

Lithium Administration During Pregnancy: Impacts And Considerations

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Abstract

Lithium is widely used in the treatment of bipolar disorder, including among women of childbearing age. Its use during pregnancy raises significant clinical concerns due to its ability to cross the placenta and potentially affect fetal development. This review evaluates both animal and human studies on lithium exposure during pregnancy, highlighting risks such as congenital anomalies, particularly cardiac malformations (e.g., Ebstein's anomaly), and spontaneous abortion. While studies indicate a higher risk of congenital defects in lithium-exposed pregnancies—especially in the first trimester—findings regarding low birth weight and preterm delivery remain inconclusive, with some evidence attributing those risks more to the underlying mood disorder than to lithium itself. The decision to use lithium during pregnancy must be individualized, carefully weighing maternal mental health stability against fetal risks. Close monitoring of serum lithium levels is crucial throughout pregnancy and postpartum due to physiological changes affecting lithium pharmacokinetics

Keywords: lithium, pregnant women, adverse outcomes, childbearing age, congenital Anomalies.

Introduction

About 1% to 2% of adults worldwide suffer from bipolar disorder, with a similar prevalence in men and women [1, 2]. The disorder typically manifests during adolescence or early adulthood [1].

Antimanic medications are most well-known for reducing acute manic episodes in bipolar disorder patients, preventing new episodes of mania, and potentially preventing depression during prolonged treatment. These drugs which include lithium, valproate, and carbamazepine are crucial in managing bipolar disorder, serving both acute and prophylactic treatment purposes. Each drug belongs to a distinct chemical class and has varying effects on the central nervous system (CNS), along with differing profiles of adverse effects.

Typically, 50% to 70% of acutely manic patients show moderate or greater improvement within three weeks of starting treatment with antimanic drugs. This improvement can include a reduction

in manic symptoms such as elevated mood, irritability, increased energy, and impulsivity. Additionally, response rates increase to 70% to 80% of patients when antimanic agents are combined together or an adjunctive medication is used for impaired sleep or psychotic symptoms. Several neurochemical effects have been found to mitigate the clinical responses seen with these drugs.

Lithium is Food and Drug Administration approved for use in both acute manic episodes and prophylaxis against the depressive phase of bipolar disorder. Lithium is considered the drug of choice for prophylaxis against bipolar affective episodes, manic type. It has also been used in acute depression for patients who not responding to other treatments, as prophylaxis against recurrence of schizoaffective illness, impulse control and episodic violence.

Lithium has been used in long-term maintenance treatment for bipolar disorder because of its demonstrated efficacy in reducing both manic and depressive relapse as well as its anti-suicidal

properties The average age of onset for bipolar disorder is usually before the age of 25 years leading to a greater likelihood that Lithium is frequently prescribed to women of childbearing age [3,4].

Lithium is a salt which has been reported to alter sodium transport in nerve and muscle cells and impacts a shift toward intraneuronal metabolism of catecholamines. However, its specific biochemical mechanism of action in mania is not known. Specifically, lithium needs to be dosed very carefully because of its narrow therapeutic window [5]. In terms of dosing, Lithium is usually given orally from 300 to 600 mg three times a day until the desired effect has been achieved. Serum levels of 0.8 to 1.2 mEq/L are considered therapeutic in acute bipolar disorder and serum levels are 0.6 to 1.2 mEq/L are desirable in the long term. Although dosing of Lithium can vary, a typical regimen of 300 mg taken three to four times daily usually maintains therapeutic levels while reducing relapse risk during maintenance therapy, primarily targeting manic episodes.

Risk to the Fetus During Pregnancy

Animals

Lithium crosses the placenta freely and its concentration in cord blood is equivalent to maternal serum[6-9]. During this review, we found six different reports that highlighted the teratogenic, fetotoxic, and embryo toxic effects of lithium in animal studies [10-15]. These included a range of detrimental effects on prenatal development across different animal models, including rats, mice, and chicks. Specifically, mice and rat studies found teratogenic effects (including eye, cleft palate, external ear, heart, pericardium, and skeletal, malformations) and fetotoxic effects (including increased perinatal death, decreased number and weight of litters and decreased number of living offspring. [10-14]. Embryotoxic effects were also reported in chicks [15]. Whereas few other studies found no congenital malformations in the rat, mice, rabbits, and monkey offsprings after Lithium exposure [14, 16-18].

Humans

There have been studies showing negative outcomes after Lithium exposure during pregnancy. This comparison of 1,349,563 pregnancies between lithium exposed and unexposed group was reported in eight studies which included from both the general population and women with affective disorders unexposed to lithium [19, 20, 22-26]. Three studies showed possible risk of low birth weight with 23,238 pregnancies, six studies reviewed risk of preterm birth in 23,695 pregnancies, two studies looked at spontaneous abortion in 1,289 pregnancies while, four studies did for cardiac congenital anomalies in 1,348,475 pregnancies while four others were on any congenital anomaly in 23,046 pregnancies.

Congenital Anomalies and Spontaneous Abortion

Lithium use during pregnancy has been linked to a significantly higher risk of congenital anomalies compared to unexposed groups. An analysis of four studies involving 23,300 participants found an odds ratio of 1.81 (95% CI = 1.35–2.41), indicating a substantial increase in risk. This association remained evident among patients with affective disorders (odds ratio = 1.75, 95% CI = 1.21–2.52) and in comparisons with the general population (odds ratio = 2.03, 95% CI = 1.03–3.99). These findings were

consistent for exposure during the first trimester. Major congenital malformations were defined as those diagnosed by age 1 year and included a range of conditions such as structural defects, syndromes, sequences (a series of related anomalies stemming from a single major defect), and associations, including cardiovascular defects, neural tube defects, hypospadias, and epispadias. Specifically, major cardiac malformations were categorized as atrial and atrioventricular septal defects, and Ebstein's anomaly [19, 20, 22, 23].

These studies demonstrated that Lithium exposure during pregnancy, particularly in the context of affective disorders, significantly increases the risk of congenital anomalies. The risk is consistent across different comparisons (any unexposed group and the general population). These findings underline the importance of careful consideration and monitoring when prescribing lithium to pregnant individuals, balancing the benefits of treatment with the potential risks to fetal development [27].

Poels and colleagues found miscarriages rate to be 20.8% of lithium-exposed pregnancies (16/77), compared to 10.9% in unexposed pregnancies (40/366) (OR = 2.14; 95% CI: 1.13–4.06, $p = 0.018$). When this was adjusted for age at conception and clustering of pregnancies per woman, the adjusted odds ratio for miscarriage after lithium use during pregnancy was found to be 2.94 (95% CI: 1.39–6.22, $p < 0.005$) [28].

This finding aligns with data from Diav-Citrin et al., who also observed a twofold higher rate of miscarriage in 183 lithium-exposed pregnancies compared to disease-matched 72 unexposed pregnancies (OR = 1.94; 95% CI: 1.08–3.48) [19].

Cardiac Anomalies Risk

Lithium carbonate use during the first trimester of pregnancy has been associated with the occurrence of cardiovascular malformations. These include Ebstein's anomaly (dilatation of the right ventricular outflow tract, severe tricuspid valve insufficiency, and patent ductus arteriosus) [29-33].

One observation indicated that the correlation between lithium and Ebstein's anomaly is minimal, as the majority of tricuspid valve malformations, including Ebstein's anomaly, were not associated with lithium therapy [14].

Lithium freely crosses the placenta equilibrating between maternal and cord serum [34]. Mizrahi and colleague found that amniotic fluid concentrations exceed cord serum levels [35].

Reported a 7% risk while studying four cases of serious heart defects (although none had Ebstein's anomaly) among 59 infants born to women who used lithium during early pregnancy [22]. Their data on lithium use during pregnancy was collected prospectively. However, the risk associated with lithium use during pregnancy was found to be lower than previously suggested in most prospective studies [38-40].

Numerous predominantly negative case-control studies have been published regarding the relationship between Ebstein's anomaly and the use of lithium during pregnancy. [39-42].

The Lithium Baby Register was implemented in Denmark to retrospectively collect information in 1968 for 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. This registry supported the cardiovascular malformation association with Lithium use in pregnancy [43-45].

Specifically, eight percent (18/225) of the offspring were born with cardiovascular malformations; out of which six were diagnosed with Ebstein's anomaly (2.7%). This was in contrast to the background risk of approximately 1:20,000 [0.005%] found by Nora et al. [29, 46].

The incidence of congenital defects in bipolar disorder not treated with lithium is not known. And even though some healthy babies exposed to lithium during the first trimester were not part of the registry report, the high incidence of cardiovascular malformations found by the researchers makes its association with Lithium likely. However, the reports from the Lithium Baby Register were also found subject to recall bias resulting in a possible overestimation of its adverse outcome data.

In a multi-center study, a comparison of the rate of major anomalies between the lithium and nonteratogenic exposure groups was performed. This included data from two additional teratology information services, one in Australia (Mother Safe, 2000–2011) and one in Canada (the Mothe risk Program, 2001–2005) [19]. Eighteen lithium cases from each service, as well as 70 and 72 non-teratogen-exposed pregnancies from the Mother Safe and Mothe risk centers, respectively, were included in the study. In this multicenter study when genetic or cytogenetic anomalies were excluded, the overall rate of major anomalies among those exposed to lithium during the first trimester was found to be higher than that in the nonteratogenic exposure group. Cardiovascular anomalies were reported to be more common when Lithium was used in the first trimester, even after excluding those cases that resolved. Furthermore, the rate of non-cardiovascular anomalies was also found to be higher in the lithium-exposed group.

There was a case reported by Lewis and Suris [47] where a baby was born with coarctation of the aorta to a mother who had used lithium during the first 8 weeks of pregnancy. Unfortunately, their study did not include details on the patient's medication or genetic history. In a different study, Rane et al. (48) observed dextrocardia and aortic coarctation in a newborn whose mother had taken lithium throughout her entire pregnancy. The mother also used other medications such as nitrazepam, ampicillin, and chlorothiazide. However, no direct link between these defects and lithium use was established. Several clinical reports have documented various congenital heart defects in newborns after lithium use during pregnancy. These defects include intra-ventricular septal defect, mitral atresia, tricuspid valve atresia, patent ductus arteriosus, tricuspid regurgitation, atrial flutter, and congestive heart failure [49-53]. A cohort study involving 350 women with manic-depressive disorder observed a trend which was not found to be significant towards an increased risk of perinatal death and congenital malformations when lithium was used during the first trimester [54]. Although this study noted a rise in cardiac defects, no cases of Ebstein's anomaly were reported.

Lithium exposure during pregnancy has been linked to a significantly higher risk of cardiac malformations. Analysis of four studies involving 1,348,475 participants found an odds ratio of 1.86 (95% CI = 1.16–2.96), indicating a notable increase in risk compared to unexposed groups and the general population [55-58]. When comparing these outcomes with three studies involving 1,324,591 participants from the general population, the risk was even more pronounced with the odds ratio of 4.00 (95% CI = 1.19–13.4, $p = 0.03$) [55, 57, 58]. However, when comparing those exposed to lithium with unexposed individuals who had affective disorders, the difference in risk of cardiac malformations was not statistically significant, based on four studies with 24,699 participants, showing an odds ratio of 1.59 (95% CI=0.91–2.77) (55-58).

When studies compared Lithium exposure specifically in first trimester, an increased risk of cardiac malformations was found compared to the group unexposed to Lithium. This was evident in four studies with 1,348,40 individuals with an odds ratio=1.96, 95% CI=1.28–3.00. In addition, all these studies found the cardiac risk compared to unexposed patients with affective disorders to be much higher with 24,627 participants (odds ratio=1.75, 95% CI=1.08–2.84) (19-22,55-58). The recommendation for fetal echocardiography and level 2 ultrasound in women treated with lithium during organogenesis was made by Diay-Citrin and colleagues [19].

Lithium, while effective in treating mood disorders, can pose risks to fetal development, particularly affecting cardiac development. Regarding the dosing schedule, Bergink and Kushner highlighted the importance of using a single medication during pregnancy to minimize potential risks associated with polypharmacy. They also suggest that dividing the daily lithium dose into twice-a-day dosing helps to avoid high peak serum levels. This approach is often recommended to maintain more stable lithium levels in the blood, which can reduce the risk of adverse effects both for the mother and the developing fetus. [59].

Birth Weight Sequelae

There have been several studies which did not show Lithium exposure during pregnancy having an increased risk of preterm birth [2, 8, 26–29]. This was during comparison with various unexposed groups: any unexposed group (OR=1.42, 95% CI=0.98–2.06), unexposed patients with affective disorders (OR=1.34, 95% CI=0.89–2.01), or the unexposed general population (OR=2.22, 95% CI=0.99–4.97). Similarly, lithium exposure during pregnancy was not found to be significantly associated with low birth weight compared with any unexposed group (OR=0.99, 95% CI=0.84–1.19) or with unexposed patients with affective disorders (OR=1.07, 95% CI=0.85–1.34) [19, 20, 60-63].

Whereas studies suggest that the increased risk of preterm deliveries observed in lithium-exposed offspring may be linked to the underlying disorder itself. For instance, another study reported that pregnant women with bipolar disorder had a twofold higher rate of preterm delivery compared to pregnant women with no history of mental illness. This suggests that factors related to bipolar disorder, rather than lithium exposure alone, could contribute to the higher incidence of preterm births in this population [64].

Women with bipolar disorder face significant risks of mood episodes during pregnancy and postpartum. Lithium is effective in reducing the risk of recurrence during pregnancy and the vulnerable postpartum period. Maternal mood stability is crucial for both maternal and child well-being. Preventing mood episodes is especially important for women with a history of severe mood episodes, as these can impact the mother's ability to care for herself and her child.

The decision to use lithium during pregnancy involves weighing the risks of maternal mood instability and recurrence against the potential risks of lithium exposure to the fetus. Lithium use during pregnancy lowers the risk of recurrence during pregnancy and postpartum for women with bipolar disorder [65, 66].

Also, lithium is less teratogenic than carbamazepine or valproate. Clearly, the risks and benefits of lithium use during pregnancy should always be weighed on an individual basis.

Table 1: Effects of Lithium during pregnancy

Congenital	- Cardiac malformations (e.g. ebstein's anomaly, atrial/atrioventricular septal defects)
	- Neural tube defects
	- Hypospadias (urogenital malformation)
	- Epispadias (urogenital malformation)
	- Structural defects (e.g. coarctation of the aorta, patent ductus arteriosus, tricuspid valve atresia, and intraventricular septal defects)
Neonatal outcome/complications	- Hypoglycemia
	- Cardiac arrhythmias
	- Thyroid dysfunction
	- Neonatal lithium toxicity

Discussion

The studies reviewed suggest that while Lithium use during pregnancy may increase the overall risks of certain adverse outcomes such as spontaneous abortion, congenital anomalies (including cardiac anomalies), it does not necessarily lead to increased risks of preterm delivery or low birth weight when compared to women with bipolar disorder who do not take lithium or to the general population. Furthermore, there was no associated increased risk for spontaneous abortion found with Lithium use during the first trimester of pregnancy though there was a significantly increased risk for congenital malformations including cardiac malformations.

The higher risk of cardiac malformations in children exposed to Lithium in first trimester of pregnancy was reported compared to patients with bipolar disorder unexposed to Lithium. This is consistent with the organogenesis timeline though this was not reported in the exposed mothers at other times during pregnancy.

It would need to be an important consideration for physicians that Lithium use during pregnancy can fluctuate its serum levels. Specifically, an increased glomerular filtration rate leads to a 24% mean reduction in lithium blood levels during the first trimester, 36% during the second trimester, and 21% during the last trimester of pregnancy; in contrast, the serum levels of lithium may rise by 9% during the postpartum period [67].

Close monitoring of the pregnant woman's serum lithium levels is therefore crucial to inform clinical choices on the basis of the physiological fluctuations occurring during pregnancy to avoid suboptimal therapeutic dosing for the pregnant woman, or potentially toxic doses thereafter, especially for the infant, in whom the adverse neonatal effects of lithium, such as hypogly-

cemia, cardiac arrhythmia, thyroid dysfunction, and neonatal lithium toxicity, are dose related [67].

It has been known that serum levels of drugs fluctuate during pregnancy. Specifically, Lithium levels lower during the first trimester to 24% due to an increased GFR glomerular filtration rate, then 36% reduction in second trimester and 21% in third trimester of pregnancy whereas Lithium levels may potentially rise up to 9% during post-partum period [67, 68].

Lithium has a narrow therapeutic range of 0.5–1.2 mmol/L with elevated levels causing potential toxicity (69). This is due to its exclusive renal excretion leading to blood plasma levels dependence on intravascular volume and glomerular filtration rate (GFR) [69, 70]. It has been reported that while pregnancy progresses, total body water, plasma volume and GFR are increased (71) with GFR starting to rise from 6 weeks of gestation to up to 50% over non-pregnant women by the end of the first trimester [72].

During first and second trimester there is a significant reduction in lithium blood levels which can lead to subtherapeutic levels. Whereas lithium levels gradually return to their preconception level in third trimester and after delivery which signifies awareness of the risk of lithium intoxication. However, there is no documented guideline for dosage adjustments for Lithium use during pregnancy and it is still best to avoid abrupt discontinuation of Lithium use whenever possible [73]. These physiological changes necessitate that monthly monitoring of lithium blood levels be done until 34 weeks and weekly monitoring thereafter until delivery [74].

It would be prudent to plan pregnancy in women with bipolar disorder to have the opportunity to adjust Lithium to lower side

of its therapeutic range especially in the first trimester. This is also important as any sudden changes or lowering of Lithium could cause relapse [75].

It's important to note that the decision to prescribe lithium during pregnancy involves careful consideration of the risks and benefits for both the mother and the developing fetus. The risks associated with lithium use during pregnancy, such as small increase in risk for malformations (4.2% for any malformation and 1.2% for cardiac malformations) should be weighed against the risks of frequent relapse of mood episodes during pregnancy of about 20% to 70% over 12 months (76,77). These relapses can be seriously detrimental to the health of both mother and fetus.

In essence, individualized approach to treating affective disorders in women who have shown stability or benefit from lithium, especially when other treatments have not been successful should be emphasized and considered at the lowest effective dosages [21, 78].

This approach would aim to not only optimize outcomes but also minimize potential risks associated with lithium therapy. Ultimately, the decision to use Lithium during pregnancy should be made on a case-by-case basis, considering the severity of the mother's condition, her history of mood episodes, the availability of alternative treatments, and the potential risks to the fetus. Close monitoring by healthcare professionals is crucial to mitigate risks and ensure the best possible outcome for both the mother and the baby.

Conclusion

The use of lithium during pregnancy is associated with increased risks of congenital anomalies, particularly cardiac malformations, especially when exposure occurs during the first trimester. However, there is no consistent evidence linking lithium use to low birth weight or preterm birth when compared to bipolar women not using lithium. Managing lithium treatment in pregnant women requires careful monitoring of serum levels due to significant fluctuations in lithium clearance during pregnancy and postpartum. Physicians must weigh the benefits of maintaining maternal mood stability against potential fetal risks. In women with a history of severe bipolar episodes, especially those stabilized on lithium, a personalized approach using the lowest effective dose, with regular monitoring, is essential to balance therapeutic efficacy and safety for both mother and child.

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