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Peripartum lithium management: early maternal and neonatal outcomes.

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Abstract:	Background: It has been suggested that a 30-50% lithium dose reduction or lithium discontinuation 24-48h before delivery could minimize neonatal complications. We investigated the maternal lithemia changes around delivery after a brief discontinuation, the placental transfer of lithium at delivery, and the association between neonatal lithemia at delivery and acute neonatal outcomes. Methods: A retrospective observational cohort study was conducted in a teaching hospital (November/2006-December/2018). Data was extracted from the medical records. We included psychopathologically stable women, with a singleton pregnancy, treated with lithium in late pregnancy, with at least one maternal and neonatal lithemia at delivery. Lithium was discontinued 12h before a scheduled caesarea section or induction, or at admission day to hospital birth; and restarted 6-12h post. Results: Sixty-six mother-infant pairs were included, and 226 maternal and 66 neonatal lithemias were obtained. We found slight maternal lithemia fluctuations close to 0.20 mEq/L, and early postpartum relapse of 6%. The mean (SD) umbilical cord/mother intrapartum lithemia ratio was 1.10 (0.17). Fifty-six percent of neonates presented transient acute complications. Neonatal hypotonia was the most frequent outcome (N=15). Mean lithemia were 0.178 mEq/L higher in those with hypotonia than in those without (p=0.028). Limitations: It is a retrospective cohort of a moderate sample size of healthy uncomplicated pregnancies and results cannot be generalized to all pregnant treated with lithium. Conclusions: Lithium transfers completely across the placenta. A brief predelivery lithium discontinuation was associated with slight maternal lithemia fluctuations. Neonates exposed intrautero to lithium present frequent but transient acute effects.
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Opposed Reviewers:	
Response to Reviewers:	

Cover Letter

Journal of Affective Disorders
Editors-in-Chief
P. Brambilla, PhD, MD
JA. Soares, MD, PhD

Ref: JAFD-D-24-03407

Barcelona, August 2, 2024

Dear Editors

On behalf of my co-authors, I have already submit through www.editorialmanager.jad/default2.aspx the revised manuscript: "Peripartum lithium management: early maternal and neonatal outcomes".

We have also upload a letter with the answers, one by one, of each referee queries. We wrote in red all changes in the revised manuscript and in the revised tables. Moreover, we have added a Supplementary Figure 1 with the flow chart of the study as the reviewer I suggested.

We hope that you find it suitable for publication in the journal. Thank you very much for the attention to this paper.

Sincerely yours,

RMartin-Santos

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ANSWERS to Reviewers

Reviewer #1: This paper reports a retrospective study of women being treated with lithium over pregnancy, examining maternal, cord and neonate lithium levels.
The authors have replicated findings that lithium transfers through the placenta and there is a strong correlation between maternal and neonate lithium levels. The introduction covers the issue well.

Methods
Q1.Did women have to consent for the study?

ANSWER Q1. In the 2. Methods section, 2.5. Ethics we added this sentence: "*The Ethics Committee for Drugs Research of the Hospital Clinic (HCB/2020/1305) approved the study. Due that all data were retrospectively extracted from the medical record, it was not necessary to obtain the written informed consent of each women".*

Q2. In the section on Neonatal outcomes - what are the '...' after neurological?

ANSWER Q2. In the 2. Methods section, 2.2. Data collection and procedures, …"acute complications (e.g. respiratory, circulatory, neurological, …) we added in line 7 and 8: "acute complications *after a general physical examination of the newborn*" and " (neurological, *and other body systems*) *neonatal intensive (NICU, level IV) and intermediate (NICU, level II) care unit…*".

We also added in Table 1. First column, *Any short complication** and, at the end of the figure * *After a completed physical examination of the newborn.*

Q3. In the statistical section - 'effect sizes' should be inserted.

ANSWER Q3: *As the referee suggested we have included the term "effect size" in the* 2. Methods section, 2.x. *Statistical section. The second sentence of this section says now: The differences of maternal characteristics of mothers with monotherapy and those with polytherapy were quantified with the effect size measures Cohen's d (numeric variables) and Cohen's h (categoric variables).*

Results.
Q4. I found that the numbers were confusing, a consort diagram would be helpful.

ANSWER Q4. *As the referee suggested we added a flow chart of the study. See Supplementary Figure 1*.

Q5. What does the term 'delivery hospitalisation' mean? does it mean admission to the delivery ward?

ANSWER Q5. *We have changed the term along the paper: Delivery hospitalization for hospital birth. It is the day admission to hospital birth.*

Q.6. What does 'multiple lithium daily dosing' mean?

ANSWER Q6. *We corrected the sentence. Now is written "lithium multiple daily dosing" on page 8, paragraph 3.*

Q.7. Suggest inserting 'no significant differences' between mothers with polytherapy and monotherapy. - Are the statistics Cohen's d or h?

ANSWER Q7: *The objective of the descriptive analysis is to describe and quantify the differences in maternal characteristics between mothers undergoing polytherapy and monotherapy. For this reason, we provide descriptive measures in Table 1 and report effect size measures, Cohen's d and Cohen's h, in the text. No hypothesis tests are conducted because hypothesis testing is a tool of inferential but not descriptive statistics. Therefore, we do not speak of significant or non-significant differences.*

Q8. Table 1 is poorly laid out - it took some time to ascertain what it meant. The other tables are confusing.

ANSWER Q8. *We have reviewed all tables to improve them. See Table 1 to 4. All changes are in red colour.*

Q9. The results are presented poorly, there is a need to this section to be written for clarity.

ANSWER Q9. *As the referee comment we try to improve the written in this section. All changes are in red in different points of the Results section. See specifically the 3.4. Neonate characteristics, first paragraph, that was reorganized for better understanding.*

Q10. A key finding was that 4 women had a relapse to Mania [not maniac] (only 1 had sub therapeutic dose).

ANSWER Q10. *Thank you. We already have corrected. In 3. Results section, 3.2. Characteristics and course of maternal serum lithium concentration around delivery, second paragraph, line 11, we added: "One over four woman showed a subtherapeutic serum lithium concentration…".*

Q11. There seemed to be high rates of fetal anomalies - microcephaly, Ebstein's, aortic coarctation.

ANSWER Q11. *One of the aims of this study was to investigate the association between neonatal serum lithium concentrations at delivery and acute neonatal outcomes in a cohort of mothers in treatment with lithium in the third trimester of pregnancy. Some of these women were treated with lithium along all pregnancy. All neonates had a complete newborn physical examination.*

Lithium theratogenicity is more likely during organogenesis (20-56 days after fertilization, in the first trimester of pregnancy). Some of the observed acute complications could be to the neonatal lithemia or/and with the congenital malformation itself (i.e. the newborn with microcephalia has also hypertonia; or the newborn with postnatal aortic coartation was diagnosed through a systolic murmur 1/6).

Q12. The discussion was overly long and over inclusive and key points (fetal anomalies, women relapsing) not commented on.

ANSWER Q12. *We reviewed the discussion section. We tried to shortened and avoid be over inclusive. See Discussion section. We did not comment specifically on fetal anomalies apart from the acute neonatal complications at birth nor women relapsing as these two points were not the aims of the study. The study was not designed to test these and does not provide proper evidence for them.*

Reviewer #2: The manuscript describes the results of a retrospective cohort study on management of lithium around delivery, the association between

maternal and neonatal lithium blood level, and the association between lithium blood level and neonatal complications. The study is well executed, methods are thorough and results are presented in a complete and precise manner both in tables and figures. The commendable effort of these authors is an important addition to the, still very sparse, literature on lithium use during pregnancy.

Several aspects of the manuscript require improvement prior to consideration for publication: In general, please improve the grammar and spelling mistakes throughout the manuscript. The authors could consider asking a native English speaker for advice.

Q1.Abstract:
- Methods: needs clarification that data was extracted from the medical files.

ANSWER Q1. *As the referee suggested we included in the abstract: Methods: "... Data was extracted from the medical files"*

Q2. Abstract- Results: the authors mention that 'neonates experienced a limited number of...', but they find 56% of your neonates experience complications, this is not limited but over half of the sample! Also, the authors mention that neonatal hypotonia was the 'only' acute outcome associated with neonatal lithemia, but this should be viewed in the light of very few complications that were tested.

ANSWER Q2. *In the Abstract, Results section we added in line fourth: "After a complete newborn physical examination, 56% of neonates presented transient acute complications. Neonatal hypotonia was the most frequent outcome (N≥15), and it was....."*

Q3. Abstract- Conclusion: The statement 'A brief predelivery lithium discontinuation does not increase the risk of maternal early postpartum relapse' is not based on evidence from your study. Please remove from the conclusion. Additionally regarding the statement ' Neonates exposed intra-utero to lithium present few transient acute effects.', 56%, is not few.

ANSWER Q3. *We have already change the sentences: "Neonates exposed intrautero to lithium present frequent but transient acute effects". Moreover, we have removed the sentence related to the risk of maternal early postpartum relapse.*

Q4. Highlights points:
Please remove the bullet point: 'Peripartum lithium interruption does not increase early postpartum maternal relapse.' The study is not designed to test this, and does not provide proper evidence for this.

ANSWER Q4. *We agree with the referee. We removed this bullet point.*

Q5. Introduction:
- Check ref (Bergink et al, 2020), it is not currently in the reference list.

ANSWER Q5. *Sorry, it was a mistake. The reference has to be Bergink, 2023. See Introduction section, first paragraph, line 16: (Bergink, 2023).*

Q6. Introduction- The authors write that in third trimester the risk of lower serum lithium concentrations is highest. However, the largest study on this subject

(Wesseloo 2017), describes lowest serum levels in 2nd trimester and an increase in lithium levels closer to delivery. Please carefully review this paper and adjust your introduction section on this topic.

ANSWER Q6. *As the referee suggested we review Wesseloo et al., 2017 study and made some changes in the 1. Introduction section, third paragraph: …"Lithium elimination clearance parallels changes in GFR (Clark et al., 2022; Schou et al., 1979) and this result in reduced maternal serumconcentrations across pregnancy (Clark et al., 2022; Schou et al., 197; Westin et al., 2017; Wesseloo et al., 2017). A retrospective study of perinatal lithium pharmacokinetics has found that serum lithium concentrations increase slightly in the third trimester but remained 21% below the pre-pregnancy baseline (Wesseloo et al., 2017)"…*

Q7. Introduction- The recent paper by Schonewille 2023, published in International Journal of Bipolar Disorders, should be discussed in your introduction and discussion.

ANSWER Q7. *We have introduced Schonewille et al., 2023 paper in the 1. Introduction section, four paragraph: "A recent retrospective observational cohort study of neonates born to women with bipolar disorders treated with various other psychopharmacs with or without lithium found that fetal exposure to lithium were not associated with greater neonatal admissions to a ward with monitoring, compare to those exposed to other psychotropic treatments (Schonewille et al., 2023)", and in the 4.Discussion section, fifth paragraph: "Recently, a retrospective cohort study found not differences in acute complications between neonates exposed and non-exposed to lithium, questioning the necessity of neonatal admission with monitoring after lithium exposure (Schonewille et al., 2023). Independently of lithium exposure, and assuming that neonatal lithemias were in the therapeutical range, a 20% of these neonates were admitted to a neonatal ward monitoring (median stay of three days) due the high obstetric vulnerability of their mothers with bipolar disorders. " See also the Reference section.*

Q8. Methods/Statistical analysis:
- In paragraph 2 it is not clear how the tests are performed on the relation between neonatal outcomes and neonatal serum lithium concentrations. On which groups are t-tests performed?

ANSWER Q8: *We acknowledge that the description of the t-tests was unclear. On 2. Methods. 2.4. Statistical analysis, second paragraph, line one, we have revised the sentence to: "The relation between neonatal serum lithium concentrations and neonatal outcomes was analyzed using t-tests. Specifically, t-tests were conducted to compare the means of levels of serum lithium concentrations between neonates with and without complications. This analysis was performed only if there were more than 10 cases of complications in the sample to avoid unreliable and invalid statistical conclusions due to small sample size."*

Q9. Results:- Maternal characteristics: after schizoaffective disorder a N and % is missing.

ANSWER Q9. *3. Results. 3.1. Maternal characteristics. In the first paragraph, line 10 it was written: "schizoaffective disorder, bipolar type (N=1, 1.6%)…" we have change for: "schizoaffective bipolar disorder (N=1, 1,6%)…"*

Q10. Results- Neonatal characteristics: it is worth mentioning the most common neonatal complications in text, in addition to in Table 1.

ANSWER Q10. *As the referee suggested we added in the 3. Results section. 3.4.Neonatal characteristics we mention the most common neonatal complications in paragraph one, line three: "Fifty-six percent of the neonates (N=37) had acute complications [hypotonia (N=15), hypertonia (N=4), tremors (N=8), sucking difficulties (N=4), systolic murmurs (N=8), respiratory distress (N=3), cyanosis (N=1), hepatomegaly (N=1), hyperbilirubinemia (N=6), hypoglycemia (N=2), skin lesions (N=3), and cefalhematoma (N=3)]. In 29 of these neonates the complications were mild and transient and did not need any medical intervention immediately after birth.*

Q11. Results-3.5, last paragraph: it is stated that: 'Among those acute neonatal complications with at least 10 cases, the only complication statistically significantly associated to umbilical cord lithium serum concentration was hypotonia [0.712 (0.298) vs. 0.534 (0.214); t = 2.25, df = 60, p = 0.028)' The authors should clarify how many complications were tested for association, i.e. had more than 10 cases. Also, it is unclear what the numbers 0.712 and 0.534 indicate, lithium levels?

ANSWER Q11: *For clarity, in the 3.5 Results we have rewritten the sentence as follows: Hypotonia (N = 15) was the most frequently acute complication of a total of 12 found. It was the only one with at least 10 cases, and it was found to be statistically significantly associated with umbilical cord serum lithium concentration. The mean neonatal serum lithium concentration was 0.712 mEq/L (SD: 0.298) among neonates with hypotonia compared to 0.534 mEq/L (SD: 0.214) among neonates without hypotonia (t = 2.25, df = 60, p = 0.028).*

Q12- Table 1: check spelling for Polytherapy and TSH.

ANSWER Q12. *We have corrected spelling for polytherapy and TSH in table 1.*

Q13. Discussion:

- The high rate (56%) of neonatal complications in this study should be discussed.

ANSWER Q13. *We added at the Discussion section, five paragraph: ... "Knowledge about the potential association between late intrauterine exposure to lithium and early neonatal effects has been limited to case report, case series and small observational studies. Before 2004, around thirty well-documented cases of neonatal toxicity associated with a transient neurodevelopmental deficit after in utero exposure to lithium were published (Kozma, 2005). Most neonates needed supportive treatment between 10-14 days improving gradually. Several cases presented paired maternal and neonatal lithemias higher than 1.50 mEq/L, maternal psychiatric decompensation or obstetric complications. In 2005, a study combining a prospective sample of 10 mothers with 14 cases from previous reports assessed the association of newborn's serum lithium concentration and obstetric and neonatal outcomes (Newport et al., 2005). Neonates were divided in two groups: those with low lithemia (0.20 to 0.58 mEq/L) and those with high lithemia (0.70 mEq/L). The neonates of high lithium exposure group presented an increased risk of lower Apgar scores, higher rates of CNS and neuromuscular complications and longer hospital stays (mean=10 days), some of them having lithium toxic levels (1.20 to >4 mEq/L) and maternal-obstetric complications. (Aoki and Ruedy, 1971; Arnon et al., 1981; Flaherty and Krenzelok, 1997; Frassetto et*

al., 1979; Morrell et al., 1983; Nishiwaki et al., 1996; Wilbanks, 1970). Subsequently, a retrospective cohort study did not find a significant association between neonatal serum lithium concentrations at delivery (0.05 to 1.16 mEq/L) and neonatal outcomes (Molenaar et al., 2021). However, a high percentage of admissions to medium/high neonatal care (44.8%) with a median duration of three days, and acute complications (48.3%), mainly metabolic, were reported during the five postnatal days of protocolized clinical monitoring. Authors interpreted that due to this monitorization period several mild and transient complications were detected might otherwise go unnoticed. Recently, a retrospective cohort study found not differences in acute complications between neonates exposed and non-exposed to lithium, questioning the necessity of neonatal admission with monitoring after lithium exposure (Schonewille et al., 2023). Independently of lithium exposure, and assuming that neonatal lithemias were in the therapeutical range, a 20% of these neonates were admitted to a neonatal ward monitoring (median stay of three days) due the high obstetric vulnerability of their mothers with bipolar disorders. In our retrospective cohort study, the neonatal serum lithium concentration at birth ranged between 0.20 to 1.42 mEq/L. We observed that half of the neonates had slightly, transient and acute neonatal complications, similar to Molenaar et al. (2021), but ours were mainly neurological. We also found a significant statistical association between neonatal hypotonia and neonatal lithemia >0.75 mEq/L, similar to the high lithium exposure group of Newport et al., (2005) study. Nine percent of our neonates required admission to a NICU (level II or IV) by pediatric indication, with an average stay of three days, due to delivery complications or congenital malformations, a figure smaller than those found in Molenaar et al., (2021) and Schonewille et al., (2023). The results of all these studies, although they did not evaluate causality, indicated that neonatal symptoms should be anticipated after in late intrauterine exposure at any concentration, although lithium toxicity is more likely to occur at high serum lithium concentration. However, this association might be confounded by the occurrence of mood episodes during pregnancy, obstetrical complications, or use of concurrent psychopharmacs.

Q14. Discussion:
- Discuss the fact that only a few neonatal complications were tested for the association with lithium use, this limits interpretation. Additionally, the authors should discuss the association with hypotonia in more detail.

ANSWER Q14. *Please see ANSWER Q8. In the Discussion section, first paragraph we wrote: "Neonatal hypotonia was the most frequent acute outcome and, it was associated with neonatal lithium serum concentration".*

Q15. Discussion:
- The authors state: 'On one hand, it has been shown that higher maternal lithium concentrations at delivery are associated with more acute neonatal complications (Newport et al., 2005).' This should be discussed in the light of recent findings of the study by Molenaar, where no association was found when lithium levels were within the therapeutic range.

ANSWER Q15: *As far as we known Molenaar et al. (2024)[Molenaar et al. Focus (Am Psychiatr Publ). 2024 Jan;22(1):120-125)] is the same paper published in 2021. In the 4. Discussion section, five paragraph we added: "....* In our retrospective cohort study, we *observed that half of the neonates had slightly, transient and acute neonatal complications, similar to Molenaar et al. (2021), but ours were mainly neurological."...*

Q16. Discussion:
The authors state: 'a pre-delivery brief discontinuation of lithium therapy does not increase the risk of maternal relapse in early postpartum' Again, the study is not designed to test this, and does not provide proper evidence for this, so this should be rephrased.

ANSWER Q16: *We agree with the referee and we have already rephrased this sentence. See Discussion section, end of the fourth paragraph:"... We found a small rate of early postpartum relapse, and three of the four women had the lithemia within the therapeutical range.*

Highlights points

- Lithium completely equilibrates across the placenta, both in mono and polytherapy
- A brief peripartum discontinuation is associated with slight lithemia fluctuations.
- Neonatal lithemia at delivery is associated with transient neonatal complications.

Abstract (N=248)

Background: It has been suggested that a 30-50% lithium dose reduction or lithium discontinuation 24-48h before delivery could minimize neonatal complications. We investigated the maternal lithemia changes around delivery after a brief discontinuation, the placental transfer of lithium at delivery, and the association between neonatal lithemia at delivery and acute neonatal outcomes.

Methods: A retrospective observational cohort study was conducted in a teaching hospital (November/2006-December/2018). Data was extracted from the medical records. We included psychopathologically stable women, with a singleton pregnancy, treated with lithium in late pregnancy, with at least one maternal and neonatal lithemia at delivery. Lithium was discontinued 12h before a scheduled caesarea section or induction, or at admission day to hospital birth; and restarted 6-12h post.

Results: Sixty-six mother-infant pairs were included, and 226 maternal and 66 neonatal lithemias were obtained. We found slight maternal lithemia fluctuations close to 0.20 mEq/L, and early postpartum relapse of 6%. The mean (SD) umbilical cord/mother intrapartum lithemia ratio was 1.10 (0.17). Fifty-six percent of neonates presented transient acute complications. Neonatal hypotonia was the most frequent outcome (N=15). Mean lithemia were 0.178 mEq/L higher in those with hypotonia than in those without (p=0.028).

Limitations: It is a retrospective cohort of a moderate sample size of healthy uncomplicated pregnancies and results cannot be generalized to all pregnant treated with lithium.

Conclusions: Lithium transfers completely across the placenta. A brief predelivery lithium discontinuation was associated with slight maternal lithemia fluctuations. Neonates exposed intrautero to lithium present frequent but transient acute effects.

Key words: bipolar disorder, lithium, mother, neonate, peripartum, placental passage.

Words: 5149

Tables: 4

Figures: 2

Supplementary Tables: 1

Supplementary Figures: 1

TITLE: Peripartum lithium management: early maternal and neonatal outcomes.

RUNNING TITLE: Lithium management around delivery.

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Declaration of competing interest

EV has received grants and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Biogen, Biohaven, Bristol-Myers Squibb, Celon, Compass, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Viatris, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the EU Horizon 2020 and the Stanley Medical Research Institute. Other authors declare no financial interests or potential conflicts of interest regarding the authorship and publication of this article.

CRediT authorship contribution statement

Maria Luisa Imaz: Conceptualization, Formal analysis, Investigation, Resources, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. **Mercè Torra**: Resources, Validation, Writing – review & editing. **Klaus Langohr:** Formal analysis, Supervision, Visualization, Writing – review & editing. **Gemma Arca:** Resources, Writing – review & editing. **Dolors Soy:** Resources, Writing – review & editing. **Ana Sandra Hernández**: Resources, Writing – review & editing. **Lluïsa Garcia-Esteve:** Resources, Writing – review & editing. **Eduard Vieta**: Conceptualization, Supervision, Writing – review & editing. **Rocio Martin-Santos:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

1. Introduction

The perinatal period is a time of increased vulnerability for women with affective and non-affective psychotic disorders (Di Florio et al., 2013; Taylor et al., 2023). Especially, women with severe bipolar disorder or untreated bipolar disorder and those with non-affective psychotic disorder are at high risk of relapse in the postpartum period that during pregnancy (Sharma et al., 2020; Viguera et al., 2011; Wesseloo et al., 2016). Lithium remains the gold standard treatment for preventing recurrences in bipolar disorder type I (with mania and eventually major depression), and II (with depression and hypomania) (Tondo et al., 2019). It also has evidence of effectiveness of lithium augmentation in the treatment of refractory depression and in the treatment of affective symptoms in schizoaffective disorder (Leucht et al., 2015; Taylor et al., 2020). During the perinatal period lithium is proven effective as maintenance therapy for bipolar disorder and to prevent postpartum psychosis (Bergink et al., 2012; Wesseloo et al., 2016). Although one of the main concerns around the use of lithium during pregnancy is teratogenicity, the risk-benefit balance has lately shifted towards maintaining lithium during pregnancy to avoid the consequences of relapse in the mother (Bergink, 2023).

Lithium is a monovalent cation that is absorbed rapidly through the upper gastrointestinal tract and is almost exclusively renal eliminated without undergoing metabolization. Serum lithium concentrations mainly depend on intravascular volume and glomerular filtration rate (GFR). Lithium clearance is usually 20% to 30% of the GFR and thus varies with it (Grandjean and Aubry, 2009; Thomsen and Schou, 1999).

Pregnancy affects all aspects of kidney physiology altering the pharmacokinetics of lithium, which may affect both its efficacy and safety. Glomerular filtration rate increases early during pregnancy at one month after conception, peaks at approximately 40-50% above pre-pregnancy levels by the early second trimester and declines slightly toward term

(Cheung and Lafayette, 2013). Lithium elimination clearance parallels changes in GFR (Clark et al., 2022; Schou et al., 1979) and this result in reduced maternal serum lithium concentrations across pregnancy (Clark et al., 2022; Schou et al., 1979, Westin et al., 2017; Wesseloo et al., 2017). A retrospective study of perinatal lithium pharmacokinetics has found that serum lithium concentrations increase slightly in the third trimester but remained 21% below the pre-pregnancy baseline (Wesseloo et al., 2017). Moreover, natrium depletion, dehydration, diet, drug interactions, obstetrical complications (e.g. pre-eclampsia) and inconsistent treatment adherence can all cause changes in maternal serum lithium concentration (Clark et al., 2022). In order to maintain serum lithium concentration within the therapeutic optimal level of 0.5-0.8 mEq/L, lithium doses generally need to be adjusted during pregnancy (Westin et al., 2017).

Lithium equilibrates completely across the placenta (Newport et al., 2005). Higher maternal serum lithium concentrations at delivery have been associated with varied neonatal complications (hypoglycaemia, cardiac dysfunction, diabetes insipidus, thyroid dysfunction, respiratory distress, hypotonia and lethargy) requiring neonatal supportive care (Kozma, 2005; Newport et al., 2005; Pinelli et al., 2002). A previous retrospective observational cohort study did not observe a significant association between neonatal serum lithium concentrations at delivery and neonatal outcomes (Molenaar et al., 2021). A recent retrospective observational cohort study of neonates born to women with bipolar disorders treated with different psychopharmacs, with or without lithium, found that exposure to lithium was not associated with greater risk of neonatal ward admission (Schonewille et al., 2023). Moreover, having a bipolar disorder or schizophrenia, has been associated to slightly increased risk of obstetric and neonatal complications independent of medication used during pregnancy (Bennedsen et al., 1999; Boden et al., 2012; Schonewille et al., 2023).

In early postpartum, vascular volume rapidly decreases by approximately 40% and renal lithium clearance decreases to pre-pregnancy levels (Grandjean and Aubry, 2009). Hyperfiltration has been shown to continue at levels of 20% above normal at postpartum week 2 and resolve by 1 month postpartum (Odutayo and Hladunewich, 2012; Wesseloo et al., 2017). Lithium has a narrow therapeutic range (0.5-1.2 mEq/L), and in consequence, increased serum lithium concentrations (>1.5 mEq/L) may manifest as adverse effects in the mother (Hiemke et al., 2018), especially when an increased dose used during pregnancy is continued into the postpartum (Blake et al., 2008; Deligiannidis et al., 2014). If lithium is discontinued during pregnancy, it should be restarted immediately after delivery. During the first month postpartum a high target therapeutic serum lithium concentration (e.g. 0.8-1.0 mEq/L) has been recommended to optimize maternal relapse prevention (Wesseloo et al., 2016; Wesseloo et al., 2017).

Adequate monitoring of pregnant women treated with lithium around delivery is needed for early detection of subtherapeutic or toxic serum lithium concentrations to minimize potential mother and fetal/neonatal adverse effects. In the current research we want to study the behaviour of lithium around delivery in a large and homogeneous cohort of mothers treated with lithium in late pregnancy and their neonates. We evaluated the maternal serum lithium concentration changes around delivery, the lithium trans placental passage, and the association between neonatal serum lithium concentrations at delivery and acute neonatal outcomes.

2. Methods

2.1. Participants

Women attended in a perinatal psychiatric outpatient clinic of a single tertiary university hospital (November 2006-December 2018), and treated with lithium in the perinatal

period, were evaluated for eligibility to participate in this retrospective observational cohort study. Only psychopathologically stable women with healthy uncomplicated singleton pregnancy who used lithium in late pregnancy, and with at least one serum lithium concentration measurement obtained both in mother (vein puncture the admission day to hospital birth or at delivery) and in neonate (umbilical cord or neonatal vein puncture 24 hours post-delivery) were included in this cohort. Stable treated hypothyroidism was not an exclusion criteria.

2.2. Data collection and procedures

Study included demographic, psychiatric, obstetric, and early neonatal data for each woman and her corresponding pregnancies obtained from the hospital medical records. Obstetric complications evaluated included gestational diabetes, gestational hypertension, pre-eclampsia, polyhydramnios, oligohydramnios and premature rupture of membranes. Neonatal outcomes evaluated included prematurity (delivery prior to 37 weeks gestational age), birth weight, Apgar score at 1 and 5 minutes, umbilical cord arterial pH (UApH) and base excess (BE) values, serum TSH value, acute complications after a completed physical examination of the newborn (e.g. respiratory, circulatory, neurological, and other body systems), neonatal intensive (NICU, level IV) and intermediate (NICU, level II) care unit admission, and hospitalization duration after birth. We extracted information of all reported prenatal and postnatal congenital malformations. Positive neonatal findings were validated with a second expert neonatologist.

In line with the current NICE guideline (NICE CG192, 2014), the standard of care of the Perinatal Mental Health Unit Clinic-BCN is to monitor serum lithium concentrations every four-weeks until 34 weeks of pregnancy and then at least once weekly until delivery. Our recommendation for the management of lithium in the peripartum included: 1) the

advise to suspend lithium administration 12 hours before a scheduled caesarean section or induction or at admission day to hospital birth in the case of spontaneous deliveries, 2) the recommendation to restart lithium treatment 6 hours after vaginal delivery, or 12 hours post-delivery in case of caesarean birth; 3) to obtain serum lithium concentrations measurements simultaneously in mother-neonate pair at delivery; 4) to obtain mother serum lithium concentration measurement at day 2±1 postpartum, followed by (bi-) weekly during the first month postpartum. At the prenatal visit (week 33-35 of gestation), the psychiatrist carries out with each woman the risk-benefit analysis of maintaining the lowest effective lithium dose, or interrupting lithium dose around delivery. Each woman was given a written delivery planning kit containing the lithium extraction instructions and the tubes to perform the maternal (venous blood) and neonatal (umbilical cord) lithium measurements at delivery.

The maternal lithium therapeutic drug-monitoring (TDM) database contained information about the prescribed lithium dose and the dosing frequency, time of last lithium intake, time of blood sampling, serum lithium concentrations and types and doses of concomitant drugs. The peripartum time course of serum lithium concentration measurement was synchronized based upon the date of delivery (D0). Different time points of extraction before and after delivery were: most recent prepartum visit under steady-state condition (D-3), day before hospital birth (D-2), admission day to hospital birth (D-1), postpartum day 1 to day 7 (D+1 to D+7) and most recent post-partum visit under steady-state condition (D+8). The neonatal TDM databases contained serum lithium concentration in umbilical cord or first day of life.

2.3. Serum lithium analysis

For lithium analysis, maternal venous blood (5 ml), umbilical cord blood (5 ml) and neonates venous blood (2 ml) samples, were collected into BD Vacutainer® no- additive Z plus tubes (BD Diagnostics, Preanalytical Systems, Franklin Lakes, NJ 07417). Lithium concentrations were determined by means of an AVL 9180 electrolyte analyser based on the ion- selective electrode (ISE) measurement principle (Roche Diagnostics 9115 Hague Road Indianapolis, IN 46256). Lithium concentrations were reported in mEq/L, with two significant digits after the decimal points. A 2-point calibration were performed every 4 hours with a measurement range between 0.10 to 6.00 mEq/L. Limit of quantification (LoQ) was 0.20 mEq/L and detection limit (LoD) was 0.10 mEq/L. The within-day precision, expressed as coefficient of variation (CV) %, was between 0.97 to 4.1 %, and the between-day precision ranged between 1.3 to 6.4 %.

2.4. Statistical analysis

A descriptive analysis was performed to characterize the sample and the placental passage of lithium using, either absolute, and relative frequencies or means, standard deviations, and ranges as appropriate. The differences of maternal characteristics of mothers with monotherapy and those with polytherapy were quantified with the effect size measures Cohen's d (numeric variables) or Cohen's h (categoric variables). According to Cohen, values of both *d* and *h* equal to 0.2, 0.5, and 0.8 may be considered small, medium, and large (Cohen, 1988). To study the course of maternal serum lithium concentrations after a briefly discontinuation of lithium treatment around delivery, mean absolute and relative changes together with the corresponding 95% confidence intervals for paired data were computed. This was done on the one hand, for the changes from both the day before hospital birth and the admission day to hospital birth and, on the other hand, for the changes from delivery until postpartum days 2, 3, and 7, respectively. The ratio of serum

lithium concentration in umbilical cord to that in maternal serum was calculated for each maternal-infant pair as index of lithium placental passage. In addition, the relation between umbilical cord and maternal serum lithium concentrations surrounding delivery was illustrated with a scatterplot and quantified by means of Pearson's correlation coefficient.

The relation between neonatal serum lithium concentrations and neonatal outcomes was analysed using t-tests. Specifically, t-tests were conducted to compare the means (SD) of serum lithium concentrations between neonates with and without complications. This analysis was performed only if there were more than 10 cases of complications in the sample to avoid unreliable statistical conclusions due to small sample size.

All data were analysed using SPSS for Windows (Version 25; IBM Corp., Armonk, NY, United States) and the R software package (V4.3.3; The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at 0.05 two sided.

2.5. Ethics

The Ethics Committee for Drugs Research of the Hospital Clinic (HCB/2020/1305) approved the study. Written informed consent was not obtained due the retrospective extraction from medical records.

3. Results

3.1. Maternal characteristics

Table 1 shows mother characteristics. We identified data from 97 women and 111 pregnancies that were eligible for study inclusion. Forty-five pregnancies were excluded because there where first trimester abortions (N=13), twin pregnancy (N=4), serum lithium concentrations measurements were not available at delivery (N=27) and the analysis was performed at another laboratory (N=1). In total, we included 60 women and six women

contributed with 2 pregnancies each. Each pregnancy was counted separately (66 mother-infant pairs). The most common psychiatric diagnosis was a bipolar disorder type I (N=54, 90%). The remaining women (N=6, 10%) were diagnosed with bipolar disorder type II (N=1, 1.6%), bipolar disorder nos (N=1, 1.6%), cyclothymic disorder (N=1, 1.6%), schizoaffective bipolar disorder (N=1, 1.6%) or recurrent depressive disorder (N=2, 3.3%). See also Supplementary Figure 1, a flow chart of the study.

Mean (SD) maternal age at time of conception was 33.79 (5.05) years. All women received psychiatric prenatal care for the majority of pregnancy. Fourteen women were treated with levothyroxine for hypothyroidism and were stable. The duration of the pregnancy was between -29 days and +9 days with respect to the estimated due date. The mean (SD) time from admission day to hospital birth (D-1) to delivery (D0) was 16.37 (11.74) hours. Thirty-four (51.50%) of the deliveries were by caesarean section, 18 (27.30%) were schedule caesarean section, and 16 (24.20%) urgent caesarean section for failed induction of labour, respectively.

All patients were treated with lithium carbonate (tablets of 400 mg of modified release of lithium carbonate, Plenur®). Most women (N=56, 85%) used lithium multiple daily dosing, and 15% of women (N=10) once-daily dose. Forty mothers (61%) were on lithium monotherapy at the time of delivery. Polytherapy combinations (N=26, 39%) included lithium and antipsychotic □quetiapine (N=14), olanzapine (N=4), haloperidol (N=1), paliperidone (N=1), aripiprazole (N=1)□, lithium combined with two antipsychotics (quetiapine plus aripipiprazole (N=1), lithium and antidepressant □fluoxetine (N=4), paroxetine (N=1), venlafaxine (N=1), imipramine (N=1)□ or lithium and antipsychotic combined with an antidepressant [quetiapine plus fluoxetine (N=1)]. None were taking other medication known to interact with lithium (e.g. diuretics or non-steroidal anti-inflammatories).

Concerning maternal characteristics, differences between mothers with lithium poly- and monotherapy with respect to age (Cohen's d=0.19), ethnicity (Cohen's h=0.08), marital status (h=0.39), education level (h=0.18), and number of prior pregnancies (d=0.10) could be considered of small or medium size, whereas a larger difference was observed for tobacco use (h=0.46).

3.2. Characteristics and course of maternal serum lithium concentration around delivery

Table 2 shows the characteristics and course of maternal serum lithium concentration at different extraction time points (D-3 to D+8). The maternal lithium TDM database around delivery (from D-2 to D+7) consisted of 226 serum lithium concentration measurements and the distribution were as follow: 26 (11.50%) at D-2, 23 (10.17%) at D-1, 64 (28.31%) at D0, 112 (49.56%) in the week after D0 [15 (13.39%) D+1, 35 (31.25%) D+2, 19 (16.96%) D+3, 13 (11.60%) D+4, 5 (4.46%) D+5, 5 (4.46%) D+6, and 21 (17.85%) at D+7]. See Supplementary Figure 1.

In the whole sample (N=66), at extraction time point D-3, 5.59 (8.94) days before delivery, the mean (SD) lithium dose was 993.94 (284.9) mg/day, and the mean (SD) serum lithium concentration was 0.58 (0.21) mEq/L. A considerable proportion of serum lithium measurements (28/66, 42.40%) were at subtherapeutic threshold for effective mood stabilisation (<0.5 mEq/L). However, all women were psychopathologically stable. The mean (SD) time to lithium treatment discontinuation before D0 was 23.61 (13.57) hours. Serum lithium concentration at D0 was 0.54 (0.26) mEq/L and 34 women (51.60%) had a subtherapeutic lithium levels. The mean (SD) time to lithium treatment reinstauration after delivery was 12.22 (8.09) hours. Despite the brief interruption in lithium therapy around delivery [(37.36 (16.25) hours], only four women (6%) relapsed in the first 7 days postpartum. One of the four woman showed a subtherapeutic serum lithium concentration

(0.41 mEq//L) at delivery and the remaining three women had serum lithium concentration of 0.76, 0.78, and 0.84 mEq/L, respectively. Two women were on lithium monotherapy and two on polytherapy. All presented a mania episode with psychotic features. One from each group (monotherapy vs. polytherapy) required hospitalization. At extraction time point D+8, 11.67 (11.32) days after delivery, 95% of the total sample (N=63) underwent lithium monitoring in our laboratory. The mean (SD) lithium dose was 977.78 (294.27) mg/day, the mean (SD) serum lithium concentration was 0.65 (0.23) mEq/L, and only 13 from 63 women (19.60%) of the whole sample had subtherapeutic serum lithium concentrations. In this period (from D-3 to D+8), any women showed serum lithium concentrations higher than 1.50 mEq/L.

Figure 1A represents the longitudinal pattern of maternal serum lithium concentration around delivery (from D-2 to D+7). We also normalised serum lithium concentrations to the total daily dose in order to accurately compare serum lithium concentrations. See Figure 1B.

Finally, Table 3 presents comparisons between delivery (D0) and different extractions time points around it (D-2, D-1, D+1 to D+7). We used those data that allowed us to perform a paired data analysis. In a subsample of 22 women, according to the 95% CI of the mean change, the maternal serum lithium concentrations at T0 were significantly lower than those obtained at D-2 [mean decrease=0.19 mEq/L, (95%CI: 0.13–0.25)]; this corresponds to a mean relative decrease of 31.7% (95%CI: 22.3 – 41%). After reinstating lithium treatment, the mean absolute and relative increases from D0 to D+2 were 0.1 mEq/L (95%CI: 0.03–0.17)] and 33.6% (95%CI: 13.0–54.3), respectively.

3.3. Lithium placental passage

Table 4A presents serum lithium concentrations in neonates [umbilical cord (UC) or neonate 1ers day of life] and mothers (at D-1 and D0) and corresponding neonates to maternal ratio in all samples and in monotherapy and/or polytherapy.

In 60 mother-infant pairs, intrapartum maternal (D0) venous blood and UC were collected simultaneously to determine serum lithium concentrations. The mean (SD) UC serum lithium concentration was 0.57 (0.26) mEq/L and the mean (SD) D0 serum lithium concentration was 0.54 (0.26) mEq/L. The mean (SD) UC/D0 serum lithium concentration ratio was 1.10 (0.17) indicating complete placental passage. The degree of placental passage was uniform across a wide range of maternal serum lithium concentrations (0.14 to 1.40 mEq/L) and of estimated pregnancy lasts (35^{+6} to 41^{+2} weeks' gestation). There was a strong positive correlation between UC and D0 serum lithium concentration [Pearson correlation coefficient 0.95 (95%CI: 0.91–0.97)], which is visualized in Figure 2. The UC lithium concentrations exceeded maternal serum lithium concentrations at delivery in 45/60 (75%) of paired analyses. There was not difference between the UC/D0 serum lithium concentration ratios in lithium monotherapy group [1.11 (0.17)] versus polytherapy group [1.08 (0.17) ($F=0.428$; df =1, 63; $p=0.515$)].

Table 4B shows paired maternal and neonatal serum lithium concentrations and corresponding neonatal/maternal ratios in a subgroup of mother-infant pairs (N=19) with lithemias in the three point of extraction: D-1, D0 and UC. The mean (SD) UC/D-1 ratio was 0.97 (0.10) and the mean (SD) UC/D0 ratio was 1.15 (0.12), after a mean (SD) of 25.25 (14.32) hours have elapsed since taking the last dose of lithium prior to delivery. In the neonate, the UC serum lithium concentrations exceeded maternal serum lithium concentrations at D-1 in 6/19 (31.58%), and maternal serum lithium concentrations at D0 in 17/19 (89.47%) of paired analysis, indicating that lithium elimination was slower in neonates.

3.4. Neonatal characteristics

Table 1 shows the neonatal characteristics at birth**.** Sixty-four (97%) neonates were born at term, whereas two neonates (3%) were spontaneously born late preterm, at 35^{+6} and 36^{+2} weeks of gestation. Ninety-one percent (N=60) of neonates roomed with their mothers on the maternity ward. Fifty-six percent of the neonates (N=37) had acute complications [hypotonia (N=15), hypertonia (N=4), tremors (N=8), sucking difficulties (N=4), systolic murmurs (N=8), respiratory distress (N=3), cyanosis (N=1), hepatomegaly (N=1), hyperbilirubinemia (N=6), hypoglycemia (N=2), skin lesions (N=3), and cefalhematoma (N=3)]. In 29 of these neonates the complications were mild and transient and did not need any medical intervention immediately after birth. Five neonates (7.6%) were admitted to the NICU level II. One neonate due to postnatal aortic coarctation was transferred to another hospital for cardiac catheterization, another required phototherapy due to non-isoimmune hyperbilirubinemia, and three-needed respiratory support due to meconium syndrome. A neonate gave birth in a pediatric monographic hospital with NICU level IV because a prenatal Ebstein´s anomaly. Moreover, another neonate presented a microcephaly and cerebral ventriculomegaly, subsequently diagnosed as spastic cerebral palsy of unknown cause. A full overview of neonatal complications with additional neonatal serum lithium concentration at delivery and maternal treatment can be found in Supplementary Table 1.

There were no significant differences between lithium monotherapy (N=18/40) and polytherapy (N=13/26) groups with regard to acute neonatal complications (p=0.69), being neurological complications (hypotonia, hypertonia, tremors, and sucking difficulties) the most frequent in both groups. The mean (SD) hospitalization stay for all neonates attended in the maternity hospital was 3.17 (1.21) days.

3.5. Neonatal serum lithium concentration and acute neonatal outcomes

The neonatal lithium TDM database consisted on 66 neonatal serum lithium concentration measurements: 61 (92.42%) were obtained from the umbilical cord and 5 (7.58%) from neonatal vein puncture within 24 hours after delivery (N=5, 7.58%). The mean (SD) umbilical cord serum lithium concentrations (N=61) was 0.57 (0.26) mEq/L, and neonatal vein puncture serum lithium concentration (N=5) was 0.49 (0.13) mEq/L. There were no incidents in the umbilical cord/neonates during blood extraction. See Table 4A.

Hypotonia (N=15) was the most frequently acute neonatal complication of a total of 12 found. It was the only one with at least 10 cases, and it was found to be statistically significantly associated with neonatal serum lithium concentration. The mean (SD) neonatal serum lithium concentration was 0.712 (0.298) mEq/L among neonates with hypotonia compared to 0.534 (0.214) mEq/L among neonates without hypotonia (t=2.25, df=60, p=0.028).

4. Discussion

In this retrospective observational cohort study of 66 mother-infant pairs, we found slightly maternal serum lithium concentration fluctuations after a briefly discontinuation of lithium around delivery. The degree of placental passage was complete across a wide range of maternal serum lithium concentrations and of estimated pregnancy lasts. Neonatal hypotonia was the most frequent acute outcome and, it was associated with neonatal serum lithium concentration.

The human placenta is a complex organ that acts as the interface between maternal and fetal blood circulation. Lithium, with a molecular weight of 7 Da, readily diffuses across the placenta (Griffiths and Campbell, 2015). Umbilical cord serum lithium concentrations

at delivery, especially when compared to maternal concentrations, provide valuable information about fetal lithium exposure *in utero* (Bank et al., 2017).

Already, in the late 1960s and early 1970s, several case reports showed that lithium crosses the placental barrier completely (Fries, 1970; Silverman et al., 1971; Weinstein and Goldfield, 1969) or partially (Aoki and Ruedy, 1971; Wilbanks, 1970), depending of the time point extraction in mother-infant pairs at delivery. In 1975, Schou and Admisen published a case series (nine new cases and two from the literature) of lithium concentration obtained in mother-infant pair at delivery carried out in different laboratories that indicated that there was a full equilibration on lithium across de placental barrier. More recent, a cohort study (Newport et al., 2005) observed a complete placental passage of lithium across an extensive range of maternal serum lithium concentrations in 10 mother-infant pairs. In a recent retrospective cohort study (Molenaar et al., 2021) showed a strong neonatal/maternal positive correlation in serum lithium concentrations for a wide range of extraction time points around delivery. All these studies were limited by the small sample sizes (Aoki and Ruedy, 1971; Fries, 1970; Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975; Silverman et al., 1971; Weinstein and Goldfield, 1969; Wilbanks, 1970) or because some samples were not taken in mothers (intrapartum) and neonates (umbilical cord) simultaneously at delivery (Aoki and Ruedy, 1971; Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975; Weinstein and Goldfield, 1969; Wilbanks, 1970) or lithemias were analyzed in different laboratories (Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975) or women took different types of lithium formulations (Molenaar et al., 2021), introducing inaccuracies in the index of lithium placental passage. In our study, all lithemias were analysed in the same laboratory and all women were taking lithium carbonate. Our results in a sample between two and six time higher than previously reported (Molenaar et al., 2021; Newport et al., 2005; Schou

and Admisen, 1975) confirm that lithium has a complete lithium placental passage, both in lithium monotherapy and polytherapy,

Due to a decrease in lithium clearance and fluid volume contraction peripartum, maternal serum lithium concentration increased in early postpartum with consequent maternal intoxication risk (Schou et al, 1973, Wesseloo et al., 2017). It has been shown that higher maternal serum lithium concentrations at delivery are associated with more acute neonatal complications (Newport et al., 2005). To minimize the early neonatal risk, different strategies have been proposed along last decades. Some authors have suggested lowering lithium dose by 30-50% some days before delivery (Goodwin, 2009; Mitchell, 2004). This approaches makes sense, as the neonatal elimination half-life of lithium is around 68-96 hours (Mackay et al., 1976; Rane et al., 1978). However, as the elimination half-life of lithium in a young adult is 18-28 hours, it could led to an increase in subtherapeutic lithemia (<0.5 mEq/L) with the consequent risk of maternal postpartum relapse. Other authors recommended stopping lithium treatment 24-48h before a planned hospital birth (cesarean section or induction) or even discontinuing lithium when a woman presents active labouring (Newport et al., 2005; Schou et al., 1973). This approach supposes an average lithemia reduction of 0.28 mEq/L (Newport et al., 2005). Some authors have observed that symptoms worsened in patients when serum lithium concentration decreases abruptly more than 0.20 mEq/L below their personal baseline concentration and/or below the therapeutic concentration of 0.40 mEq/L (Severus et al., 2008). Finally, the most recent proposed strategy was to careful monitoring serum lithium concentrations around delivery, and to use the maternal lowest effective lithium dose instead of discontinuation in all cases (Deligiannidis et al., 2014). Because, after excluding women with complications or preterm births, there is a considerable variation in gestational lengths (Jukic et al., 2013), this approach needs a close coordination of hospital

multidisciplinary team (psychiatric, obstetric, and neonatologist) around delivery (Frayne et al., 2018). Our study showed that maintaining predelivery the minimal individualized effective serum lithium concentration, stopping lithium 12 hours before to planned hospital birth, or at hospital admission in active labour, and restarting lithium treatment as soon as the mother is medically stable (6-12h after delivery), allow to obtain around delivery a mean lithemia fluctuation close to 0.20 mEq/L. We found a small rate of early postpartum relapse, and three of the four women had the lithemia within the therapeutical range.

Knowledge about the potential association between late intrauterine exposure to lithium and early neonatal effects has been limited to case report, case series and small observational studies. Before 2004, around thirty well-documented cases of neonatal toxicity associated with a transient neurodevelopmental deficit after in utero exposure to lithium were published (Kozma, 2005). Most neonates needed supportive treatment between 10-14 days improving gradually. Several cases presented paired maternal and neonatal lithemias higher than 1.50 mEq/L, maternal psychiatric decompensation or obstetric complications. In 2005, a study combining a prospective sample of 10 mothers with 14 cases from previous reports assessed the association of newborn's serum lithium concentration and obstetric and neonatal outcomes (Newport et al., 2005). Neonates were divided in two groups: those with low lithemia (0.20 to 0.58 mEq/L) and those with high lithemia (0.70 mEq/L). The neonates of high lithium exposure group presented an increased risk of lower Apgar scores, higher rates of CNS and neuromuscular complications and longer hospital stays (mean=10 days), some of them having lithium toxic levels (1.20 to >4 mEq/L) and maternal-obstetric complications. (Aoki and Ruedy, 1971; Arnon et al., 1981; Flaherty and Krenzelok, 1997; Frassetto et al., 1979; Morrell et al., 1983; Nishiwaki et al., 1996; Wilbanks, 1970). Subsequently, a retrospective cohort study did not find a significant association between neonatal serum lithium concentrations

at delivery (0.05 to 1.16 mEq/L) and neonatal outcomes (Molenaar et al., 2021). However, a high percentage of admissions to medium/high neonatal care (44.8%) with a median duration of three days, and acute complications (48.3%), mainly metabolic, were reported during the five postnatal days of protocolized clinical monitoring. Authors interpreted that due to this monitorization period several mild and transient complications were detected might otherwise go unnoticed. Recently, a retrospective cohort study found not differences in acute complications between neonates exposed and non-exposed to lithium, questioning the necessity of neonatal admission with monitoring after lithium exposure (Schonewille et al., 2023). Independently of lithium exposure, and assuming that neonatal lithemias were in the therapeutical range, a 20% of these neonates were admitted to a neonatal ward monitoring (median stay of three days) due the high obstetric vulnerability of their mothers with bipolar disorders. In our retrospective cohort study, the neonatal serum lithium concentration at birth ranged between 0.20 to 1.42 mEq/L. We observed that half of the neonates had slightly, transient and acute neonatal complications, similar to Molenaar et al. (2021), but ours were mainly neurological. We also found a significant statistical association between neonatal hypotonia and neonatal lithemia >0.75 mEq/L, similar to the high lithium exposure group of Newport et al., (2005) study. Nine percent of our neonates required admission to a NICU (level II or IV) by pediatric indication, with an average stay of three days, due to delivery complications or congenital malformations, a figure smaller than those found in Molenaar et al., (2021) and Schonewille et al., (2023). The results of all these studies, although they did not evaluate causality, indicated that neonatal symptoms should be anticipated after in late intrauterine exposure at any concentration, although lithium toxicity is more likely to occur at high serum lithium concentration. However, this association might be confounded by the occurrence of mood episodes during pregnancy, obstetrical complications, or use of concurrent psychopharmacs.

4.1. Strengths and limitations

As far as we known, this is the largest sample size study analysing the lithium behavior in mother-infant pairs around delivery and the acute neonatal outcomes after late intrauterine lithium exposure. Strengths of the study were the homogeneity of the sample, the use of a single lithium manufacturer and that all serum lithium concentration measurements were done in a single laboratory. However, the study is not without limitations. It is a retrospective cohort of a sample of healthy uncomplicated pregnancies. For this reason, the results of the study cannot be generalized to all pregnant women treated with lithium. On the other hand, this was a naturalistic study done in real life and we cannot have a paired maternal lithium measurements in each extraction time point at peripartum and in all mother-infant pairs simultaneously at delivery. We do not have data of a cohort control group of women and their neonates of the same characteristics not exposed to lithium treatment, on the same period of follow-up. Finally, sample size was moderate given that there are not big numbers of pregnancies exposed to lithium since we started our standard procedures (De Prisco and Vieta, 2024).

4.2. Implications and conclusions

Appropriate management of lithium treatment around delivery is a difficult balancing act. Lithium equilibrates completely across the placental barrier and maintaining pre-delivery maternal serum lithium concentrations at the minimal individualized effective level and briefly discontinuing lithium at delivery may minimize the risk of maternal and neonatal complications. Additional investigations in bigger samples, prospective design, other perinatal bipolar subgroups and control groups are warranted to better describe the relationship between quantified maternal and fetal lithium exposure near to delivery and maternal and neonatal acute complications.

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CRediT authorship contribution statement

ML: Conceptualization, Formal analysis, Investigation, Resources, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. MT: Resources, Validation, Writing – review & editing. KL: Formal analysis, Supervision, Visualization, Writing – review & editing. GA: Resources, Writing – review & editing. DS: Resources, Writing – review & editing. ASH: Resources, Writing – review & editing. LGE: Resources, Writing – review & editing. EV: Conceptualization, Supervision, Writing – review & editing. RMS: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

EV has received grants and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Biogen, Biohaven, Bristol-Myers Squibb, Celon, Compass, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Viatris, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the EU Horizon 2020 and the Stanley Medical Research Institute. Other authors declare no

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Appendix A. Supplementary data

Supplementary table 1 and supplementary figure 1 can be found online.

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Table 1. Maternal and neonatal characteristics and serum lithium concentrations around delivery.

		Lithium therapy				
	All cases	Monotherapy	Polytherapy			
	N=66	N=40	All N=26	Li+AP N=19	Li+AD N=6	Li+AP+AD N=1
Maternal characteristics Mean /SD) / N (%)						
Age at time of delivery	34.80 (5.02)	34.40 (5.11)	35.35 (4.93)	36 (5.16)	33.50 (4.41)	34
Caucasian	64 (97.00)	39 (97.50)	25 (96.20)	18 (94.70)	6 (100)	1
University degree	32 (48.50)	18 (45.00)	14 (53.80)	10 (52.60)	3 (50.0)	1
Married or living together	65 (98.50)	40 (100)	25 (96.20)	18 (94.70)	6 (100)	1
Smoking in late pregnancy	15 (22.7)	6 (15.00)	9 (34.60)	8 (42.10)	1 (16.70)	0
Primiparous	49 (74.20)	29 (72.50)	20 (76.90)	15 (78.90)	4 (66.70)	1
Caesarean section	34 (51.50)	15 (37.50)	19 (73.10)	16 (84.20)	3 (50.00)	0
Meconium in amniotic fluid	6 (9.10)	6 (15.00)	0	0	0	0
Prolonged rupture of membranes[a]	11 (16.70)	6 (15.00)	5 (19.20)	3 (15.80)	2 (33.30)	0
Lithium dosage closest to delivery	993.94 (284.94)	935.00 (257.75)	1084.62 (305.53)	1136.84 (326.96)	966.67 (196.63)	800
Neonatal characteristics Mean /SD) / N (%)						
Preterm birth (<37 weeks)	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Macrosomia (>4000 gr)	10 (15.20)	7 (17.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Apgar score $_{1\ min}$ <6	3 (4.50)	3 (7.50)	0	0	0	0
Apgar score $_{5\ min}$ < 8	0	0	0	0	0	0
pH-value cord arterial	7.22 (0.07)	7.21 (0.08)	7.23 (0.07)	7.24 (0.06)	7.18 (0.07)	-
BE-value cord arterial (mmol/L)	-7.48 (2.62)	-7.76 (2.46)	-6.99 (2.88)	-6.56 (2.50)	-8.37 (3.98)	-
Acute complications[b]:						
Hypotonia	15 (22.72)	10 (25.00)	5 (19.23)	2 (10.50)	3 (50.00)	0
Hypertonía	4 (6.10)	2 (5.00)	2 (7.70)	1 (10.50)	0	0
Tremors	8 (12.10)	3 (7.50)	5 (19.20)	4 (21.10)	1 (16.70)	0
Sucking difficulties	4 (6.00)	3 (7.50)	1 (3.85)	1 (5.26)	0	0
Systolic murmur	8 (12.10)	5 (12.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Respiratory distress[c]	3 (4.50)	3 (7.50)	0	0	0	0
Cyanosis	1 (1.50)	1 (2.50)	0	0	0	0
Hepatomegaly	1 (1.50)	1 (2.50)	0	0	0	0
Hyperbilirrubinemia	6 (9.10)	3 (7.50)	3 (11.50)	3 (15.80)	0	0
Hypoglycemia	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Skin lesions[d]	3 (4.50)	2 (5.00)	1 (3.85)	0	1 (16.70)	0
Cefalhematoma	3 (4.50)	2 (5.00)	0	0	1 (16.70)	0
THS serum (mUI/L)	5.04 (3.48)	4.97 (3.33)	5.19 (3.78)	5.45 (3.70)	4.94 (4.39)	1.63
Hospital stay (days) (N=65)	3.17 (1.21)	3.05 (1.20)	3.38 (1.27)	3.44 (1.42)	3.33 (0.81)	2

Abbreviations: BE=base excess; Li= lithium; Li+AP= lithium + antipsychotic; Li+AD= lithium + antidepressant; Li+AP+AD= lithium + antipsychotic + antidepressant; D-2= day before delivery hospitalization. TSH=tyroid stimulating hormone

[a]Prolonged rupture of membranes (>24 hours): preterm (n=1), term (n=10); [b]After a newborn complete physical examination; [c]Respiratory distress due to meconium syndrome; [d]Skin lesions: pustulose (n=1), ecchymosis (n=2).

Table 2. Characteristics and course of maternal serum lithium concentrations (mEq/L) at the different extraction time points (from T-3 to T+8) around delivery.

	Lithium therapy							
Extraction time point	**Dose (mg/d)**		**[Li] (mEq/L)**		**[Li] <0.5 (mEq/L)**	**Steady state**	**Pre-dose 12±2 h**	**Treatment adherence**
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N (%)**	**N (%)**	**N (%)**	
D-3 Pregnancy most recent visit	66	993.94 (284.94)	66	0.58 (0.21)	28 (42.40)	66 (100)	66 (100)	Some partial
D-**2** Day before hospital birth	66	993.9 (284.94)	26	0.65 (0.20)	8 (30.80)	26 (100)	26 (100)	Some partial
D-**1** Admission day to hospital birth	0	_	23	0.59 (0.30)	10 (43.50)	_	_	Some partial
D0 Delivery[a]	41	643.90 (317.84)	64	0.54 (0.26)	33 (51.60)	_	_	Complete
D+**1** Postpartum day 1	64	981.25 (288.8)	15	0.61(0.33)	7 (46.70)	_	15 (100)	Complete
D+2 Postpartum day 2	65	984.62 (296.45)	35	0.63 (0.26)	9 (25.70)	_	25 (100)	Complete
D+3 Postpartum day 3	66	984.8 (302.42)	19	0.73 (0.29)	4 (21.10)	_	19 (100)	Complete
D+4 Postpartum day 4	66	987.88 (295.36)	13	0.71 (0.28)	4 (30.80)	_	13 (100)	Some partial
D+5 Postpartum day 5	66	984.85 (294.70)	5	0.76 (0.29)	1 (20.00)	1 (20)	5 (100)	Some partial
D+6 Postpartum day 6	66	984.85(294.70)	5	0.59 (0.26)	2 (40.00)	5 (100)	5 (100)	Some partial
D+7 Postpartum day 7	66	984.85(294.70)	21	0.65 (0.26)	4 (19.00)	21 (100)	21 (100)	Some partial
D+8 Postpartum most recent visit	63	977.78 (294.27)	63	0.65 (0.23)	13 (19.70)	63 (100)	63 (100)	Some partial

[a]Lithium dosage was restarted 6-12 hours after delivery.

Table 3. Comparison of maternal mean (SD) serum lithium concentration [Li] (mEq/L) around delivery. Analysis of paired data between different extraction time points (day before hospital birth, admission day for hospital birth, postpartum day 2, 3 and 7) with delivery.

Time point of extraction			[Li] Δ mean (mEq/L) to delivery [95%CI]	% change of [Li] related to delivery [95%CI]
N	**Delivery time point (D0) [Li] Mean (SD)**	**Other time points (D-2, D-1, D+2, D+3, D+7) [Li] Mean (SD)**		
22	**D0 Delivery** 0.45 (0.23)	**D-2** Day before hospital birth[a] 0.64 (0.21)	-0.19 [-0.25, -0.13]	-31.7 [-41.0, -22.3]
22	**D0 Delivery** 0.54 (0.29)	**D-1** Admission day to hospital birth 0.60 (0.31)	-0.07 [-0.09, -0.05]	-12.8 [-16.5, -9.1]
34	**D0 Delivery** 0.52 (0.24)	**D+2** Postpartum day 2 0.62 (0.26)	0.1 [0.03, 0.17]	33.6 [13.0, 54.3]
18	**D0 Delivery** 0.66 (0.27)	**D+3** Postpartum day 2 0.72 (0.29)	0.06 [-0.06, 0.18]	15.0 [-9.2, 39.2]
19	**D0 Delivery** 0.59 (0.28)	**D+7** Postpartum day 7[a] 0.63 (0.26)	0.04 [-0.1, 0.19]	26.8 [-11.4, 64.9]

Abbreviation: [Li]= Lithium concentration; CI= Confidence interval;
Symbol: Δ=Mean difference.
[a]Serum lithium concentrations were measured at steady-state and 12±2 hours post-dose.

Table 4-A. Serum lithium concentrations in neonates [umbilical cord or neonate 1er day of life] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	23	0.59 (0.30)	17	0.61 (0.33)	6	0.55 (0.23)	5	0.62 (0.18)	1	0.23 (0)	0	-
D0	64	0.54 (0.26)	39	0.50 (0.27)	25	0.61 (0.23)	18	0.63 (0.23)	6	0.55 (0.25)	1	0.74
UC	61	0.57 (0.26)	38	0.52 (0.26)	23	0.66 (0.24)	18	0.66 (0.23)	4	0.65 (0.25)	1	0.74
N1	5	0.49 (0.13)	2	0.54 (0.17)	3	0.46 (0.13)	1	0.31 (0)	2	0.54 (0.01)	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.97 (0.10)	4	0.99 (0.13)	3	1.03 (0.12)	1	0.87 (0)	0	-
UC/D0	60	1.10 (0.17)	37	1.09 (0.17)	23	1.11 (0.17)	18	1.07 (0.13)	4	1.31 (0.19)	1	1.00
N1/D-1	3	0.83 (0.14)	2	0.82 (0.20)	1	0.84 (0)	1	0.84(0)	0	-	0	-
N1/D0	4	0.96 (0.26)	2	0.98 (0.30)	2	0.93 (0.33)	0	-	2	0.93 (0.33)	0	-

Table 4-B. Paired serum lithium concentrations in neonates [umbilical cord] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	19	0.59 (0.33)	15	0.60 (0.35)	4	0.55 (0.25)	3	0.66 (0.16)	1	0.23	0	-
D0	19	0.53 (0.31)	15	0.54 (0.33)	4	0.48 (0.26)	3	0.60 (0.16)	1	0.14	0	-
UC	19	0.58 (0.31)	15	0.57 (0.33)	4	0.58 (0.37)	3	0.71 (0.11)	1	0.20	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.96 (0.10)	4	1.02 (0.13)	3	1.08 (0.09)	1	0.86	0	-
UC/D0	19	1.15 (0.12)	15	1.07 (0.09)	4	1.25 (0.15)	3	1.19 (0.12)	1	1.42	0	-

Abbreviations:Li= Lithium; Li+AP= Lithium+antipsychotic; Li+AD= Lithium+antidepressant; Li+AP+AD= Lithium+antipsychotic+ antidepressant; D-1=Admission day to hospital birth; D0=Delivery (intrapartum); UC=Umbilical cord; N1=Neonate 1st day of life.

Figure 1. Course of maternal serum lithium concentration around delivery (N=66). Figure (A) shows the measured serum concentrations (not adjusted for dose). Figure (B) shows the same observations after being adjusted for lithium dose. Vertical line represents delivery (delivery=zero hour).

Figure 2. Joint distribution of maternal and paired umbilical cord serum lithium concentrations at delivery (N=60). Maternal serum lithium concentration and umbilical cord serum lithium concentrations were obtained simultaneously at delivery. Lithium monotherapy (N=37) in black, Lithium + Antidepressant (N=4) in red, in green Lithium + Antipsychotic (N=18) in green, and Lithium + Antipsychotic + Antidepressant (N=1) in blue.

1. Introduction

The perinatal period is a time of increased vulnerability for women with affective and non-affective psychotic disorders (Di Florio et al., 2013; Taylor et al., 2023). Especially, women with severe bipolar disorder or untreated bipolar disorder and those with non-affective psychotic disorder are at high risk of relapse in the postpartum period that during pregnancy (Sharma et al., 2020; Viguera et al., 2011; Wesseloo et al., 2016). Lithium remains the gold standard treatment for preventing recurrences in bipolar disorder type I (with mania and eventually major depression), and II (with depression and hypomania) (Tondo et al., 2019). It also has evidence of effectiveness of lithium augmentation in the treatment of refractory depression and in the treatment of affective symptoms in schizoaffective disorder (Leucht et al., 2015; Taylor et al., 2020). During the perinatal period lithium is proven effective as maintenance therapy for bipolar disorder and to prevent postpartum psychosis (Bergink et al., 2012; Wesseloo et al., 2016). Although one of the main concerns around the use of lithium during pregnancy is teratogenicity, the risk-benefit balance has lately shifted towards maintaining lithium during pregnancy to avoid the consequences of relapse in the mother (Bergink, 2023).

Lithium is a monovalent cation that is absorbed rapidly through the upper gastrointestinal tract and is almost exclusively renal eliminated without undergoing metabolization. Serum lithium concentrations mainly depend on intravascular volume and glomerular filtration rate (GFR). Lithium clearance is usually 20% to 30% of the GFR and thus varies with it (Grandjean and Aubry, 2009; Thomsen and Schou, 1999).

Pregnancy affects all aspects of kidney physiology altering the pharmacokinetics of lithium, which may affect both its efficacy and safety. Glomerular filtration rate increases early during pregnancy at one month after conception, peaks at approximately 40-50% above pre-pregnancy levels by the early second trimester and declines slightly toward term

(Cheung and Lafayette, 2013). Lithium elimination clearance parallels changes in GFR (Clark et al., 2022; Schou et al., 1979) and this result in reduced maternal serum lithium concentrations across pregnancy (Clark et al., 2022; Schou et al., 1979, Westin et al., 2017; Wesseloo et al., 2017). A retrospective study of perinatal lithium pharmacokinetics has found that serum lithium concentrations increase slightly in the third trimester but remained 21% below the pre-pregnancy baseline (Wesseloo et al., 2017). Moreover, natrium depletion, dehydration, diet, drug interactions, obstetrical complications (e.g. pre-eclampsia) and inconsistent treatment adherence can all cause changes in maternal serum lithium concentration (Clark et al., 2022). In order to maintain serum lithium concentration within the therapeutic optimal level of 0.5-0.8 mEq/L, lithium doses generally need to be adjusted during pregnancy (Westin et al., 2017).

Lithium equilibrates completely across the placenta (Newport et al., 2005). Higher maternal serum lithium concentrations at delivery have been associated with varied neonatal complications (hypoglycaemia, cardiac dysfunction, diabetes insipidus, thyroid dysfunction, respiratory distress, hypotonia and lethargy) requiring neonatal supportive care (Kozma, 2005; Newport et al., 2005; Pinelli et al., 2002). A previous retrospective observational cohort study did not observe a significant association between neonatal serum lithium concentrations at delivery and neonatal outcomes (Molenaar et al., 2021). A recent retrospective observational cohort study of neonates born to women with bipolar disorders treated with different psychopharmacs, with or without lithium, found that exposure to lithium was not associated with greater risk of neonatal ward admission (Schonewille et al., 2023). Moreover, having a bipolar disorder or schizophrenia, has been associated to slightly increased risk of obstetric and neonatal complications independent of medication used during pregnancy (Bennedsen et al., 1999; Boden et al., 2012; Schonewille et al., 2023).

In early postpartum, vascular volume rapidly decreases by approximately 40% and renal lithium clearance decreases to pre-pregnancy levels (Grandjean and Aubry, 2009). Hyperfiltration has been shown to continue at levels of 20% above normal at postpartum week 2 and resolve by 1 month postpartum (Odutayo and Hladunewich, 2012; Wesseloo et al., 2017). Lithium has a narrow therapeutic range (0.5-1.2 mEq/L), and in consequence, increased serum lithium concentrations (>1.5 mEq/L) may manifest as adverse effects in the mother (Hiemke et al., 2018), especially when an increased dose used during pregnancy is continued into the postpartum (Blake et al., 2008; Deligiannidis et al., 2014). If lithium is discontinued during pregnancy, it should be restarted immediately after delivery. During the first month postpartum a high target therapeutic serum lithium concentration (e.g. 0.8-1.0 mEq/L) has been recommended to optimize maternal relapse prevention (Wesseloo et al., 2016; Wesseloo et al., 2017).

Adequate monitoring of pregnant women treated with lithium around delivery is needed for early detection of subtherapeutic or toxic serum lithium concentrations to minimize potential mother and fetal/neonatal adverse effects. In the current research we want to study the behaviour of lithium around delivery in a large and homogeneous cohort of mothers treated with lithium in late pregnancy and their neonates. We evaluated the maternal serum lithium concentration changes around delivery, the lithium trans placental passage, and the association between neonatal serum lithium concentrations at delivery and acute neonatal outcomes.

2. Methods

2.1. Participants

Women attended in a perinatal psychiatric outpatient clinic of a single tertiary university hospital (November 2006-December 2018), and treated with lithium in the perinatal

period, were evaluated for eligibility to participate in this retrospective observational cohort study. Only psychopathologically stable women with healthy uncomplicated singleton pregnancy who used lithium in late pregnancy, and with at least one serum lithium concentration measurement obtained both in mother (vein puncture the admission day to hospital birth or at delivery) and in neonate (umbilical cord or neonatal vein puncture 24 hours post-delivery) were included in this cohort. Stable treated hypothyroidism was not an exclusion criteria.

2.2. Data collection and procedures

Study included demographic, psychiatric, obstetric, and early neonatal data for each woman and her corresponding pregnancies obtained from the hospital medical records. Obstetric complications evaluated included gestational diabetes, gestational hypertension, pre-eclampsia, polyhydramnios, oligohydramnios and premature rupture of membranes. Neonatal outcomes evaluated included prematurity (delivery prior to 37 weeks gestational age), birth weight, Apgar score at 1 and 5 minutes, umbilical cord arterial pH (UApH) and base excess (BE) values, serum TSH value, acute complications after a completed physical examination of the newborn (e.g. respiratory, circulatory, neurological, and other body systems), neonatal intensive (NICU, level IV) and intermediate (NICU, level II) care unit admission, and hospitalization duration after birth. We extracted information of all reported prenatal and postnatal congenital malformations. Positive neonatal findings were validated with a second expert neonatologist.

In line with the current NICE guideline (NICE CG192, 2014), the standard of care of the Perinatal Mental Health Unit Clinic-BCN is to monitor serum lithium concentrations every four-weeks until 34 weeks of pregnancy and then at least once weekly until delivery. Our recommendation for the management of lithium in the peripartum included: 1) the

advise to suspend lithium administration 12 hours before a scheduled caesarean section or induction or at admission day to hospital birth in the case of spontaneous deliveries, 2) the recommendation to restart lithium treatment 6 hours after vaginal delivery, or 12 hours post-delivery in case of caesarean birth; 3) to obtain serum lithium concentrations measurements simultaneously in mother-neonate pair at delivery; 4) to obtain mother serum lithium concentration measurement at day 2±1 postpartum, followed by (bi-) weekly during the first month postpartum. At the prenatal visit (week 33-35 of gestation), the psychiatrist carries out with each woman the risk-benefit analysis of maintaining the lowest effective lithium dose, or interrupting lithium dose around delivery. Each woman was given a written delivery planning kit containing the lithium extraction instructions and the tubes to perform the maternal (venous blood) and neonatal (umbilical cord) lithium measurements at delivery.

The maternal lithium therapeutic drug-monitoring (TDM) database contained information about the prescribed lithium dose and the dosing frequency, time of last lithium intake, time of blood sampling, serum lithium concentrations and types and doses of concomitant drugs. The peripartum time course of serum lithium concentration measurement was synchronized based upon the date of delivery (D0). Different time points of extraction before and after delivery were: most recent prepartum visit under steady-state condition (D-3), day before hospital birth (D-2), admission day to hospital birth (D-1), postpartum day 1 to day 7 (D+1 to D+7) and most recent post-partum visit under steady-state condition (D+8). The neonatal TDM databases contained serum lithium concentration in umbilical cord or first day of life.

2.3. Serum lithium analysis

For lithium analysis, maternal venous blood (5 ml), umbilical cord blood (5 ml) and neonates venous blood (2 ml) samples, were collected into BD Vacutainer® no- additive Z plus tubes (BD Diagnostics, Preanalytical Systems, Franklin Lakes, NJ 07417). Lithium concentrations were determined by means of an AVL 9180 electrolyte analyser based on the ion- selective electrode (ISE) measurement principle (Roche Diagnostics 9115 Hague Road Indianapolis, IN 46256). Lithium concentrations were reported in mEq/L, with two significant digits after the decimal points. A 2-point calibration were performed every 4 hours with a measurement range between 0.10 to 6.00 mEq/L. Limit of quantification (LoQ) was 0.20 mEq/L and detection limit (LoD) was 0.10 mEq/L. The within-day precision, expressed as coefficient of variation (CV) %, was between 0.97 to 4.1 %, and the between-day precision ranged between 1.3 to 6.4 %.

2.4. Statistical analysis

A descriptive analysis was performed to characterize the sample and the placental passage of lithium using, either absolute, and relative frequencies or means, standard deviations, and ranges as appropriate. The differences of maternal characteristics of mothers with monotherapy and those with polytherapy were quantified with the effect size measures Cohen's d (numeric variables) or Cohen's h (categoric variables). According to Cohen, values of both *d* and *h* equal to 0.2, 0.5, and 0.8 may be considered small, medium, and large (Cohen, 1988). To study the course of maternal serum lithium concentrations after a briefly discontinuation of lithium treatment around delivery, mean absolute and relative changes together with the corresponding 95% confidence intervals for paired data were computed. This was done on the one hand, for the changes from both the day before hospital birth and the admission day to hospital birth and, on the other hand, for the changes from delivery until postpartum days 2, 3, and 7, respectively. The ratio of serum

lithium concentration in umbilical cord to that in maternal serum was calculated for each maternal-infant pair as index of lithium placental passage. In addition, the relation between umbilical cord and maternal serum lithium concentrations surrounding delivery was illustrated with a scatterplot and quantified by means of Pearson's correlation coefficient.

The relation between neonatal serum lithium concentrations and neonatal outcomes was analysed using t-tests. Specifically, t-tests were conducted to compare the means (SD) of serum lithium concentrations between neonates with and without complications. This analysis was performed only if there were more than 10 cases of complications in the sample to avoid unreliable statistical conclusions due to small sample size.

All data were analysed using SPSS for Windows (Version 25; IBM Corp., Armonk, NY, United States) and the R software package (V4.3.3; The R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at 0.05 two sided.

2.5. Ethics

The Ethics Committee for Drugs Research of the Hospital Clinic (HCB/2020/1305) approved the study. Written informed consent was not obtained due the retrospective extraction from medical records.

3. Results

3.1. Maternal characteristics

Table 1 shows mother characteristics. We identified data from 97 women and 111 pregnancies that were eligible for study inclusion. Forty-five pregnancies were excluded because there where first trimester abortions (N=13), twin pregnancy (N=4), serum lithium concentrations measurements were not available at delivery (N=27) and the analysis was performed at another laboratory (N=1). In total, we included 60 women and six women

contributed with 2 pregnancies each. Each pregnancy was counted separately (66 mother-infant pairs). The most common psychiatric diagnosis was a bipolar disorder type I (N=54, 90%). The remaining women (N=6, 10%) were diagnosed with bipolar disorder type II (N=1, 1.6%), bipolar disorder nos (N=1, 1.6%), cyclothymic disorder (N=1, 1.6%), schizoaffective bipolar disorder (N=1, 1.6%) or recurrent depressive disorder (N=2, 3.3%). See also Supplementary Figure 1, a flow chart of the study.

Mean (SD) maternal age at time of conception was 33.79 (5.05) years. All women received psychiatric prenatal care for the majority of pregnancy. Fourteen women were treated with levothyroxine for hypothyroidism and were stable. The duration of the pregnancy was between -29 days and +9 days with respect to the estimated due date. The mean (SD) time from admission day to hospital birth (D-1) to delivery (D0) was 16.37 (11.74) hours. Thirty-four (51.50%) of the deliveries were by caesarean section, 18 (27.30%) were schedule caesarean section, and 16 (24.20%) urgent caesarean section for failed induction of labour, respectively.

All patients were treated with lithium carbonate (tablets of 400 mg of modified release of lithium carbonate, Plenur®). Most women (N=56, 85%) used lithium multiple daily dosing, and 15% of women (N=10) once-daily dose. Forty mothers (61%) were on lithium monotherapy at the time of delivery. Polytherapy combinations (N=26, 39%) included lithium and antipsychotic □quetiapine (N=14), olanzapine (N=4), haloperidol (N=1), paliperidone (N=1), aripiprazole (N=1)□, lithium combined with two antipsychotics (quetiapine plus aripipiprazole (N=1), lithium and antidepressant □fluoxetine (N=4), paroxetine (N=1), venlafaxine (N=1), imipramine (N=1)□ or lithium and antipsychotic combined with an antidepressant [quetiapine plus fluoxetine (N=1)]. None were taking other medication known to interact with lithium (e.g. diuretics or non-steroidal anti-inflammatories).

Concerning maternal characteristics, differences between mothers with lithium poly- and monotherapy with respect to age (Cohen's d=0.19), ethnicity (Cohen's h=0.08), marital status (h=0.39), education level (h=0.18), and number of prior pregnancies (d=0.10) could be considered of small or medium size, whereas a larger difference was observed for tobacco use (h=0.46).

3.2. Characteristics and course of maternal serum lithium concentration around delivery

Table 2 shows the characteristics and course of maternal serum lithium concentration at different extraction time points (D-3 to D+8). The maternal lithium TDM database around delivery (from D-2 to D+7) consisted of 226 serum lithium concentration measurements and the distribution were as follow: 26 (11.50%) at D-2, 23 (10.17%) at D-1, 64 (28.31%) at D0, 112 (49.56%) in the week after D0 [15 (13.39%) D+1, 35 (31.25%) D+2, 19 (16.96%) D+3, 13 (11.60%) D+4, 5 (4.46%) D+5, 5 (4.46%) D+6, and 21 (17.85%) at D+7]. See Supplementary Figure 1.

In the whole sample (N=66), at extraction time point D-3, 5.59 (8.94) days before delivery, the mean (SD) lithium dose was 993.94 (284.9) mg/day, and the mean (SD) serum lithium concentration was 0.58 (0.21) mEq/L. A considerable proportion of serum lithium measurements (28/66, 42.40%) were at subtherapeutic threshold for effective mood stabilisation (<0.5 mEq/L). However, all women were psychopathologically stable. The mean (SD) time to lithium treatment discontinuation before D0 was 23.61 (13.57) hours. Serum lithium concentration at D0 was 0.54 (0.26) mEq/L and 34 women (51.60%) had a subtherapeutic lithium levels. The mean (SD) time to lithium treatment reinstauration after delivery was 12.22 (8.09) hours. Despite the brief interruption in lithium therapy around delivery [(37.36 (16.25) hours], only four women (6%) relapsed in the first 7 days postpartum. One of the four woman showed a subtherapeutic serum lithium concentration

(0.41 mEq//L) at delivery and the remaining three women had serum lithium concentration of 0.76, 0.78, and 0.84 mEq/L, respectively. Two women were on lithium monotherapy and two on polytherapy. All presented a mania episode with psychotic features. One from each group (monotherapy vs. polytherapy) required hospitalization. At extraction time point D+8, 11.67 (11.32) days after delivery, 95% of the total sample (N=63) underwent lithium monitoring in our laboratory. The mean (SD) lithium dose was 977.78 (294.27) mg/day, the mean (SD) serum lithium concentration was 0.65 (0.23) mEq/L, and only 13 from 63 women (19.60%) of the whole sample had subtherapeutic serum lithium concentrations. In this period (from D-3 to D+8), any women showed serum lithium concentrations higher than 1.50 mEq/L.

Figure 1A represents the longitudinal pattern of maternal serum lithium concentration around delivery (from D-2 to D+7). We also normalised serum lithium concentrations to the total daily dose in order to accurately compare serum lithium concentrations. See Figure 1B.

Finally, Table 3 presents comparisons between delivery (D0) and different extractions time points around it (D-2, D-1, D+1 to D+7). We used those data that allowed us to perform a paired data analysis. In a subsample of 22 women, according to the 95% CI of the mean change, the maternal serum lithium concentrations at T0 were significantly lower than those obtained at D-2 [mean decrease=0.19 mEq/L, (95%CI: 0.13–0.25)]; this corresponds to a mean relative decrease of 31.7% (95%CI: 22.3 – 41%). After reinstating lithium treatment, the mean absolute and relative increases from D0 to D+2 were 0.1 mEq/L (95%CI: 0.03–0.17)] and 33.6% (95%CI: 13.0–54.3), respectively.

3.3. Lithium placental passage

Table 4A presents serum lithium concentrations in neonates [umbilical cord (UC) or neonate 1ers day of life] and mothers (at D-1 and D0) and corresponding neonates to maternal ratio in all samples and in monotherapy and/or polytherapy.

In 60 mother-infant pairs, intrapartum maternal (D0) venous blood and UC were collected simultaneously to determine serum lithium concentrations. The mean (SD) UC serum lithium concentration was 0.57 (0.26) mEq/L and the mean (SD) D0 serum lithium concentration was 0.54 (0.26) mEq/L. The mean (SD) UC/D0 serum lithium concentration ratio was 1.10 (0.17) indicating complete placental passage. The degree of placental passage was uniform across a wide range of maternal serum lithium concentrations (0.14 to 1.40 mEq/L) and of estimated pregnancy lasts (35^{+6} to 41^{+2} weeks' gestation). There was a strong positive correlation between UC and D0 serum lithium concentration [Pearson correlation coefficient 0.95 (95%CI: 0.91–0.97)], which is visualized in Figure 2. The UC lithium concentrations exceeded maternal serum lithium concentrations at delivery in 45/60 (75%) of paired analyses. There was not difference between the UC/D0 serum lithium concentration ratios in lithium monotherapy group [1.11 (0.17)] versus polytherapy group [1.08 (0.17) ($F=0.428$; df =1, 63; $p=0.515$)].

Table 4B shows paired maternal and neonatal serum lithium concentrations and corresponding neonatal/maternal ratios in a subgroup of mother-infant pairs (N=19) with lithemias in the three point of extraction: D-1, D0 and UC. The mean (SD) UC/D-1 ratio was 0.97 (0.10) and the mean (SD) UC/D0 ratio was 1.15 (0.12), after a mean (SD) of 25.25 (14.32) hours have elapsed since taking the last dose of lithium prior to delivery. In the neonate, the UC serum lithium concentrations exceeded maternal serum lithium concentrations at D-1 in 6/19 (31.58%), and maternal serum lithium concentrations at D0 in 17/19 (89.47%) of paired analysis, indicating that lithium elimination was slower in neonates.

3.4. Neonatal characteristics

Table 1 shows the neonatal characteristics at birth**.** Sixty-four (97%) neonates were born at term, whereas two neonates (3%) were spontaneously born late preterm, at 35^{+6} and 36^{+2} weeks of gestation. Ninety-one percent (N=60) of neonates roomed with their mothers on the maternity ward. Fifty-six percent of the neonates (N=37) had acute complications [hypotonia (N=15), hypertonia (N=4), tremors (N=8), sucking difficulties (N=4), systolic murmurs (N=8), respiratory distress (N=3), cyanosis (N=1), hepatomegaly (N=1), hyperbilirubinemia (N=6), hypoglycemia (N=2), skin lesions (N=3), and cefalhematoma (N=3)]. In 29 of these neonates the complications were mild and transient and did not need any medical intervention immediately after birth. Five neonates (7.6%) were admitted to the NICU level II. One neonate due to postnatal aortic coarctation was transferred to another hospital for cardiac catheterization, another required phototherapy due to non-isoimmune hyperbilirubinemia, and three-needed respiratory support due to meconium syndrome. A neonate gave birth in a pediatric monographic hospital with NICU level IV because a prenatal Ebstein´s anomaly. Moreover, another neonate presented a microcephaly and cerebral ventriculomegaly, subsequently diagnosed as spastic cerebral palsy of unknown cause. A full overview of neonatal complications with additional neonatal serum lithium concentration at delivery and maternal treatment can be found in Supplementary Table 1.

There were no significant differences between lithium monotherapy (N=18/40) and polytherapy (N=13/26) groups with regard to acute neonatal complications (p=0.69), being neurological complications (hypotonia, hypertonia, tremors, and sucking difficulties) the most frequent in both groups. The mean (SD) hospitalization stay for all neonates attended in the maternity hospital was 3.17 (1.21) days.

3.5. Neonatal serum lithium concentration and acute neonatal outcomes

The neonatal lithium TDM database consisted on 66 neonatal serum lithium concentration measurements: 61 (92.42%) were obtained from the umbilical cord and 5 (7.58%) from neonatal vein puncture within 24 hours after delivery (N=5, 7.58%). The mean (SD) umbilical cord serum lithium concentrations (N=61) was 0.57 (0.26) mEq/L, and neonatal vein puncture serum lithium concentration (N=5) was 0.49 (0.13) mEq/L. There were no incidents in the umbilical cord/neonates during blood extraction. See Table 4A.

Hypotonia (N=15) was the most frequently acute neonatal complication of a total of 12 found. It was the only one with at least 10 cases, and it was found to be statistically significantly associated with neonatal serum lithium concentration. The mean (SD) neonatal serum lithium concentration was 0.712 (0.298) mEq/L among neonates with hypotonia compared to 0.534 (0.214) mEq/L among neonates without hypotonia (t=2.25, df=60, p=0.028).

4. Discussion

In this retrospective observational cohort study of 66 mother-infant pairs, we found slightly maternal serum lithium concentration fluctuations after a briefly discontinuation of lithium around delivery. The degree of placental passage was complete across a wide range of maternal serum lithium concentrations and of estimated pregnancy lasts. Neonatal hypotonia was the most frequent acute outcome and, it was associated with neonatal serum lithium concentration.

The human placenta is a complex organ that acts as the interface between maternal and fetal blood circulation. Lithium, with a molecular weight of 7 Da, readily diffuses across the placenta (Griffiths and Campbell, 2015). Umbilical cord serum lithium concentrations

at delivery, especially when compared to maternal concentrations, provide valuable information about fetal lithium exposure *in utero* (Bank et al., 2017).

Already, in the late 1960s and early 1970s, several case reports showed that lithium crosses the placental barrier completely (Fries, 1970; Silverman et al., 1971; Weinstein and Goldfield, 1969) or partially (Aoki and Ruedy, 1971; Wilbanks, 1970), depending of the time point extraction in mother-infant pairs at delivery. In 1975, Schou and Admisen published a case series (nine new cases and two from the literature) of lithium concentration obtained in mother-infant pair at delivery carried out in different laboratories that indicated that there was a full equilibration on lithium across de placental barrier. More recent, a cohort study (Newport et al., 2005) observed a complete placental passage of lithium across an extensive range of maternal serum lithium concentrations in 10 mother-infant pairs. In a recent retrospective cohort study (Molenaar et al., 2021) showed a strong neonatal/maternal positive correlation in serum lithium concentrations for a wide range of extraction time points around delivery. All these studies were limited by the small sample sizes (Aoki and Ruedy, 1971; Fries, 1970; Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975; Silverman et al., 1971; Weinstein and Goldfield, 1969; Wilbanks, 1970) or because some samples were not taken in mothers (intrapartum) and neonates (umbilical cord) simultaneously at delivery (Aoki and Ruedy, 1971; Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975; Weinstein and Goldfield, 1969; Wilbanks, 1970) or lithemias were analyzed in different laboratories (Molenaar et al., 2021; Newport et al., 2005; Schou and Admisen, 1975) or women took different types of lithium formulations (Molenaar et al., 2021), introducing inaccuracies in the index of lithium placental passage. In our study, all lithemias were analysed in the same laboratory and all women were taking lithium carbonate. Our results in a sample between two and six time higher than previously reported (Molenaar et al., 2021; Newport et al., 2005; Schou

and Admisen, 1975) confirm that lithium has a complete lithium placental passage, both in lithium monotherapy and polytherapy,

Due to a decrease in lithium clearance and fluid volume contraction peripartum, maternal serum lithium concentration increased in early postpartum with consequent maternal intoxication risk (Schou et al, 1973, Wesseloo et al., 2017). It has been shown that higher maternal serum lithium concentrations at delivery are associated with more acute neonatal complications (Newport et al., 2005). To minimize the early neonatal risk, different strategies have been proposed along last decades. Some authors have suggested lowering lithium dose by 30-50% some days before delivery (Goodwin, 2009; Mitchell, 2004). This approaches makes sense, as the neonatal elimination half-life of lithium is around 68-96 hours (Mackay et al., 1976; Rane et al., 1978). However, as the elimination half-life of lithium in a young adult is 18-28 hours, it could led to an increase in subtherapeutic lithemia (<0.5 mEq/L) with the consequent risk of maternal postpartum relapse. Other authors recommended stopping lithium treatment 24-48h before a planned hospital birth (cesarean section or induction) or even discontinuing lithium when a woman presents active labouring (Newport et al., 2005; Schou et al., 1973). This approach supposes an average lithemia reduction of 0.28 mEq/L (Newport et al., 2005). Some authors have observed that symptoms worsened in patients when serum lithium concentration decreases abruptly more than 0.20 mEq/L below their personal baseline concentration and/or below the therapeutic concentration of 0.40 mEq/L (Severus et al., 2008). Finally, the most recent proposed strategy was to careful monitoring serum lithium concentrations around delivery, and to use the maternal lowest effective lithium dose instead of discontinuation in all cases (Deligiannidis et al., 2014). Because, after excluding women with complications or preterm births, there is a considerable variation in gestational lengths (Jukic et al., 2013), this approach needs a close coordination of hospital

multidisciplinary team (psychiatric, obstetric, and neonatologist) around delivery (Frayne et al., 2018). Our study showed that maintaining predelivery the minimal individualized effective serum lithium concentration, stopping lithium 12 hours before to planned hospital birth, or at hospital admission in active labour, and restarting lithium treatment as soon as the mother is medically stable (6-12h after delivery), allow to obtain around delivery a mean lithemia fluctuation close to 0.20 mEq/L. We found a small rate of early postpartum relapse, and three of the four women had the lithemia within the therapeutical range.

Knowledge about the potential association between late intrauterine exposure to lithium and early neonatal effects has been limited to case report, case series and small observational studies. Before 2004, around thirty well-documented cases of neonatal toxicity associated with a transient neurodevelopmental deficit after in utero exposure to lithium were published (Kozma, 2005). Most neonates needed supportive treatment between 10-14 days improving gradually. Several cases presented paired maternal and neonatal lithemias higher than 1.50 mEq/L, maternal psychiatric decompensation or obstetric complications. In 2005, a study combining a prospective sample of 10 mothers with 14 cases from previous reports assessed the association of newborn's serum lithium concentration and obstetric and neonatal outcomes (Newport et al., 2005). Neonates were divided in two groups: those with low lithemia (0.20 to 0.58 mEq/L) and those with high lithemia (0.70 mEq/L). The neonates of high lithium exposure group presented an increased risk of lower Apgar scores, higher rates of CNS and neuromuscular complications and longer hospital stays (mean=10 days), some of them having lithium toxic levels (1.20 to >4 mEq/L) and maternal-obstetric complications. (Aoki and Ruedy, 1971; Arnon et al., 1981; Flaherty and Krenzelok, 1997; Frassetto et al., 1979; Morrell et al., 1983; Nishiwaki et al., 1996; Wilbanks, 1970). Subsequently, a retrospective cohort study did not find a significant association between neonatal serum lithium concentrations

at delivery (0.05 to 1.16 mEq/L) and neonatal outcomes (Molenaar et al., 2021). However, a high percentage of admissions to medium/high neonatal care (44.8%) with a median duration of three days, and acute complications (48.3%), mainly metabolic, were reported during the five postnatal days of protocolized clinical monitoring. Authors interpreted that due to this monitorization period several mild and transient complications were detected might otherwise go unnoticed. Recently, a retrospective cohort study found not differences in acute complications between neonates exposed and non-exposed to lithium, questioning the necessity of neonatal admission with monitoring after lithium exposure (Schonewille et al., 2023). Independently of lithium exposure, and assuming that neonatal lithemias were in the therapeutical range, a 20% of these neonates were admitted to a neonatal ward monitoring (median stay of three days) due the high obstetric vulnerability of their mothers with bipolar disorders. In our retrospective cohort study, the neonatal serum lithium concentration at birth ranged between 0.20 to 1.42 mEq/L. We observed that half of the neonates had slightly, transient and acute neonatal complications, similar to Molenaar et al. (2021), but ours were mainly neurological. We also found a significant statistical association between neonatal hypotonia and neonatal lithemia >0.75 mEq/L, similar to the high lithium exposure group of Newport et al., (2005) study. Nine percent of our neonates required admission to a NICU (level II or IV) by pediatric indication, with an average stay of three days, due to delivery complications or congenital malformations, a figure smaller than those found in Molenaar et al., (2021) and Schonewille et al., (2023). The results of all these studies, although they did not evaluate causality, indicated that neonatal symptoms should be anticipated after in late intrauterine exposure at any concentration, although lithium toxicity is more likely to occur at high serum lithium concentration. However, this association might be confounded by the occurrence of mood episodes during pregnancy, obstetrical complications, or use of concurrent psychopharmacs.

4.1. Strengths and limitations

As far as we known, this is the largest sample size study analysing the lithium behavior in mother-infant pairs around delivery and the acute neonatal outcomes after late intrauterine lithium exposure. Strengths of the study were the homogeneity of the sample, the use of a single lithium manufacturer and that all serum lithium concentration measurements were done in a single laboratory. However, the study is not without limitations. It is a retrospective cohort of a sample of healthy uncomplicated pregnancies. For this reason, the results of the study cannot be generalized to all pregnant women treated with lithium. On the other hand, this was a naturalistic study done in real life and we cannot have a paired maternal lithium measurements in each extraction time point at peripartum and in all mother-infant pairs simultaneously at delivery. We do not have data of a cohort control group of women and their neonates of the same characteristics not exposed to lithium treatment, on the same period of follow-up. Finally, sample size was moderate given that there are not big numbers of pregnancies exposed to lithium since we started our standard procedures (De Prisco and Vieta, 2024).

4.2. Implications and conclusions

Appropriate management of lithium treatment around delivery is a difficult balancing act. Lithium equilibrates completely across the placental barrier and maintaining pre-delivery maternal serum lithium concentrations at the minimal individualized effective level and briefly discontinuing lithium at delivery may minimize the risk of maternal and neonatal complications. Additional investigations in bigger samples, prospective design, other perinatal bipolar subgroups and control groups are warranted to better describe the relationship between quantified maternal and fetal lithium exposure near to delivery and maternal and neonatal acute complications.

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CRediT authorship contribution statement

ML: Conceptualization, Formal analysis, Investigation, Resources, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. MT: Resources, Validation, Writing – review & editing. KL: Formal analysis, Supervision, Visualization, Writing – review & editing. GA: Resources, Writing – review & editing. DS: Resources, Writing – review & editing. ASH: Resources, Writing – review & editing. LGE: Resources, Writing – review & editing. EV: Conceptualization, Supervision, Writing – review & editing. RMS: Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

EV has received grants and served as a consultant, advisor or CME speaker for the following entities: AB-Biotics, Abbott, Allergan, Angelini, AstraZeneca, Biogen, Biohaven, Bristol-Myers Squibb, Celon, Compass, Dainippon Sumitomo Pharma, Farmindustria, Ferrer, Forest Research Institute, Gedeon Richter, Glaxo-Smith-Kline, HMNC, Idorsia, Janssen, Lundbeck, Medincell, Merck, Novartis, Orion, Otsuka, Pfizer, Roche, SAGE, Sanofi-Aventis, Servier, Shire, Sunovion, Takeda, Viatris, the Brain and Behaviour Foundation, the Spanish Ministry of Science and Innovation (CIBERSAM), the EU Horizon 2020 and the Stanley Medical Research Institute. Other authors declare no

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Appendix A. Supplementary data

Supplementary table 1 and supplementary figure 1 can be found online.

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Table 1. Maternal and neonatal characteristics and serum lithium concentrations around delivery.

		Lithium therapy				
	All cases	**Monotherapy**	**Polytherapy**			
	N=66	**N=40**	**All N=26**	**Li+AP N=19**	**Li+AD N=6**	**Li+AP+AD N=1**
Maternal characteristics Mean /SD) / N (%)						
Age at time of delivery	34.80 (5.02)	34.40 (5.11)	35.35 (4.93)	36 (5.16)	33.50 (4.41)	34
Caucasian	64 (97.00)	39 (97.50)	25 (96.20)	18 (94.70)	6 (100)	1
University degree	32 (48.50)	18 (45.00)	14 (53.80)	10 (52.60)	3 (50.0)	1
Married or living together	65 (98.50)	40 (100)	25 (96.20)	18 (94.70)	6 (100)	1
Smoking in late pregnancy	15 (22.7)	6 (15.00)	9 (34.60)	8 (42.10)	1 (16.70)	0
Primiparous	49 (74.20)	29 (72.50)	20 (76.90)	15 (78.90)	4 (66.70)	1
Caesarean section	34 (51.50)	15 (37.50)	19 (73.10)	16 (84.20)	3 (50.00)	0
Meconium in amniotic fluid	6 (9.10)	6 (15.00)	0	0	0	0
Prolonged rupture of membranes[a]	11 (16.70)	6 (15.00)	5 (19.20)	3 (15.80)	2 (33.30)	0
Lithium dosage closest to delivery	993.94 (284.94)	935.00 (257.75)	1084.62 (305.53)	1136.84 (326.96)	966.67 (196.63)	800
Neonatal characteristics Mean /SD) / N (%)						
Preterm birth (<37 weeks)	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Macrosomia (>4000 gr)	10 (15.20)	7 (17.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Apgar score $_{1\ min}$ <6	3 (4.50)	3 (7.50)	0	0	0	0
Apgar score $_{5\ min}$ < 8	0	0	0	0	0	0
pH-value cord arterial	7.22 (0.07)	7.21 (0.08)	7.23 (0.07)	7.24 (0.06)	7.18 (0.07)	-
BE-value cord arterial (mmol/L)	-7.48 (2.62)	-7.76 (2.46)	-6.99 (2.88)	-6.56 (2.50)	-8.37 (3.98)	-
Acute complications[b]:						
Hypotonia	15 (22.72)	10 (25.00)	5 (19.23)	2 (10.50)	3 (50.00)	0
Hypertonía	4 (6.10)	2 (5.00)	2 (7.70)	1 (10.50)	0	0
Tremors	8 (12.10)	3 (7.50)	5 (19.20)	4 (21.10)	1 (16.70)	0
Sucking difficulties	4 (6.00)	3 (7.50)	1 (3.85)	1 (5.26)	0	0
Systolic murmur	8 (12.10)	5 (12.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Respiratory distress[c]	3 (4.50)	3 (7.50)	0	0	0	0
Cyanosis	1 (1.50)	1 (2.50)	0	0	0	0
Hepatomegaly	1 (1.50)	1 (2.50)	0	0	0	0
Hyperbilirrubinemia	6 (9.10)	3 (7.50)	3 (11.50)	3 (15.80)	0	0
Hypoglycemia	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Skin lesions[d]	3 (4.50)	2 (5.00)	1 (3.85)	0	1 (16.70)	0
Cefalhematoma	3 (4.50)	2 (5.00)	0	0	1 (16.70)	0
THS serum (mUI/L)	5.04 (3.48)	4.97 (3.33)	5.19 (3.78)	5.45 (3.70)	4.94 (4.39)	1.63
Hospital stay (days) (N=65)	3.17 (1.21)	3.05 (1.20)	3.38 (1.27)	3.44 (1.42)	3.33 (0.81)	2

Abbreviations: BE=base excess; Li= lithium; Li+AP= lithium + antipsychotic; Li+AD= lithium + antidepressant; Li+AP+AD= lithium + antipsychotic + antidepressant; D-2= day before delivery hospitalization. TSH=tyroid stimulating hormone

[a]Prolonged rupture of membranes (>24 hours): preterm (n=1), term (n=10); [b]After a newborn complete physical examination; [c]Respiratory distress due to meconium syndrome; [d]Skin lesions: pustulose (n=1), ecchymosis (n=2).

Table 2. Characteristics and course of maternal serum lithium concentrations (mEq/L) at the different extraction time points (from T-3 to T+8) around delivery.

	Lithium therapy							
Extraction time point	**Dose (mg/d)**		**[Li] (mEq/L)**		**[Li] <0.5 (mEq/L)**	**Steady state**	**Pre-dose 12±2 h**	**Treatment adherence**
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N (%)**	**N (%)**	**N (%)**	
D-3 Pregnancy most recent visit	66	993.94 (284.94)	66	0.58 (0.21)	28 (42.40)	66 (100)	66 (100)	Some partial
D-**2** Day before hospital birth	66	993.9 (284.94)	26	0.65 (0.20)	8 (30.80)	26 (100)	26 (100)	Some partial
D-**1** Admission day to hospital birth	0	_	23	0.59 (0.30)	10 (43.50)	_	_	Some partial
D0 Delivery[a]	41	643.90 (317.84)	64	0.54 (0.26)	33 (51.60)	_	_	Complete
D+**1** Postpartum day 1	64	981.25 (288.8)	15	0.61(0.33)	7 (46.70)	_	15 (100)	Complete
D+2 Postpartum day 2	65	984.62 (296.45)	35	0.63 (0.26)	9 (25.70)	_	25 (100)	Complete
D+3 Postpartum day 3	66	984.8 (302.42)	19	0.73 (0.29)	4 (21.10)	_	19 (100)	Complete
D+4 Postpartum day 4	66	987.88 (295.36)	13	0.71 (0.28)	4 (30.80)	_	13 (100)	Some partial
D+5 Postpartum day 5	66	984.85 (294.70)	5	0.76 (0.29)	1 (20.00)	1 (20)	5 (100)	Some partial
D+6 Postpartum day 6	66	984.85(294.70)	5	0.59 (0.26)	2 (40.00)	5 (100)	5 (100)	Some partial
D+7 Postpartum day 7	66	984.85(294.70)	21	0.65 (0.26)	4 (19.00)	21 (100)	21 (100)	Some partial
D+8 Postpartum most recent visit	63	977.78 (294.27)	63	0.65 (0.23)	13 (19.70)	63 (100)	63 (100)	Some partial

[a]Lithium dosage was restarted 6-12 hours after delivery.

Table 3. Comparison of maternal mean (SD) serum lithium concentration [Li] (mEq/L) around delivery. Analysis of paired data between different extraction time points (day before hospital birth, admission day for hospital birth, postpartum day 2, 3 and 7) with delivery.

Time point of extraction			[Li] Δ mean (mEq/L) to delivery [95%CI]	% change of [Li] related to delivery [95%CI]
N	**Delivery time point (D0) [Li] Mean (SD)**	**Other time points (D-2, D-1, D+2, D+3, D+7) [Li] Mean (SD)**		
22	**D0 Delivery** 0.45 (0.23)	**D-2** Day before hospital birth[a] 0.64 (0.21)	-0.19 [-0.25, -0.13]	-31.7 [-41.0, -22.3]
22	**D0 Delivery** 0.54 (0.29)	**D-1** Admission day to hospital birth 0.60 (0.31)	-0.07 [-0.09, -0.05]	-12.8 [-16.5, -9.1]
34	**D0 Delivery** 0.52 (0.24)	**D+2** Postpartum day 2 0.62 (0.26)	0.1 [0.03, 0.17]	33.6 [13.0, 54.3]
18	**D0 Delivery** 0.66 (0.27)	**D+3** Postpartum day 2 0.72 (0.29)	0.06 [-0.06, 0.18]	15.0 [-9.2, 39.2]
19	**D0 Delivery** 0.59 (0.28)	**D+7** Postpartum day 7[a] 0.63 (0.26)	0.04 [-0.1, 0.19]	26.8 [-11.4, 64.9]

Abbreviation: [Li]= Lithium concentration; CI= Confidence interval;
Symbol: Δ=Mean difference.
[a]Serum lithium concentrations were measured at steady-state and 12±2 hours post-dose.

Table 4-A. Serum lithium concentrations in neonates [umbilical cord or neonate 1er day of life] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	23	0.59 (0.30)	17	0.61 (0.33)	6	0.55 (0.23)	5	0.62 (0.18)	1	0.23 (0)	0	-
D0	64	0.54 (0.26)	39	0.50 (0.27)	25	0.61 (0.23)	18	0.63 (0.23)	6	0.55 (0.25)	1	0.74
UC	61	0.57 (0.26)	38	0.52 (0.26)	23	0.66 (0.24)	18	0.66 (0.23)	4	0.65 (0.25)	1	0.74
N1	5	0.49 (0.13)	2	0.54 (0.17)	3	0.46 (0.13)	1	0.31 (0)	2	0.54 (0.01)	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.97 (0.10)	4	0.99 (0.13)	3	1.03 (0.12)	1	0.87 (0)	0	-
UC/D0	60	1.10 (0.17)	37	1.09 (0.17)	23	1.11 (0.17)	18	1.07 (0.13)	4	1.31 (0.19)	1	1.00
N1/D-1	3	0.83 (0.14)	2	0.82 (0.20)	1	0.84 (0)	1	0.84(0)	0	-	0	-
N1/D0	4	0.96 (0.26)	2	0.98 (0.30)	2	0.93 (0.33)	0	-	2	0.93 (0.33)	0	-

Table 4-B. Paired serum lithium concentrations in neonates [umbilical cord] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	19	0.59 (0.33)	15	0.60 (0.35)	4	0.55 (0.25)	3	0.66 (0.16)	1	0.23	0	-
D0	19	0.53 (0.31)	15	0.54 (0.33)	4	0.48 (0.26)	3	0.60 (0.16)	1	0.14	0	-
UC	19	0.58 (0.31)	15	0.57 (0.33)	4	0.58 (0.37)	3	0.71 (0.11)	1	0.20	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.96 (0.10)	4	1.02 (0.13)	3	1.08 (0.09)	1	0.86	0	-
UC/D0	19	1.15 (0.12)	15	1.07 (0.09)	4	1.25 (0.15)	3	1.19 (0.12)	1	1.42	0	-

Abbreviations:Li= Lithium; Li+AP= Lithium+antipsychotic; Li+AD= Lithium+antidepressant; Li+AP+AD= Lithium+antipsychotic+ antidepressant; D-1=Admission day to hospital birth; D0=Delivery (intrapartum); UC=Umbilical cord; N1=Neonate 1st day of life.

Figure 1. Course of maternal serum lithium concentration around delivery (N=66). Figure (A) shows the measured serum concentrations (not adjusted for dose). Figure (B) shows the same observations after being adjusted for lithium dose. Vertical line represents delivery (delivery=zero hour).

Figure 2. Joint distribution of maternal and paired umbilical cord serum lithium concentrations at delivery (N=60). Maternal serum lithium concentration and umbilical cord serum lithium concentrations were obtained simultaneously at delivery. Lithium monotherapy (N=37) in black, Lithium + Antidepressant (N=4) in red, in green Lithium + Antipsychotic (N=18) in green, and Lithium + Antipsychotic + Antidepressant (N=1) in blue.

Figure 1

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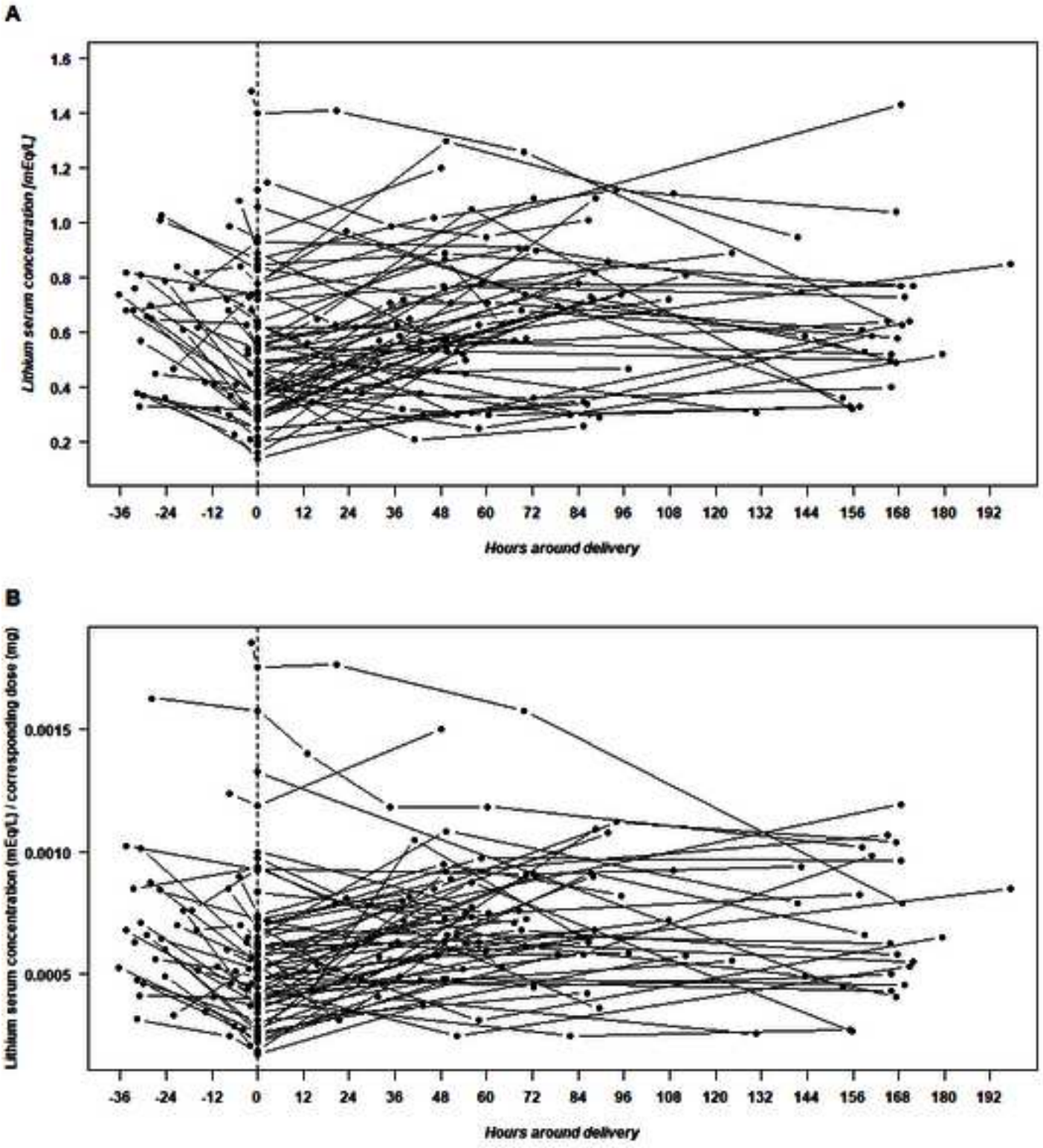

Figure 2

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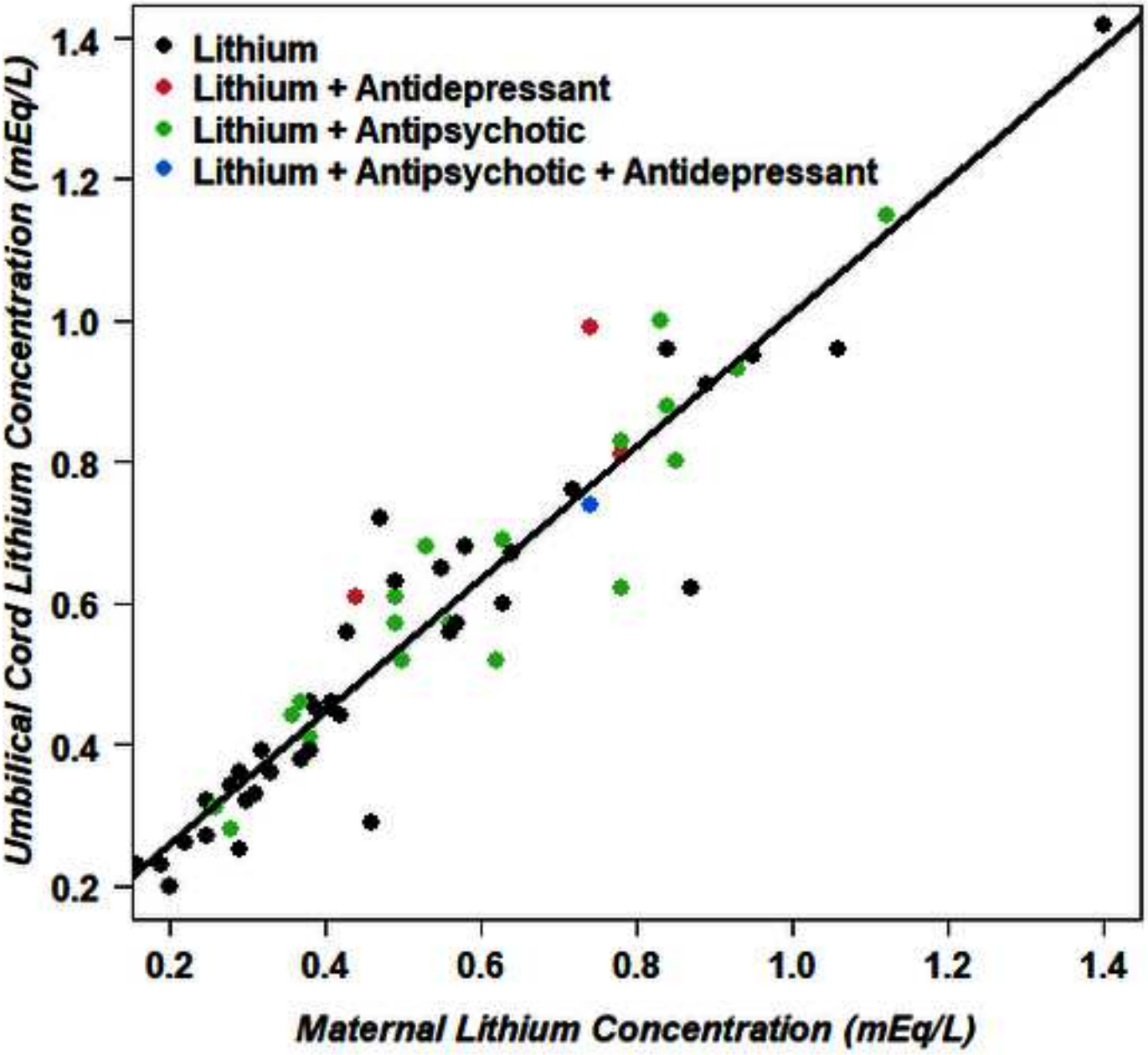

Table 1. Maternal and neonatal characteristics and serum lithium serum concentrations around delivery.

		Lithium therapy				
	All cases	Monotherapy	Polytherapy			
			All	Li + AP	Li + AD	Li+AP+AD
	N=66	N=40	N=26	N=19	N=6	N=1
Maternal characteristics						
Mean /SD) / N (%)						
Age at time of delivery	34.80 (5.02)	34.40 (5.11)	35.35 (4.93)	36 (5.16)	33.50 (4.41)	34
Caucasian	64 (97.00)	39 (97.50)	25 (96.20)	18 (94.70)	6 (100)	1
University degree	32 (48.50)	18 (45.00)	14 (53.80)	10 (52.60)	3 (50.0)	1
Married or living together	65 (98.50)	40 (100)	25 (96.20)	18 (94.70)	6 (100)	1
Smoking in late pregnancy	15 (22.7)	6 (15.00)	9 (34.60)	8 (42.10)	1 (16.70)	0
Primiparous	49 (74.20)	29 (72.50)	20 (76.90)	15 (78.90)	4 (66.70)	1
Caesarean_section	34 (51.50)	15 (37.50)	19 (73.10)	16 (84.20)	3 (50.00)	0
Meconium in amniotic fluid	6 (9.10)	6 (15.00)	0	0	0	0
Prolonged rupture of membranes[a]	11 (16.70)	6 (15.00)	5 (19.20)	3 (15.80)	2 (33.30)	0
Lithium dosage closest to delivery	993.94 (284.94)	935.00 (257.75)	1084.62 (305.53)	1136.84 (326.96)	966.67 (196.63)	800
Neonatal characteristics						
Mean /SD) / N (%)						
Preterm birth (<37 weeks)	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Macrosomia (>4000 gr)	10 (15.20)	7 (17.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Apgar score $_{1\ min}$ <6	3 (4.50)	3 (7.50)	0	0	0	0
Apgar score $_{5\ min}$ < 8	0	0	0	0	0	0
pH UC arterial	7.22 (0.07)	7.21 (0.08)	7.23 (0.07)	7.24 (0.06)	7.18 (0.07)	-
BE UC arterial (mmol/L)	-7.48 (2.62)	-7.76 (2.46)	-6.99 (2.88)	-6.56 (2.50)	-8.37 (3.98)	-
Acute complications[b]:						
Hypotonia	15 (22.72)	10 (25.00)	5 (19.23)	2 (10.50)	3 (50.00)	0
Hypertonía	4 (6.10)	2 (5.00)	2 (7.70)	1 (10.50)	0	0
Tremors	8 (12.10)	3 (7.50)	5 (19.20)	4 (21.10)	1 (16.70)	0
Sucking difficulties	4 (6.00)	3 (7.50)	1(3.85)	1(5.26)	0	0
Systolic murmur	8 (12.10)	5 (12.50)	3 (11.50)	2 (10.50)	1 (16.70)	0
Respiratory distress[c]	3 (4.50)	3 (7.50)	0	0	0	0
Cyanosis	1 (1.50)	1 (2.50)	0	0	0	0
Hepatomegaly	1 (1.50)	1 (2.50)	0	0	0	0
Hyperbilirubinemia	6 (9.10)	3 (7.50)	3 (11.50)	3 (15.80)	0	0
Hypoglycemia	2 (3.00)	1 (2.50)	1 (3.80)	1 (5.30)	0	0
Skin lesions[d]	3 (4.50)	2 (5.00)	1(3.85)	0	1(16.70)	0
Cefalhematoma	3 (4.50)	2 (5.00)	0	0	1(16.70)	0
TSH serum (mUI/L)	5.04 (3.48)	4.97 (3.33)	5.19 (3.78)	5.45 (3.70)	4.94 (4.39)	1.63
Hospital stay (days) (N=65)	3.17 (1.21)	3.05 (1.20)	3.38 (1.27)	3.44 (1.42)	3.33 (0.81)	2

Abbreviations: BE=base excess; Li=lithium; Li+AP=lithium + antipsychotic; Li+AD=lithium + antidepressant; Li+AP+AD= lithium + antipsychotic + antidepressant; T-2=day before delivery hospitalization. TSH=tyroid stimulating hormone

[a]Prolonged rupture of membranes (>24 hours): preterm (n=1), term (n=10); [b]After a newborn complete physical examination; [c]Respiratory distress due to meconium syndrome; [d]Skin lesions: pustulose (n=1), and ecchymosis (n=2).

Table 2. Characteristics and course of maternal serum lithium concentrations (mEq/L) at the different extraction time points (from D-3 to D+8) around delivery.

	Lithium therapy							
Extraction time point	**Dose (mg/d)**		**[Li] (mEq/L)**		**[Li] <0.5 (mEq/L)**	**Steady state**	**Pre-dose**	**Treatment adherence**
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N (%)**	**N (%)**	**N (%)**	
D-3 Pregnancy most recent visit	66	993.94 (284.94)	66	0.58 (0.21)	28 (42.40)	66 (100)	66 (100)	Some partial
D-2 Day before delivery hospilization	66	993.9 (284.94)	26	0.65 (0.20)	8 (30.80)	26 (100)	26 (100)	Some partial
D-1 Admission day to delivery hospitalization	0	_	23	0.59 (0.30)	10 (43.50)	_	_	Some partial
D0 Delivery[a]	41	643.90 (317.84)	64	0.54 (0.26)	33 (51.60)	_	_	Complete
D+1 Postpartum day 1	64	981.25 (288.8)	15	0.61(0.33)	7 (46.70)	_	15 (100)	Complete
D+2 Postpartum day 2	65	984.62 (296.45)	35	0.63 (0.26)	9 (25.70)	_	25 (100)	Complete
D+3 Postpartum day 3	66	984.8 (302.42)	19	0.73 (0.29)	4 (21.10)	_	19 (100)	Complete
D+4 Postpartum day 4	66	987.88 (295.36)	13	0.71 (0.28)	4 (30.80)	_	13 (100)	Some partial
D+5 Postpartum day 5	66	984.85 (294.70)	5	0.76 (0.29)	1 (20.00)	1 (20)	5 (100)	Some partial
D+6 Postpartum day 6	66	984.85(294.70)	5	0.59 (0.26)	2 (40.00)	5 (100)	5 (100)	Some partial
D+7 Postpartum day 7	66	984.85(294.70)	21	0.65 (0.26)	4 (19.00)	21 (100)	21 (100)	Some partial
D+8 Postpartum most recent visit	63	977.78 (294.27)	63	0.65 (0.23)	13 (19.70)	63 (100)	63 (100)	Some partial

[a]Lithium dosage was restarted 6-12 hours after delivery.

Table 3. Comparison of maternal mean (SD) serum lithium concentration [Li] (mEq/L) around delivery. Analysis of paired data between different extraction time points (day before hospital birth, admission day for hospital birth, postpartum day 2, 3 and 7) with delivery.

Time point of extraction			[Li] (mEq/L) Δ mean to delivery [95%CI]	% change of [Li] related to delivery [95%CI]
N	Delivery time point (D0) [Li] Mean (SD)	Other time points (D-2, D-1, D+2, D+3, D+7) [Li] Mean (SD)		
22	**D0 Delivery** 0.45 (0.23)	**D-2** Day before hospital birth[a] 0.64 (0.21)	-0.19 [-0.25, -0.13]	-31.7 [-41.0, -22.3]
22	**D0 Delivery** 0.54 (0.29)	**D-1** Admission day to hospital birth 0.60 (0.31)	-0.07 [-0.09, -0.05]	-12.8 [-16.5, -9.1]
34	**D0 Delivery** 0.52 (0.24)	**D+2** Postpartum day 2 0.62 (0.26)	0.1 [0.03, 0.17]	33.6 [13.0, 54.3]
18	**D0 Delivery** 0.66 (0.27)	**D+3** Postpartum day 2 0.72 (0.29)	0.06 [-0.06, 0.18]	15.0 [-9.2, 39.2]
19	**D0 Delivery** 0.59 (0.28)	**D+7** Postpartum day 7[a] 0.63 (0.26)	0.04 [-0.1, 0.19]	26.8 [-11.4, 64.9]

Abbreviation: [Li]= Lithium concentration; CI= Confidence interval;
Symbol: Δ=Mean difference.
[a]Serum lithium serum concentrations were measured at steady-state and 12±2 hours post-dose.

Table 4-A. Serum lithium concentrations in neonates [umbilical cord or neonate 1er day of life] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	23	0.59 (0.30)	17	0.61 (0.33)	6	0.55 (0.23)	5	0.62 (0.18)	1	0.23 (0)	0	-
D0	64	0.54 (0.26)	39	0.50 (0.27)	25	0.61 (0.23)	18	0.63 (0.23)	6	0.55 (0.25)	1	0.74
UC	61	0.57 (0.26)	38	0.52 (0.26)	23	0.66 (0.24)	18	0.66 (0.23)	4	0.65 (0.25)	1	0.74
N1	5	0.49 (0.13)	2	0.54 (0.17)	3	0.46 (0.13)	1	0.31 (0)	2	0.54 (0.01)	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.97 (0.10)	4	0.99 (0.13)	3	1.03 (0.12)	1	0.87 (0)	0	-
UC/D0	60	1.10 (0.17)	37	1.09 (0.17)	23	1.11 (0.17)	18	1.07 (0.13)	4	1.31 (0.19)	1	1.00
N1/D-1	3	0.83 (0.14)	2	0.82 (0.20)	1	0.84 (0)	1	0.84(0)	0	-	0	-
N1/D0	4	0.96 (0.26)	2	0.98 (0.30)	2	0.93 (0.33)	0	-	2	0.93 (0.33)	0	-

Table 4-B. Paired serum lithium concentrations in neonates [umbilical cord] and mothers [admission day to hospital birth and delivery] and corresponding neonatal/maternal ratios.

Maternal and Neonatal serum lithium concentration (mEq/L)												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
D-1	19	0.59 (0.33)	15	0.60 (0.35)	4	0.55 (0.25)	3	0.66 (0.16)	1	0.23	0	-
D0	19	0.53 (0.31)	15	0.54 (0.33)	4	0.48 (0.26)	3	0.60 (0.16)	1	0.14	0	-
UC	19	0.58 (0.31)	15	0.57 (0.33)	4	0.58 (0.37)	3	0.71 (0.11)	1	0.20	0	-
Neonatal/Maternal [Li] ratios												
	All cases		**Monotherapy**		**Polytherapy**							
					All		**Li+AP**		**Li+AD**		**Li+AP+AD**	
	N	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
UC/D-1	19	0.97 (0.10)	15	0.96 (0.10)	4	1.02 (0.13)	3	1.08 (0.09)	1	0.86	0	-
UC/D0	19	1.15 (0.12)	15	1.07 (0.09)	4	1.25 (0.15)	3	1.19 (0.12)	1	1.42	0	-

Abbreviations: Li= Lithium; Li+AP= Lithium+antipsychotic; Li+AD= Lithium+antidepressant; Li+AP+AD= Lithium+antipsychotic+ antidepressant; D-1=Admission day to hospital birth; D0=Delivery (intrapartum); UC=Umbilical cord; N1=Neonate 1st day of life.