*Case Report*

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# Congenital Diaphragmatic Hernia Following Usage of Lithium Carbonate; Is Lithium a Teratogen?

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## Abstract

***Background:*** Lithium is used mainly for the treatment of Bipolar Disorder (BD). Case reports and several retrospective studies have demonstrated possible teratogenicity, but the data in different studies is inconclusive. The risk for cardiovascular malformations, particularly Ebstein's anomaly and other congenital abnormalities have been reported.

***Case Presentation:*** A 25-year-old gravida 1, para 1 woman at 38 weeks of gestation was admitted for an elective caesarean section. She had a history of BP for which she was treated with lithium 600mg q12h in the first trimester of pregnancy. There was no familial history of birth defects, any antenatal infection or exposure to any other medications, alcohol, smoking, or X-rays. A baby boy (3500g) was born. After 2 to 3 hours respiratory distress clinical picture and chest radiograph suggested diagnosis of congenital diaphragmatic hernia. Repair of his diaphragm was preformed and patient discharged after 12 days.

***Conclusion:*** Lithium *probably* produces a defect in normal development of the diaphragm and may pose specific risk for an anomaly known as congenital diaphragmatic hernia (CDH).

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***Key Words:*** Diaphragmatic Hernia; Lithium Carbonate; Pregnancy; Teratogens; Bipolar Disorder

## Introduction

Bipolar Disorder (BD) is common among women of childbearing age. Experts agree that acute and maintenance management of BD requires somatic prophylaxis[1]. Unfortunately, all psychotropic medications diffuse across the placenta, which exposes the fetus to some degree of risk[2]. On the other hand, a number of medications used to treat acute mania and to prevent episodes of depression and mania are associated with structural teratogenicity[1].

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Lithium carbonate is used as a standard treatment for BD[2]. In the last four decades, there has been much concern regarding the association between prenatal exposure to lithium and risk for major congenital anomalies. The risk for cardiovascular malformations, particularly Ebstein's anomaly, was initially proposed to be 400 times higher than the background baseline[3,4]. Herein, we suggest that lithium may pose specific risk for congenital diaphragmatic hernia (CDH) as a new abnormality in some pregnancies. We reviewed all published studies in English, including case reports and did not find any report pertaining to this association.

## Case Presentation

A 25-year-old gravida 1, para 1 woman at 38 weeks of gestation was admitted for an elective caesarean section. She had a history of BD for which she was treated with lithium 600mg q12h in the first trimester of pregnancy.

It changed to doxepine 10 mg every night and continued until delivery. Other medications were ferrous sulfate and folic acid in usual dosage. The father was 32 years old and there was no consanguinity. There was no familial history of birth defects, any antenatal infection or exposure to any other medications, alcohol, smoking, or X-ray. Pregnancy was uncomplicated and a baby boy (3500g) was born. After 2 to 3 hours of respiratory distress clinical picture and chest radiograph suggested diagnosis of congenital diaphragmatic hernia. X-ray (Fig. 1) showed air-filled intestine herniated into the left chest and the trachea and nasogastric tube displaced to the right side. The operation and repair of his diaphragm was preformed and patient discharged after 12 days.

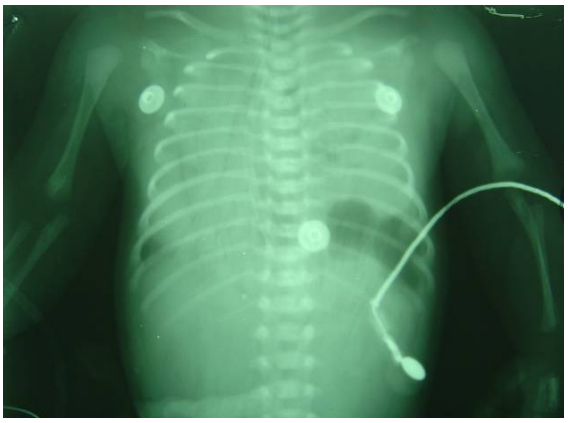

**Fig. 1:** Congenital diaphragmatic hernia

To date, there has been no report of human congenital diaphragmatic hernia after prenatal lithium exposure.

## Discussion

The management of BD during pregnancy remains one of the most daunting challenges of psychiatric practice[5]. Unfortunately, a number of medications used to treat acute mania and prophylaxis of BD are associated with structural teratogenicity. Among the mood stabilizers, lithium should be considered a first-line treatment option in pregnancy[2].

This drug is used mainly for the treatment of BD; however, Weinstein has shown that no placental barrier exists to free diffusion of lithium ions[6].

Case reports and several retrospective studies have demonstrated possible teratogenicity, but the discussion on the teratogenic effects of lithium in world literature has not reached a final conclusion[7-9]. There are numerous reproductive safety concerns regarding the medications used to treat BD.

Moreover, there is a low incidence of neonatal toxicity with lithium exposure[2,10,11].

Since 1950, lithium has been the cornerstone of pharmacotherapy for BD. Initial retrospective analyses suggested that lithium exposure was associated with a 400-fold increase in the rate of Ebstein's anomaly and a tricuspid valve malformation in offspring exposed *in utero*[11,12,13], but subsequent meta-analyses indicated that the risk ratio for cardiac malformations after lithium exposure is only 1.2 to 7.7[4] and the risk for Ebstein's anomaly rises from 1 in 20,000 to 1 in 1,000[14].

Other congenital abnormalities reported include large volume for gestational age infants[15], anencephaly[16] and oromandibular-limb hypogenesis[17].

Marathe showed in Wistar rats a reduction in number and weight of the litter, wavy ribs, short and deformed bones of the limbs, or an increased incidence of incomplete ossification of Sterne brae and wide bone separation in the skull. These important findings suggest the nature and extent of embryo toxicity and teratogenicity of lithium carbonate[18].

Craniofacial anomalies can also occur after the first trimester[1]. In addition, exposure up to the third and fourth weeks of gestation can affect the development of the diaphragm[19].

Here, we have a neonate with congenital diaphragmatic hernia (CDH) which is a significant clinical problem, occurring once in every 2,500 to 3,000 human births[19]. This condition continues to have a high mortality rate due to the lethal combination of pulmonary hyperplasia and pulmonary hypertension [20,21].

Normal diaphragm development is initiated between the third and fourth week of gestation. It means that any embryotoxicity and teratogenicity at this period causes the congenital disease[22].

## Conclusion

Our study suggests that lithium *probably* produces a defect in normal development of the diaphragm; additional research is needed to provide information regarding this association. The risks and benefits need to be carefully balanced based on an accurate review of the evidence. Each of these risks should be discussed openly with the patient and her spouse.

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