Received: 11 September 2023 | Revised: 5 January 2024 | Accepted: 6 January 2024

DOI: 10.1111/acps.13663

ORIGINAL ARTICLE

Acta Psychiatrica Scandinavica WILEY

Dose response relationship between lithium serum levels during pregnancy and birth outcomes

Lisanne Schrijver[1,2] | **Astrid M. Kamperman**[1] | **Hilmar Bijma**[3] | **Inge L. van Kamp**[4] | **Richard Wesseloo**[1,5] | **Witte J. G. Hoogendijk**[1] | **Veerle Bergink**[1,6] | **Eline M. P. Poels**[1]

[1]Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands

[2]Molemann Mental Health, Amersfoort, The Netherlands

[3]Department of Obstetrics and Gynecology, Division Obstetrics and Fetal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands

[4]Department of Obstetrics, Leiden University Medical Center, Leiden, The Netherlands

[5]GGZ Delfland, Delft, The Netherlands

[6]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Correspondence
Lisanne Schrijver, Erasmus University Medical Center, Dr. Molenwaterplein 50, 3000 CA Rotterdam, The Netherlands.
Email: l.schrijver.1@erasmusmc.nl

Abstract

Introduction: Lithium use during pregnancy reduces the risk of mood episodes in the perinatal period for women with bipolar disorder. Some previous studies found deleterious effects of intrauterine lithium exposure on birth outcomes, yet little is known about a dose response relationship. The current study investigated the influence of maternal lithium serum levels on birth outcomes.

Methods: This retrospective observational cohort study included women with a bipolar spectrum disorder who were referred to a specialized psychiatric and obstetric outpatient clinic from 2003 to 2019 and used lithium during the entire pregnancy. For 101 pregnancies at least one lithium level during pregnancy was available. A weighted average lithium level was calculated for the entire pregnancy, as well as for each trimester. Detailed information on maternal, obstetric and neonatal outcomes were retrieved from the medical records. Linear and logistic regression models were used to investigate the association between weighted average lithium level and pregnancy duration, birth weight percentiles, preterm birth and large for gestational age births (LGA). In subsequent exploratory analyses, we studied the role of thyroid-stimulating hormone (TSH) and thyroxine (T4) as a mediator in the found associations.

Results: The weighted average lithium serum level during pregnancy was negatively associated with pregnancy duration and positively with preterm birth, but not with birth weight percentile or LGA. In exploratory analyses, TSH and T4 did not mediate the association between average lithium serum level and pregnancy duration.

Conclusion: The results of this cohort study during pregnancy indicate a dose response relationship between maternal lithium serum levels and pregnancy duration.

KEYWORDS

bipolar disorder, birth outcome, lithium, offspring, pregnancy

1 | INTRODUCTION

Lithium is widely considered as first-line treatment for bipolar disorder, an episodic condition affecting approximately 1%–2% of the population.[1,2] Lithium is an effective treatment during both depressive and manic episodes and it strongly reduces the risk of relapse.[3] It is also effective as adjunctive treatment in severe unipolar depression.[4] Since bipolar disorder often has its onset during early adulthood,[1] lithium is frequently prescribed to women of reproductive age. For mood stability of the mother, continuation of lithium is beneficial, both during pregnancy and in the postpartum period, given that lithium during pregnancy strongly reduces the risk of relapse.[5–7] However, those benefits of continuation of treatment should be weighed against potential negative effects of intrauterine exposure to lithium for the fetus and newborn.

First trimester lithium exposure has been associated with a slightly increased risk of congenital malformations and miscarriage.[8–10] Based on a meta-analysis, the odds ratios for any congenital malformation and for cardiac malformations were 1.81 (95% CI: 1.35, 2.41) and 1.86 (95% CI: 1.16, 2.96) respectively.[11] Lithium exposure has also been associated with an increased risk of preterm birth (gestational age < 37 weeks) and shorter pregnancy duration in multiple studies.[9,12–14] A recent population-based cohort study by Hastie et al., estimated the adjusted relative risk for preterm birth to be 2.64 (95% CI: 1.82, 3.82).[13] In contrast, a meta-analysis of six study sites, using a shared protocol, showed no significant differences in the occurrence of preterm birth.[8] Moreover, several studies have reported increased birth weights and higher rates of large for gestational age births (LGA) in association with lithium (i.e., birth weight above the 90th percentile, corrected for gestational age and sex).[13–15] Based on the same population-based cohort study, the adjusted relative risk for LGA was estimated to be 2.64 (95% CI: 1.91, 3.66).[13]

For patients and clinicians it is relevant to know to which extent these potential adverse outcomes are related to lithium dose. Unfortunately, thus far, only a few studies investigated the association between dosing, maternal serum levels and adverse perinatal outcomes. Patorno et al.[16] found a relationship between lithium dose and the risk of cardiac malformations. Another study investigated the influence of lithium serum level on long-term neuropsychological development in the child and did not find a dose response effect.[17] Finally, Newport et al.[18] found an increased risk of perinatal complications for higher lithium concentrations at delivery, but this was not confirmed by the study of Molenaar et al.[19] No previous studies investigated the influence of lithium levels during the entire pregnancy on birth outcomes. Clinicians and patients usually search for the lowest effective dose in order to minimize side effects, and it is therefore useful to know to which extent birth outcomes are related to maternal lithium serum levels.

Moreover, a potential dose response relationship strengthens evidence for a causal relationship between lithium exposure and adverse birth outcomes. Previous studies have compared pregnancy outcomes in women with bipolar disorder and lithium use with women from control populations (i.e., women without bipolar disorder or with a potentially less severe type of bipolar disorder), which means that results may have been influenced by confounding by indication. It is difficult to distinguish whether associations result from lithium exposure or from maternal disease severity, yet a dose response relationship is highly suggestive for an effect of lithium exposure.

It is currently unknown via which physiological mechanism lithium might affect birth outcomes. A potential pathway could be linked to maternal thyroid function. Lithium can cause both clinical and subclinical hypothyroidism and (sub)clinical hypothyroidism has in some studies been associated with preterm birth.[20–22] No clinical studies to date have investigated the potential role of thyroid function in the association between intrauterine lithium exposure and birth outcomes.

The main aim of this study was to investigate the association between the weighted average lithium serum level during pregnancy and pregnancy duration, preterm birth, birth weight percentiles and LGA. We studied associations with the weighted average lithium serum level for the entire pregnancy as well as for each separate trimester. Our secondary aim was to explore a potential

Significant outcomes

- In this observational pregnancy cohort, higher average lithium serum level was associated with shorter pregnancy duration and increased risk of preterm birth.
- In exploratory analyses, TSH and T4 did not mediate the association between lithium serum level and pregnancy duration.

Limitations

- The number of lithium serum levels was limited in some of the included pregnancies.
- TSH and T4 measurements were only available for a subset of our sample, thereby limiting the power of the exploratory mediation analyses.

pathophysiological mechanism, by studying thyroid function as a mediator in the found associations.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This retrospective observational cohort study was part of the NP3 study (National postpartum psychosis prevention offspring study), that included women with a history of bipolar spectrum disorder or postpartum psychosis that were referred to a psychiatric and obstetric outpatient clinic from 2003 to 2019.[23] Most women were included at Erasmus Medical Center or Leiden University Medical Center and a small number of women were included at other Dutch clinics. Data were collected during clinical visits as part of the regular treatment and were later retrieved from the medical records. The study was approved by the medical ethical review board of Erasmus University Medical Center (MEC 2013-319). Part of these data ($n = 56$) were also used in an earlier study on fetal growth during lithium exposure.[14]

A total of 277 pregnancies were eligible for inclusion in the larger study. For the current study, women were included if they used lithium during pregnancy and if at least one lithium serum level during pregnancy was available ($n = 126$). Pregnancies were excluded if lithium was only used during part of the pregnancy ($n = 16$), in case of miscarriage or stillbirth ($n = 6$) or multiple pregnancy ($n = 3$). This resulted in a final study sample of 101 pregnancies and infants from 81 women. Sixty-one women had one pregnancy and 20 women had two pregnancies included.

2.2 | Birth outcomes

Continuous outcome measures were pregnancy duration in days and birth weight percentiles. Pregnancy duration was based on the estimated due date. Delivery date, estimated due dates and birth weights were retrieved from the medical records. The Hoftiezer standards[24] were used to calculate percentiles for birth weight adjusted for gestational age. The Hoftiezer charts are based on singleton children born in The Netherlands between 2000 and 2014. Dichotomous outcome measures were preterm birth (<37 weeks gestation) and large for gestational age (LGA) infants. Birth weights below the 10th percentile or above the 90th percentile for the corresponding age and sex, are classified as small for gestational age (SGA) and large for gestational age (LGA) respectively. In addition, relevant demographic and obstetric data, lithium levels and information on maternal psychiatric episodes and treatment during pregnancy were obtained from the medical records.

2.3 | Estimated weighted average lithium levels

The estimated weighted average lithium level per pregnancy was calculated as follows: (1) each lithium level was multiplied by the number of days between that measurement and the previous measurement, (2) the first level measured was multiplied by the number of days between that measurement and the start of pregnancy (term date minus 280), (3) the last known lithium level was also multiplied by the number of days between that measurement and the day of delivery, (4) a weighted average lithium level was calculated by summing these products and subsequently dividing this sum by the pregnancy duration in days. The same approach for calculating the weighted average lithium level was used in our previous study on the neuropsychological outcomes of lithium-exposed offspring.[17]

Average lithium levels per trimester were calculated in a similar manner. In this case, the number of days was limited by the duration per trimester (trimester 1: day 0–90, trimester 2: day 91–195, trimester 3: day 196—day of delivery).

2.4 | Confounding factors

A relationship between lithium level and birth outcomes might be confounded by the occurrence of mood episodes during pregnancy. Mood episodes during pregnancy are often a reason for dosage change and are also found to be a risk factor for adverse birth outcomes. We therefore selected the occurrence of a mood episode (i.e., depression, (hypo) mania or psychosis) during pregnancy as a covariate. Information on mood episodes was derived from the medical records and via self-report questionnaires at 12 months postpartum, the latter being available for only a small number of pregnancies ($n = 13$). In addition, we selected the use of other psychotropic medication as covariate, as other psychotropics could also influence birth outcomes and its prescription may not be independent from the lithium dose and serum level. Use of psychotropics included temporary prescriptions and pro re nata medication.

2.5 | Statistical analysis

Statistical analyses and descriptive statistics were performed with the Statistical Package for Social Sciences (SPSS, version 28, IBM). We used separate linear

regression models to investigate the association between weighted average lithium levels and the continuous birth outcome variables (pregnancy duration, birthweight percentiles). A square root transformation was used to normalize the birth weight percentile outcome. Logistic regression models were used to investigate the association between weighted lithium levels and the dichotomous birth outcome variables (preterm birth and large for gestational age). For all analyses, weighted lithium levels were transformed by multiplying by 10. This in particular enhanced the interpretation of logistic regression outcomes, as the odds ratios (OR) represent the increase in odds of the outcome with every 1 unit increase of the predictor (lithium level), but all lithium levels are between 0 and 1 without transformation. After transformation, the odds ratios represent the increase in odds of the outcome with every 0.1 mmol/L increase in lithium level. We defined a simple univariate model and an adjusted multivariate model for analysis. In the simple model, weighted average lithium level was the independent variable. In the adjusted model, the occurrence of a mood episode during pregnancy and the use of at least one other psychiatric medication were added to the analysis. There was one missing value for mood episode during pregnancy, which was imputed with the mode. There were no missing values for the other variables. Unstandardized betas, confidence intervals for the beta and *p*-levels are reported for linear regression; for logistic regression, odds ratios, corresponding confidence intervals and *p*-levels are reported. *p*-Levels <0.05 are considered as statistically significant.

2.6 | Exploratory mediator analysis

We explored the role of T4 and TSH as mediators in the associations that were found to be statistically significant in our primary analyses. We calculated the mean T4 and TSH values for each trimester and then conducted path analyses using the PROCESS macro for SPSS,[25] as visualized in Figure 1. We reported average TSH and T4 concentrations per trimester, as thyroid function changes throughout pregnancy and reference ranges are thus trimester specific. For each analysis, both direct and indirect effects are reported with unstandardized coefficients, including 95% confidence intervals. The indirect effect a · b represents the change in pregnancy duration associated with a 0.1 mmol/L increase in lithium level through the mediator. The direct effect *c′* is the direct effect of lithium level on pregnancy duration.

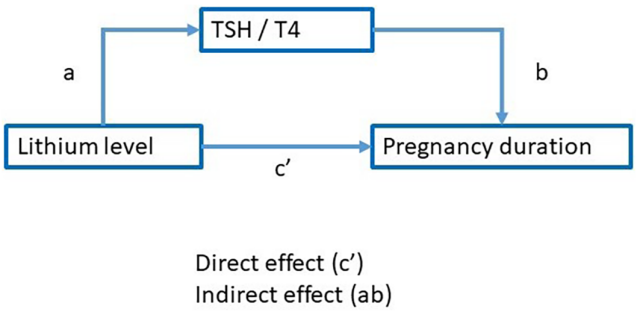

FIGURE 1 Model of TSH and T4 as mediators in the association between lithium level and pregnancy duration.

2.7 | Sensitivity analyses

In separate sensitivity analyses, patients with induced labor ($n = 29$), gestational diabetes ($n = 7$), obesity (BMI ≥30) ($n = 14$), or pre-eclampsia ($n = 8$) were excluded from the analyses to see if results were driven by these factors. Patients were considered obese with a reported BMI ≥30 before pregnancy. BMI data were missing for 42 women. Data on mode of delivery and pregnancy complications were retrieved from the obstetrical records and were available in 100 out of 101 pregnancies.

3 | RESULTS

3.1 | Descriptive results

Maternal, pregnancy and child characteristics are presented in Table 1.

The median number of lithium serum level measurements per pregnancy was 7 (IQR = 6). For 89 cases (88%), there were at least three lithium serum levels per pregnancy. At least one lithium serum level was available for the first trimester in 61 cases, for the second trimester in 86 cases and for the third trimester in 93 cases. Lithium carbonate (Camcolit, Priadel or generic lithium) was used in 63 pregnancies and lithium citrate (Litarex, slow release) was used in the other 38 pregnancies. At least one TSH measurement was available for the first trimester in 47 cases, for the second trimester in 55 cases and for the third trimester in 60 cases. At least one T4 measurement was available for the first trimester in 38 cases, for the second trimester in 33 cases and for the third trimester in 39 cases.

3.2 | Main analyses

Results from the regression analyses are shown in Table 2 and Figure 2. We found a negative linear association

TABLE 1 Maternal, pregnancy and child characteristics of the study sample.

N	101
Maternal characteristics	
Age, mean (SD)	34.6 (4.0)
Diagnosis, *n* (%)	
Bipolar I disorder	68 (67.3)
Bipolar II disorder	18 (17.8)
Bipolar disorder, unspecified	3 (3.0)
Postpartum psychosis	3 (3.0)
Other[a]	9 (8.9)
Mood episode during pregnancy, *n* (%)	10 (10.0)
BMI before pregnancy ($n = 59$), mean (SD)	26.4 (5.6)
Obesity ($n = 59$) (BMI ≥ 30), *n* (%)	14 (23.7)
Pregnancy characteristics	
Parity	
0, *n* (%)	48 (47.5)
≥1, *n* (%)	53 (52.5)
Smoking, *n* (%)	6 (5.9)
Alcohol use, *n* (%)	5 (5.0)
Recreational drugs use, *n* (%)	0 (0.0)
Weighted average lithium level, mean in mmol/L (SD)	
Total pregnancy ($n = 101$)	0.49 (0.11)
Trimester 1 ($n = 61$)	0.48 (0.14)
Trimester 2 ($n = 86$)	0.46 (0.12)
Trimester 3 ($n = 93$)	0.58 (0.17)
Use of psychotropic medications other than lithium, *n* (%)[b]	45 (44.6)
Benzodiazepines, *n* (%)	18 (17.8)
Antipsychotics, *n* (%)	21 (20.8)
Antidepressants, *n* (%)	15 (14.9)
Thyroid disorder past or current, *n* (%)	29 (28.7)
TSH median (mU/L) (IQR)	
Trimester 1 ($n = 47$)	1.05 (1.62)
Trimester 2 ($n = 55$)	1.22 (1.02)
Trimester 3 ($n = 60$)	1.63 (1.87)
fT4 median (pmol/L) (IQR)	
Trimester 1 ($n = 38$)	15.9 (4.34)
Trimester 2 ($n = 33$)	14.00 (5.00)
Trimester 3 ($n = 39$)	12.60 (4.15)
Induced labor, *n* (%)	29 (28.7)
Pre-eclampsia, *n* (%)	8 (7.9)
Gestational diabetes, *n* (%)	7 (6.9)
Child characteristics	
Sex, *n* female (%)	61 (60.4)
Birth weight in grams, mean (SD)	3505 (565.63)
Gestational age at birth in weeks, mean (SD)	38.6 (2.0)
Preterm birth (<37 weeks) *n*, (%)	20 (19.8)
Large for gestational age (≥90th percentile), *n* (%)	23 (23.0)

Note: In case of missingness, valid means and percentages are presented.
Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation; TSH, thyroid stimulating hormone; fT4, free thyroxine.
[a]Other diagnoses: schizoaffective disorder ($n = 2$), schizoaffective disorder and history of postpartum psychosis ($n = 3$), major depressive disorder ($n = 3$), unknown ($n = 1$).
[b]Included temporary prescriptions and pro re nata medication. Some subjects used multiple medications.

between the average lithium level during pregnancy and pregnancy duration. For each increase of lithium level with 0.1 mmol/L, pregnancy duration decreased with 2.58 days (95% CI: −5.01, −0.14, $p = 0.04$) in the simple model and with 2.81 days (95% CI: −5.26, −0.36, $p = 0.03$) in the adjusted model. Accordingly, there was a positive association between average lithium level and the risk of preterm birth (OR = 1.66 (95% CI: 1.05, 2.61), $p = 0.03$ simple model, OR = 1.69 (95% CI: 1.06, 2.68) $p = 0.03$ adjusted model). When examining the average lithium level calculated per trimester, similar associations with pregnancy duration and preterm birth were found for trimester 2 and 3 (Table A1, Appendix A). No significant associations were found between average lithium level and birth weight percentiles and the risk of LGA birth (Table 2, Figure A1 (Appendix A) and Table A1 (Appendix A)).

3.3 | Exploratory analyses

In separate path analyses, mean TSH and T4 for each trimester were studied as mediator in the association between average lithium level and pregnancy duration, as visualized in Figure 1. For TSH in trimester 1 the direct effect was −2.33 (95% CI −5.52, 0.86) and the indirect effect was −0.04 (95% CI −0.63, 0.59). For TSH in trimester 2 the direct effect was −3.16 (95% CI −6.33, 0.003) and the indirect effect was 0.56 (95% CI −0.17, 1.50). For TSH in trimester 3 the direct effect was −2.74 (95% CI −5.88, 0.40) and the indirect effect was 0.28 (−0.20, 2.08). For T4 in trimester 1 the direct effect was −2.45 (95% CI −5.99, 1.08) and the indirect effect was −0.03 (95% CI −0.87, 0.61). For T4 in trimester 2 the

TABLE 2 Associations of weighted average lithium level per pregnancy with birth outcome measures ($n = 101$).

	Simple model[a]		Adjusted model[b]	
	β (95% CI)	***p*-value**	**β (95% CI)**	***p*-value**
Pregnancy duration (in days)	**−2.58 (−5.01, −0.14)**	**0.04**	**−2.81 (−5.26, −0.36)**	**0.03**
Birth weight percentiles	0.10 (−0.33, 0.54)	0.64	0.09 (−0.35, 0.53)	0.69
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Preterm birth	**1.66 (1.05, 2.61)**	**0.03**	**1.69 (1.06, 2.68)**	**0.03**
Large for Gestational Age (LGA)	1.10 (0.74, 1.66)	0.63	1.11 (0.74, 1.68)	0.62

Note: Bold values denote statistical significance (p-value < 0.05).
Abbreviations: OR, odds ratio; CI, confidence interval.
[a]Weighted average lithium level (multiplied by 10) as independent variable.
[b]Adjusted for mood episode during pregnancy and use of other psychotropics.

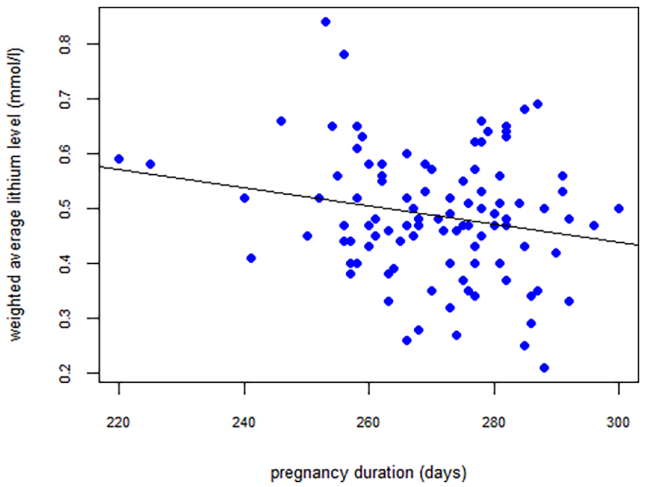

FIGURE 2 Scatter plot of pregnancy duration and weighted average serum lithium level during pregnancy.

direct effect was −4.73 (95% CI −11.13, 1.66) and the indirect effect was 0.07 (95% CI −1.51, 0.60). For T4 in trimester 3 the direct effect was −2.74 (95% CI −6.51, 1.04) and the indirect effect was 0.08 (95% CI −1.47, 1.19). Thus, we found no indication for a mediating effect of thyroid function on the association between lithium level and pregnancy duration.

3.4 | Sensitivity analyses

A sensitivity analysis, excluding 29 patients with induced labor, did not alter the findings. In a separate sensitivity analysis, excluding 7 patients with gestational diabetes, the association with both pregnancy duration ($\beta = -2.41$, (95% CI: −4.96, 0.14), $p = 0.06$ adjusted model) and preterm birth (OR = 1.67 (95% CI: 0.99, 2.83), $p = 0.06$, adjusted model) showed comparable coefficients. In a separate sensitivity analysis, excluding 14 patients with obesity, the association with both pregnancy duration ($\beta = -1.94$, (95% CI: −4.53, 0.66), $p = 0.14$, adjusted model) and preterm birth (OR = 1.43 (95% CI: 0.89, 2.29), $p = 0.14$) showed comparable coefficients. In a separate sensitivity analysis, excluding 8 patients with pre-eclampsia, the association with both pregnancy duration ($\beta = -2.25$, (95% CI: −4.71, 0.23), $p = 0.07$ adjusted model) and preterm birth (OR = 1.48 (95% CI: 0.89, 2.48), $p = 0.13$) showed similar results.

4 | DISCUSSION

In this observational cohort study we found that the average lithium level during pregnancy was negatively associated with pregnancy duration and positively with preterm birth, but not with birth weight percentiles or the risk of large for gestational age birth. Our findings may be relevant for clinical decision making and show that trying to find the lowest optimally effective dose is especially important during pregnancy. Patients with lithium levels in the lower range might have a lower risk of preterm birth.

Our findings are in line with several previous studies that found an association between lithium exposure and preterm birth.[9,12,13] Not only did we find a high rate of preterm birth for the entire sample (19.8%), but also a dose response relationship. Even though no dose response relationship was found for birth weight percentiles, the entire sample contained a high rate of LGA (23%), which corresponds to a recent study that related lithium exposure to increased risk of LGA births.[13]

We focused on a dose response relation for clinical purposes and to gain more insight into the causality of the association between lithium exposure and birth outcomes. Whereas some studies have investigated a dose response effect of SSRIs on birth outcomes,[26] to our knowledge no study has investigated this for lithium.

Our findings are suggestive for a possible dose related effect of lithium on birth outcomes. However, confounding by indication is an important limitation of these type of studies, including ours. Even though all women in our study had bipolar spectrum disorder, confounding due to severity of the underlying disorder cannot be excluded.

Our secondary aim was to explore a potential pathophysiological mechanism for the associations found. No previous study investigated mediating factors in the association between lithium use and pregnancy duration and thus far the pathophysiological mechanism remains unknown. Lithium use increases the risk of hypothyroidism and maternal hypothyroidism has in some studies been associated with preterm birth.[20–22] We therefore studied the role of TSH and T4 as a mediator in the association between maternal lithium levels and pregnancy duration. We chose to report average TSH and T4 concentrations per trimester, as thyroid function changes throughout pregnancy and reference ranges are thus trimester specific. We did not find an effect of thyroid function on the association of lithium level and pregnancy duration. Possible explanations are (1) the association between lithium serum level and pregnancy duration is not mediated by thyroid function and (2) we were underpowered to study this relationship in detail as for most trimesters TSH and fT4 levels were available in <50% of subjects. Furthermore, we studied an association between TSH and T4 and lithium serum level but not with lithium use. It is therefore still possible that TSH and T4 are on the causal pathway, but without a dose response relationship in this association. More research is needed to explore thyroid function as a potential pathophysiological mechanism, preferably by using larger datasets and performing systematic thyroid function measurements.

Other factors potentially influencing pregnancy duration are induced labor, gestational diabetes, obesity and pre-eclampsia. Separate sensitivity analyses excluding these factors did not change the direction or effect size of our results. In previous literature no clear association was found between lithium use and these parameters.[8,27]

Our study has several strengths. Detailed data on lithium levels during all trimesters of pregnancy were available, as well as obstetric data, neonatal outcome data and detailed information on maternal diagnosis and treatment. We considered actual serum level to be a more accurate predictor for the effects of lithium than the daily dosage, because of its known therapeutic window and due to the physiological changes of renal function during pregnancy.[23] By focusing on a dose response relationship, the risk of confounding by maternal psychiatric disorder was substantially smaller than in studies comparing exposure versus non-exposure. To account for any remaining confounding factors, we adjusted for the occurrence of a mood episode and the use of additional psychotropic medication during pregnancy. Interestingly, the associations remained significant in the adjusted model, suggesting that these associations were not confounded by the occurrence of mood episodes during pregnancy or other psychotropic use, and strengthening the evidence for an effect of lithium serum level on pregnancy duration and preterm birth.

Several limitations of this study need to be considered. Firstly, the number of lithium serum levels was limited in some of the included pregnancies, with only 1 or 2 serum levels in 12 cases. It is possible that the serum level changed throughout pregnancy and that the estimated weighted average in these cases is an under or overestimation of the actual serum level. Secondly, TSH and T4 serum levels were only available in a subset of our sample and the mediation analyses may therefore have been underpowered. Furthermore, detailed medical information about thyroid status and levothyroxine use was limited.

The dose response relationship in our study adds to existing evidence that lithium may negatively influence pregnancy duration. This information is important for clinical practice, as women need to be well informed about all risks and benefits of lithium use during pregnancy, in order to make an individual and well-informed decision. Our results suggest that careful dosing and maintaining a minimal effective lithium level may benefit infant outcomes. Individual decisions on pharmacological treatment should preferably be based on shared decision making by the patient and health care provider, including a careful and personalized weighing of all risks and benefits.

ACKNOWLEDGMENTS

The authors would like to thank all the women that participated in this study.

CONFLICT OF INTEREST STATEMENT

All authors declare that there is no conflict of interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/acps.13663.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Lisanne Schrijver https://orcid.org/0000-0002-4575-6237

REFERENCES

1. Merikangas KR, Jin R, He JP, et al. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry*. 2011;68(3):241-251. doi:10.1001/archgenpsychiatry.2011.12
2. Malhi GS, Bauer M. Lithium first: not merely first line. *Bipolar Disord*. 2023;25(1):7-8. doi:10.1111/bdi.13299
3. Geddes JR, Miklowitz DJ. Treatment of bipolar disorder. *Lancet*. 2013;381(9878):1672-1682. doi:10.1016/S0140-6736(13)60857-0
4. Cipriani A, Hawton K, Stockton S, Geddes JR. Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ*. 2013;346:f3646f3646. doi:10.1136/bmj.f3646
5. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJ, Kushner SA, Bergink V. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. *Am J Psychiatry*. 2016;173(2):117-127. doi:10.1176/appi.ajp.2015.15010124
6. Stevens A, Goossens PJJ, Knoppert-van der Klein EAM, Draisma S, Honig A, Kupka RW. Risk of recurrence of mood disorders during pregnancy and the impact of medication: a systematic review. *J Affect Disord*. 2019;249:96-103. doi:10.1016/j.jad.2019.02.018
7. Viguera AC, Whitfield T, Baldessarini RJ, et al. Risk of recurrence in women with bipolar disorder during pregnancy: prospective study of mood stabilizer discontinuation. *Am J Psychiatry*. 2007;164(12):1817-1824. doi:10.1176/appi.ajp.2007.06101639
8. Munk-Olsen T, Liu X, Viktorin A, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. *Lancet Psychiatry*. 2018;5(8):644-652. doi:10.1016/S2215-0366(18)30180-9
9. Diav-Citrin O, Shechtman S, Tahover E, et al. Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. *Am J Psychiatry*. 2014;171(7):785-794. doi:10.1176/appi.ajp.2014.12111402
10. Poels EMP, Kamperman AM, Vreeker A, et al. Lithium use during pregnancy and the risk of miscarriage. *J Clin Med*. 2020;9(6):1819. doi:10.3390/jcm9061819
11. Fornaro M, Maritan E, Ferranti R, et al. Lithium exposure during pregnancy and the postpartum period: a systematic review and meta-analysis of safety and efficacy outcomes. *Am J Psychiatry*. 2020;177(1):76-92. doi:10.1176/appi.ajp.2019.19030228
12. Troyer WA, Pereira GR, Lannon RA, Belik J, Yoder MC. Association of maternal lithium exposure and premature delivery. *J Perinatol*. 1993;13(2):123-127.
13. Hastie R, Tong S, Hiscock R, et al. Maternal lithium use and the risk of adverse pregnancy and neonatal outcomes: a Swedish population-based cohort study. *BMC Med*. 2021;19(1):291. doi:10.1186/s12916-021-02170-7
14. Poels EM, Sterrenburg K, Wierdsma AI, et al. Lithium exposure during pregnancy increases fetal growth. *J Psychopharmacol*. 2021;35(2):178-183. doi:10.1177/0269881120940914
15. Jacobson SJ, Jones K, Johnson K, et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet*. 1992;339(8792):530-533. doi:10.1016/0140-6736(92)90346-5
16. Patorno E, Huybrechts KF, Bateman BT, et al. Lithium use in pregnancy and the risk of cardiac malformations. *N Engl J Med*. 2017;376(23):2245-2254. doi:10.1056/NEJMoa1612222
17. Poels EMP, Schrijver L, White TJH, et al. The effect of prenatal lithium exposure on the neuropsychological development of the child. *Bipolar Disord*. 2022;24(3):310-319. doi:10.1111/bdi.13133
18. Newport DJ, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. *Am J Psychiatry*. 2005;162(11):2162-2170. doi:10.1176/appi.ajp.162.11.2162
19. Molenaar NM, Poels EMP, Robakis T, Wesseloo R, Bergink V. Management of lithium dosing around delivery: an observational study. *Bipolar Disord*. 2021;23(1):49-54. doi:10.1111/bdi.12955
20. Maraka S, Ospina NM, O'Keeffe DT, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid*. 2016;26(4):580-590. doi:10.1089/thy.2015.0418
21. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012;379(9817):721-728. doi:10.1016/S0140-6736(11)61516-X
22. Korevaar TI, Schalekamp-Timmermans S, de Rijke YB, et al. Hypothyroxinemia and TPO-antibody positivity are risk factors for premature delivery: the generation R study. *J Clin Endocrinol Metab*. 2013;98(11):4382-4390. doi:10.1210/jc.2013-2855
23. Wesseloo R, Wierdsma AI, van Kamp IL, et al. Lithium dosing strategies during pregnancy and the postpartum period. *Br J Psychiatry*. 2017;211(1):31-36. doi:10.1192/bjp.bp.116.192799
24. Hoftiezer L, Hof MHP, Dijs-Elsinga J, Hogeveen M, Hukkelhoven C, van Lingen RA. From population reference to national standard: new and improved birthweight charts. *Am J Obstet Gynecol*. 2019;220(4):383.e1-383.e17. doi:10.1016/j.ajog.2018.12.023
25. Hayes A. *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. 3rd ed. Guilford Press; 2022.
26. Molenaar NM, Houtman D, Bijma HH, et al. Dose-effect of maternal serotonin reuptake inhibitor use during pregnancy on birth outcomes: a prospective cohort study. *J Affect Disord*. 2020;267:57-62. doi:10.1016/j.jad.2020.02.003
27. Gomes-da-Costa S, Marx W, Corponi F, et al. Lithium therapy and weight change in people with bipolar disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2022;134:104266104266. doi:10.1016/j.neubiorev.2021.07.011

How to cite this article: Schrijver L, Kamperman AM, Bijma H, et al. Dose response relationship between lithium serum levels during pregnancy and birth outcomes. *Acta Psychiatr Scand*. 2024;1-9. doi:10.1111/acps.13663

APPENDIX A

TABLE A1 Associations between weighted average lithium level per trimester and birth outcome measures (trimester 1: $n = 61$, trimester 2: $n = 86$, trimester 3: $n = 93$).

	Simple model[a]		Adjusted model[b]	
	β (95% CI)	***p*-value**	**β (95% CI)**	***p*-value**
Gestational duration (in days)				
Trimester 1	−0.81 (−3.19, 1.56)	0.50	−1.32 (−3.61, 0.98)	0.26
Trimester 2	**−3.59 (−6.06, −1.12)**	**0.01**	**−3.59 (−6.10, −1.08)**	**0.01**
Trimester 3	−1.62 (−3.28, 0.05)	0.06	**−1.71 (−3.40, −0.02)**	**0.047**
Birth weight percentiles				
Trimester 1	0.24 (−0.21, 0.68)	0.30	0.27 (−0.19, 0.72)	0.25
Trimester 2	−0.26 (−0.70, 0.18)	0.24	−0.28 (−0.73, 0.16)	0.21)
Trimester 3	0.18 (−0.13, 0.49)	0.26	0.19 (−0.13, 0.51)	0.24
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Preterm birth				
Trimester 1	1.13 (0.71, 1.78)	0.61	1.18 (0.74, 1.87)	0.49
Trimester 2	1.55 (0.99, 2.43)	0.06	1.56 (0.97, 2.49)	0.07
Trimester 3	**1.40 (1.03, 1.89)**	**0.03**	**1.42 (1.05, 1.94)**	**0.03**
Large for gestational age (LGA)				
Trimester 1	0.84 (0.52, 1.37)	0.49	0.81 (0.49, 1.35)	0.42
Trimester 2	1.36 (0.88, 2.09)	0.16	1.50 (0.93, 2.42)	0.09
Trimester 3	1.01 (0.76, 1.34)	0.96	1.06 (0.79, 1.43)	0.69

Note: Bold values denote statistical significance ($p < 0.05$).
Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Weighted average lithium level (multiplied by 10) as independent variable.
[b]Adjusted for mood episode during pregnancy and use of other psychotropics.

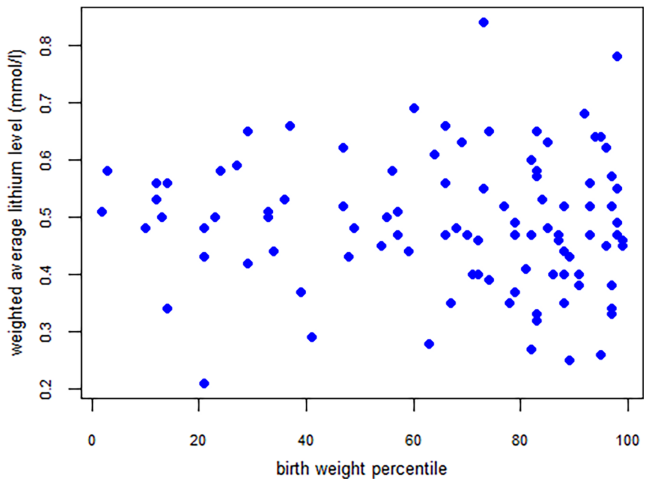

FIGURE A1 Scatter plot of weighted average serum lithium level during pregnancy and birthweight percentiles.