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Exploring Lithium Concentrations in Maternal blood, Amniotic fluid and Umbilical cord blood: Babies Born to Mothers Treated with Lithium Carbonate for Bipolar Disorder

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ABSTRACT

Introduction: The distribution of lithium in amniotic fluid, maternal blood, and umbilical cord blood during pregnancy is poorly understood. Additionally, there is a need to describe neonatal complications observed among mothers using lithium for the treatment of bipolar disorder.

Methods: In an observational case-series study, we identified 37 pregnancies from 31 women with bipolar disorder who underwent lithium treatment throughout gestation from 2011 to 2018. We compared lithium levels in maternal blood, umbilical cord blood, and amniotic fluid using a mixed effects model. Additionally, we described the occurrence of maternal polyhydramnios and neonatal complications observed in our cohort.

Results: Mean lithium concentrations were 1.03 mM in amniotic fluid, 0.50 mM in umbilical cord blood, and 0.61 mM in maternal blood. Amniotic fluid exhibited significantly higher lithium levels compared to maternal blood (mean difference: 0.39 mM, 95% confidence Interval: [0.19-0.58], p<0.001).

Conclusion: Amniotic fluid had higher lithium levels than maternal blood, while umbilical cord blood levels were similar, suggesting that amniotic fluid accumulates lithium during pregnancy. Our study highlights potential complications for pregnant women with bipolar disorder using lithium, identifying important outcomes of concern for future research.

Keywords: Amniotic fluid; Bipolar disorder; Lithium; Neonatal outcome; Polyhydramnios

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INTRODUCTION

Lithium is a widely used mood stabilizer among patients with bipolar disorder and has long been the drug of choice [1]. Among women with severe and more unstable bipolar disorder, it is recommended to continue lithium administration under close monitoring to prevent depressive and dysphoric states during pregnancy [2][3].

The use of lithium during pregnancy has been associated with neonatal complications including congenital abnormalities [4], particularly cardiac malformations [5], with significant relationship to lithium consumption during first trimester [6][7]. Use of lithium late in pregnancy has also been associated with increased neonatal complications during and after birth [5][8]. While current literature does indicate a potential negative effect of lithium, no study has yet found a consistent association and, it remains unknown how lithium distributes between maternal blood, umbilical cord blood and amniotic fluid. Furthermore, it is unclear if the fetus could be showing signs of the known complication of lithium intoxication known as "nephrogenic diabetes insipidus" [9], which may lead to polyhydramnios—a condition affecting 0.5–2% of all pregnancies [10].

Given that lithium is believed to cross the placenta without obstruction, the fetus may be exposed by lithium levels during pregnancy, potentially leading to accumulation or symptoms of intoxication after birth. To explore this, we conducted an observational study involving 31 pregnant women with bipolar disorder who were using lithium as a mood stabilizer and compared levels of lithium in maternal blood, umbilical cord blood and amniotic fluid. We also describe the occurrence of maternal polyhydramnios and neonatal adverse outcomes related to lithium intoxication observed in our cohort.

METHODS

Study population

Through a local administrative patient database at Rigshospitalet, Copenhagen, Denmark (no longer accessible). The local administrative database was part of the mandatory electronic registration of International Classification of Diseases, 10th revision system (ICD-10) codes. We identified 31 women with bipolar disorder who were also receiving lithium treatment during their pregnancies from January 1, 2011, to December 31, 2018.The inclusion criteria included lithium administration throughout pregnancy, age over 18, and a singleton pregnancy. Women could contribute with multiple pregnancies during the study period if they continued to meet the inclusion criteria.

Measurements of lithium concentration

The concentration of lithium in maternal peripheral blood was monitored according to local guidelines throughout pregnancy and was kept stable

Table 1: Maternal, pregnancy and delivery characteristics of 31 women with bipolar disorder and receiving treatment with lithium, 2011-2018, Copenhagen, Denmark.

	No.	Median	Min	Max	IQR
Maternal age	37	35	26	44	31-38
Body mass index	32	25	18	37	23-31
Gestational age at delivery	36	38.4	26.7	41.7	37.3-39.6
Birth weight	35	3508	1035	4208	3178-3680
				Number	**%**
Mode of delivery				37	100
Induction				12	32.4
Elective cesarean				9	24.3
Acute cesarean				5	13.5
Vaginal				23	62.1
Smoking				<5	*
Alcohol consumption during pregnancy				<5	*
Type of disorder				37	100
Bipolar type 1				7	18.9
Bipolar type 2				21	56.8
Unspecified bipolar disorder				9	24.3
Medication during pregnancy				37	100
No other drugs than lithium				6	16.2
Lamotrigine				12	32.4
Quetiapine				12	32.4
Perphanazine				7	18.9
Other prescription medications**				13	35.1

No. Number of women with available information, Min, minimum. Max, maximum, IQR, Interquartile range

*Some numbers will be hidden to avoid potential identification of individuals

** Including levothyroxine, risperidone, pregabalin, olanzapine, phenelzine sulfate, zolpidem, melatonin, sertraline, ondansetron, simvastatin and escitalopram.

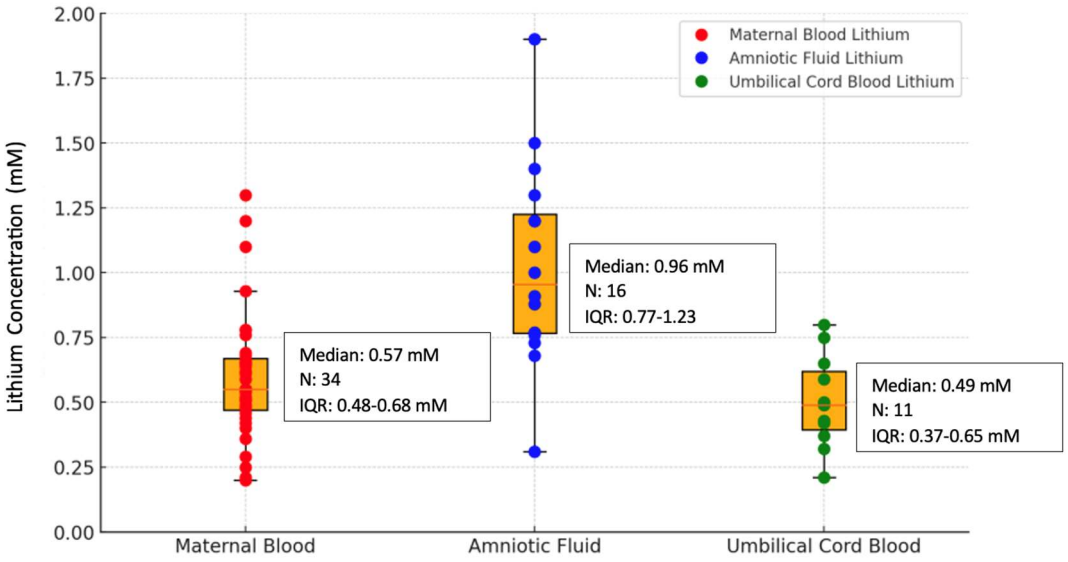

Figure 1: Lithium concentration in maternal blood, amniotic fluid and umbilical cord blood.
Figure 1 presents the distribution of lithium concentrations across three different biological samples: maternal blood (red dots), amniotic fluid (blue dots), and umbilical cord blood (green dots). The boxes in the plot represent the interquartile range (IQR) with the median marked by a line inside each box. The whiskers extend to the smallest and largest values within 1.5 times the IQR.

within a therapeutic index of 0.5-0.8 mmol/L [11]. In cases of unstable lithium levels, blood samples were taken more frequently, and doses were adjusted as needed. The maternal serum blood sample collected closest to delivery, up to a maximum of 14 days prior, was used in the analysis. Blood samples from both the mother and the umbilical cord were collected in Vacutainer sample tubes without gel and without the addition of an anticoagulant. These samples were stored at 18–24°C and centrifuged within 24 hours (typically 3–4 hours) for 10 minutes at 2200 rpm. The lithium assays were conducted using an ion-selective electrode instrument. Since the electrode is also sensitive to sodium, the results were adjusted by a factor of 0.017 to compensate for cross-sensitivity. The procedure was the same for amniotic fluid samples, except these were collected in regular glass containers without gel. The collection of amniotic fluid samples was part of the routine during birth.

Polyhydramnios and neonatal complications

Through medical records, we determined the incidence of neonatal adverse outcomes (occurring up to 7 days postpartum) and the occurrence of polyhydramnios during pregnancy, defined as an amniotic fluid index >24 cm. Neonatal complications of interest included: 1) signs of lithium intoxication (e.g., decreased muscle tone, tremor, hypoglycemia, cyanosis, bradycardia, hypotension, and lack of urination) and 2) other neonatal outcomes (e.g., chromosomal abnormalities, congenital malformations, bleeding and infarctions, respiratory distress syndrome, any type of ventilation support, admission to the neonatal intensive care unit before discharge, neonatal or fetal death, and an APGAR score below 7 at five minutes).

Maternal and pregnancy characteristics

Through medical records, we recorded information about maternal age, maternal body mass index (BMI), type of bipolar disorder (Type 1, Type 2, or unspecified), other prescription medications used, smoking status, alcohol use during pregnancy, gestational age at delivery, mode of delivery, and birthweight.

Statistical analysis

This study used an observational case series design to describe lithium concentrations in maternal blood, amniotic fluid, and umbilical cord blood, as well as maternal polyhydramnios and neonatal outcomes, in pregnant women with bipolar disorder treated with lithium. To investigate whether

Table 2: Mixed effects model for test of difference in lithium concentration between maternal blood serum, umbilical cord blood and amniotic fluid in 31 women with bipolar disorder and receiving treatment with lithium, 2011-2018, Copenhagen, Denmark.

Lithium concentration, mM	Number of tests	Mean (95% CI)	Median (95% CI)	Minimum (95% CI)	Maximum (95% CI)
Maternal blood serum	34	0.61 (0.53-0.70)	0.57	0.21	1.30
Umbilical cord blood	11	0.50 (0.38-0.62) p=0.14*	0.49	0.21	0.80
Amniotic fluid	16	1.03 (0.82-1.23) p<0.001*	0.96	0.31	1.90

CI, Confidence Interval

*Comparing concentrations of lithium to maternal blood serum

concentrations of lithium in maternal blood serum differed from those in umbilical cord blood and amniotic fluid, we employed a mixed effects model using 'PROC MIXED in SAS statistical software. This mixed-effects model includes a fixed effect reflecting the overall mean difference in lithium concentration between the different fluids (using all available samples) and a random effect to account for individual differences. This model was chosen as the best approach to handle missing data in some sample collections. Additionally, we describe the maternal occurrence of polyhydramnios and the aforementioned neonatal complications in descriptive terms.

Ethical approval

The study was approved by the Danish Data Protection regulations (j. no.: RH-2017-65) and was granted exemption from obtaining written and oral consent from the study participants by the Danish Patient Safety Authority (J. no.: 3-3013-1995/1). Samples were collected as part of routine clinical care, and data access in medical records was permitted under the exemption.

RESULTS

We identified 31 women who received lithium carbonate throughout their pregnancies. These women contributed a total of 37 pregnancies in the study. Three pregnancies lacked a blood sample; two were excluded entirely, while the third contributed amniotic fluid and umbilical cord blood samples. All pregnancies, except the two without any samples, were included in the mixed model, which accommodates missing data. In total, 34 maternal blood samples, 16 amniotic fluid samples, and 11 umbilical cord blood samples were collected. Maternal, clinical, and pregnancy characteristics are presented in Table 1. Fewer than five women reported smoking or alcohol use during pregnancy. The majority of women had vaginal deliveries (62%), while 38% underwent cesarean sections. Additionally, 32% of women underwent labor induction (defined as the use of misoprostol, a balloon catheter, and/or amniotomy). Most deliveries occurred at term, between 37 and 40 weeks' gestation, with only 11% occurring before 37 weeks. Six women (16%) used no additional medi cations during pregnancy, 12 (32%) received lamotrigine, another 12 (32%) received quetiapine, and 7 (19%) received perphenazine. Other commonly used drugs included levothyroxine, risperidone, pregabalin, olanzapine, phenelzine

Table 3: Maternal and neonatal outcomes of 31 women and 37 pregnancies imprinted by lithium consumption throughout pregnancy, 2011-2018, Copenhagen, Denmark.

	N. of assessed group	N. with outcomes (%)
Maternal outcomes		
Polyhydramnios	33	16 (48.5)
Neonatal outcomes		
Signs of lithium intoxication*	32	15 (46.8)
Decreased muscle tone	32	<5 (*)
Tremor	32	<5 (*)
Hypoglycemia	32	6 (18.8)
Cyanosis	32	<5 (*)
Bradycardia	32	<5 (*)
Hypotension	32	<5 (*)
Lack of urination	32	<5 (*)
Other neonatal outcomes**	33	16 (48.5)
Chromosomal abnormalities	32	<5 (*)
Congenital malformations	32	<5 (*)
Bleedings and infarctions	32	<5 (*)
Respiratory distress syndrome	32	<5 (*)
Any type of ventilation support	32	10 (31.3)
Admission to NICU	32	11 (34.4)
APGAR <7 at five minutes	32	0 (0.0)
Neonatal or fetal death	33	<5 (*)

NICU, Neonatal Intensive Care Unit.

* Some neonates showed more than one sign of lithium intoxication

**Some neonates had more than one adverse outcome

sulfate, zolpidem, melatonin, sertraline, ondansetron, simvastatin, and escitalopram. The highest number of medications used in addition to lithium was six.

Table 2 and Figure 1 present the comparison of lithium concentrations in maternal blood, umbilical cord blood, and amniotic fluid. The mean lithium concentration in maternal blood serum was 0.61 mM, 0.5 mM in umbilical cord blood, and 1.03 mM in amniotic fluid. Significantly higher concentrations of lithium were observed in amniotic fluid compared to maternal blood serum, with a mean difference of 0.39 mM (95% Confidence Interval [CI]: 0.19–0.58, $p<0.001$).

Looking at the development of maternal and neonatal complications, we found that 16/33 (48.5%) pregnancies were affected by polyhydramnios at some point during pregnancy.

For neonatal outcomes, we observed in 15 out of 32 pregnancies (46.8%) had neonates with signs of lithium intoxication and 16 out of 33 neonates developed other neonatal outcomes, as presented in Table 3. Among other neonatal outcomes, we observed 10 neonates requiring ventilation support, particularly treatment with CPAP and some of these also in need of life support Additionally, we observed a few cases of chromosomal abnormalities, including trisomy 21, and congenital malformations, such as Ebstein's anomaly, left-sided heart hypertrophy, hydronephrosis, and hypospadias. We also found infants with infarct changes in the right cerebral artery, confirmed by MRI, as well as cerebral bleeding.

Regarding the six women who received lithium as only medical treatment, two (33.3%) developed polyhydramnios, two neonates (33.3%) showed signs of lithium intoxication and two (33.3%) had other neonatal outcomes including neonatal or fetal death.

DISCUSSION

In our study, we found that concentrations of lithium in amniotic fluid were higher than those in maternal blood. However, concentrations of lithium in umbilical cord blood were similar to those in maternal blood, indicating that lithium fully crosses the placental barrier.

Our study has some clear limitations. Although adverse neonatal outcomes and maternal polyhydramnios were observed, concurrent medication use among study participants limits causal conclusions regarding lithium use in pregnancy. Furthermore, our sample size was very small making it practically impossible to conduct a well-proportioned and meaningful statistical analysis of the risk of developing adverse pregnancy and neonatal outcomes and their association with lithium concentration levels. We were unable to include a comparison group of pregnant women with bipolar disorder who were not using lithium treatment. Without this group, we could not investigate whether the risk of adverse outcomes was increased in our population compared to women who did not use lithium during pregnancy. As a result, our analysis was limited to descriptive data only. In addition to the small sample size, not all pregnancies had samples available from all three body fluids, making comparisons less reliable than if we had been able to use each woman as her own control. Our study has some strengths too. Despite the small sample size, we had data on lithium levels from three different tissues in the same women over a relatively short time period, which strengthens the credibility of our findings regarding lithium accumulation in amniotic fluid. Additionally, we had access to real-time documentation of adverse outcomes from medical records, minimizing recall bias that could occur if patients were asked later through questionnaires. Our study also reduced selection bias, as all samples were collected as part of routine clinical care for patients receiving lithium for bipolar disorder treatment.

Current literature exploring the impact of lithium use during pregnancy on neonatal health suggests an association with congenital abnormalities [5], particularly when used in the first trimester [4]. Some studies even indicate an elevated risk, particularly for cardiac malformations [7][6]. However, retrospective investigations have yielded differing results, showing no discernible link between lithium use during pregnancy and cognitive development, structural brain changes observed via MRI, or IQ variations in children aged six to 14 [12][13][14]. Administration of lithium throughout the third trimester, and particularly its continuation during labor, has been previously demonstrated to increase the risk of neonatal complications [5][8]. Yet, the literature remains in a state of controversy on this matter. A meta-analysis from

2018 pooled data from six cohort studies, involving 727 pregnancies with lithium exposure, and found no increased risk of neonatal complications but did identify an increased rate of neonatal readmissions [4]. Another population-based cohort study included 434 pregnancies with lithium exposure and found an association to preterm birth and other adverse neonatal outcomes [5]. Furthermore, a recent observational study suggests that discontinuing lithium dosage before delivery, as has been customary, should be reconsidered to prevent postpartum relapse [15]. We observed numerous cases with a variety of outcomes. Whereas previous research has primarily focused on congenital malformations, our study design does not permit confirmation or refutation of an increased risk. However, we identified several relevant cases within this relatively small population. Unlike previous studies, we also examined a range of additional outcomes not previously reported. This aspect makes our study relevant, as it could guide future research toward investigating associations with complications warranting further study, such as polyhydramnios and lithium intoxication.

In our study we observed several cases of polyhydramnios. Literature generally states, that polyhydramnios is a known side effect to lithium treatment during pregnancy, but we could only identify two case-reports confirming the hypothesis [16][17]. One might readily speculate that the emergence of polyhydramnios during pregnancy is linked to nephrogenic diabetes insipidus, with the fetus experiencing lithium exposure as a consequential factor [9] given the fact, that the amniotic space is a closed compartment and the fetal nephrogenic outlet consequently must contribute to a growing amount of amniotic fluid. 16/33(48.5%) pregnancies in our study population was affected by polyhydramnios which only affects 0.5-2% of all pregnancies in background population [10]. We did also discover a notable accumulation of lithium in amniotic fluid. Given that it is likely that fetal oral intake of amniotic fluid rises in the later stages of pregnancy, it's plausible to infer that this could contribute to an elevated lithium concentration in the combined fetal and maternal bloodstream. This emphasizes the significance of close monitoring of lithium concentration in maternal blood during the later stages of pregnancy. It also suggests that lithium concentration in amniotic fluid might be lower in the early stages of pregnancy, when fetal development is more susceptible to the influence of drugs.

In our population, we did observe a substantial proportion of severe complications. However, it is difficult to determine if these observations could be attributed to factors other than the use of lithium during pregnancy. Women in our population often used other prescription medications and/or delivered preterm, which could potentially contribute to adverse outcomes. Additionally, other unmeasured factors, such as socioeconomic status, might also have played a role.

Although our study cannot directly establish a relationship between the concentration of lithium and adverse outcomes, our dataset contains a high amount of different neonatal outcomes and complications in relation to pregnancy and birth. This emphasizes the necessity for close monitoring of both the mother and neonate, particularly in the immediate postpartum period in that we can neither exclude lithium as contributing factor to this matter. Our study highlights potential complications for pregnant women with bipolar disorder using lithium, identifying important outcomes of concern for future research.

CONCLUSION

The concentration of lithium in amniotic fluid was significantly higher than in maternal blood serum, indicating an accumulation. Our study highlights potential complications for pregnant women with bipolar disorder using lithium, identifying important outcomes of concern for future research.

Conflict of interest: The authors have no conflicts of interest to declare. All authors have completed the ICMJE uniform at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organization that might have an interest in the submitted work in the previous three years; no relationships or activities that could appear to have influenced the submitted work.

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Data availability: Permission to share data was not granted by the Danish Patient Safety Authority. The participants of this study did not give written consent for inclusion, nor for their data to be shared and given the sensitive nature of the research, data is not available.

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