiography. Am J Perinatol 1984; 1: 182-84.

[6] Fries H. Lithium in pregnancy. Lancet 1970; i: 1233.

[7] Frankenberg FR, Lipinski JF. Congenital malformations. N Engl J Med 1983; 309: 311-12.

[8] Koren G. Retinoid embryopathy. N. Engl J Med 1986; 315: 262.

[9] Kallen B. Commens on teratogen update: lithium. Teratology 1988; 38: 597-98.

[10] Kallen B, Tandberg A. Lithium and pregnancy. Acta

- Reprinted with permission. Additional copying is prohibited. -

GALE GROUP

Information Integrity

Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester.

Psychiatr Scand 1983; 68: 134-39.

[11] American Hospital Formulary Service. In: McEvoy GK, ed. New York: American Society of Hospital Pharmacists, 1989: 1245.

[12] Marden PM, Smith DW, McDonald MJ. Congenital anomalies in the newborn infant, including minor variations. J Pediatr 1964; 64: 357-71.

[13] Koren G. Teratogenic drugs and chemicals in humans. In: Koren G, ed. Maternal-fetal toxicology. New York: Marcel Dekker, 1990: 17.

[14] Rosa F. Spina Bifida in infants of woman treated with carbamazepine during preganancy. N Engl J Med 1991; 324: 674-77.

[15] Goodman L, Gilman A, eds. The pharmacological basis of therapeutics. 7th ed. New York: Macmillan, 1985: 429.

[16] Koren G, Bologa M, Pastuszak A. The way women perceive teratogenic risk: The decision to terminate pregnancy. In: Koren G, ed. Maternal fetal toxicology. New York: Marcel Dekker, 1990: 373-81.

[17] Belik J, Yoder M, Pereira GR. Fetal macrosomia: an unrecognised adverse effect of maternal lithium therapy. Pediatr Res 1983; 17: 304A.

[18] Yoder MC. Belic J, Lannon RA, et al. Infants of mothers treated with lithium during pregnancy have an increased incidence of prematurity, macrosomia and perinatal mortality. Pediatr Res 1984; 18: 404A.

[19] Schou M. What happened later to the lithium babies? Acta Psychiatr Scand 1976; 54: 193-97.

TABLE I—PREGNANCY OUTCOME*

Outcome	Lithium (n=138)	Control (n=148)
Normal live births	105 *(76%)*	123 *(83%)*
Full term	99 *(72%)*	116 *(78%)*
Premature (<36 weeks)	6 *(4%)*	7 *(5%)*
Congenital defects	3 *(3%)*	3 *(2%)*
Spontaneous abortion	13 *(9%)*	12 *(8%)*
Therapeutic abortion†	15 *(10%)*	9 *(6%)*
Stillbirth	1	0
Ectopic pregnancy	1	1
Unknown	10 *(7%)*	0

*Ectopic pregnancies and spontaneous and therapeutic abortions are expressed as percentages of all outcomes (n = 148). Stillbirths and normal livebirths are expressed as percentages of known outcomes (n = 138). Congenital defects are expressed as a percentage of all livebirths.
†One therapeutic abortion because of Ebstein's anomaly diagnosed in utero

TABLE II—COMPARISON OF SAMPLE CHARACTERISTICS IN LITHIUM-EXPOSED AND CONTROL GROUPS*

—	Lithium group	Control group	p
Birthweight (g)	3475 (660) (539–5024)	3383 (566) (950–4896)	0·025
Gestational age (wk)	39·1 (3·0) (23–42·5)	39·2 (2·5) (26–43)	0·562
Maternal age (yr)	30·0 (5·3) (15–40)	29·8 (5·3) (16–40)	0·614

*Mean (SD) (range) shown

- Reprinted with permission. Additional copying is prohibited. -

GALE GROUP

Information Integrity