LITHIUM USE DURING PREGNANCY

Consequences for development: from conception to childhood

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CHAPTER 1

GENERAL INTRODUCTION

Lisa is a 31-year-old woman with a diagnosis of bipolar I disorder. In the past six years she has experienced one manic and two depressive episodes for which she was once admitted to a psychiatric hospital. Over the last year she used lithium at therapeutic doses and her mood has been stable. Lisa has a steady relationship with David and they decided to try for a baby. Today Lisa visits her psychiatrist for a follow-up appointment and discusses her desire to have a child. She has many questions for her psychiatrist. Although this is an exciting phase in her life, Lisa is worried that a pregnancy might not be without complications due to her bipolar disorder and medication. She wants to know if it is safe to be pregnant while using lithium. Could the medication cause harm to her baby? She read somewhere that lithium increases the risk of Epstein anomaly, but does not really know what that means. And what is known about the development of the child later in life?

Pregnancy and childbirth are major life events for any woman. For women with bipolar disorder, pregnancy, delivery and the months thereafter are even more challenging. The treatment of bipolar disorder during the perinatal period is complex. During pregnancy, fetal exposure to medication should be minimised, but women might need medication to maintain mood stability or to treat an episode. The period after delivery is a very high risk period for bipolar recurrence. Lisa and her psychiatrist will need to weigh the risks and benefits of lithium use during pregnancy and make an individual treatment plan for pregnancy, delivery and the period after delivery. The research in this thesis might help this decision making.

Bipolar disorder

Bipolar disorder is a chronic disorder characterised by recurrent episodes of depression and (hypo)mania. The DSM-5 classification system differentiates between bipolar type I and type II disorder based on the occurrence of mania (type I) or hypomania (type II) (1). In a worldwide mental health survey, the aggregate lifetime prevalence was 0.6% for bipolar I disorder, 0.4% for bipolar II disorder and 2.4% for bipolar spectrum disorders (2). Pharmacological treatment plays an important role in the management of bipolar disorder. In the acute management of mania or depression, mood stabilisers and antipsychotic drugs are the treatment of choice with the goal to achieve clinical and functional stabilisation (3). Long-term management has the aim to prevent new manic or depressive episodes and should combine pharmacological treatment with psychological treatment and lifestyle approaches (3). Bipolar disorder typically begins in adolescence or early adulthood and it is therefore a disorder that affects women of childbearing age. Women with bipolar disorder have been reported to have lower fertility rates (4). They have less children when compared to individuals without psychopathology (5, 6) and a higher risk of menstruation dysfunction

regardless of psychotropic medication use (7, 8). Even though, most women with bipolar disorder do have children. Their pregnancies are more likely to be unplanned (9) compared to the general population. Pregnancy is a challenging period for women with bipolar disorder due to psychotropic medication use with its associated side-effects and risks for the baby, and the high risk of a postpartum episode which may be complicated by poor bonding with the baby and the inability to care for the infant (10, 11). Besides that, there is a high risk of psychopathology in children of women with bipolar disorder (12). Women with bipolar disorder have a particularly high risk of a manic or depressive episode following childbirth. In a meta-analysis, the risk of recurrence was estimated to be 37% (13). Women with bipolar disorder who used prophylactic pharmacotherapy during pregnancy had a lower recurrence risk compared with medication-free women (23% vs. 66% respectively). This emphasizes the importance of medication continuation for some women. Recurrence risk is not only high after childbirth but also substantial after miscarriage and abortion (14). Recurrence risks during pregnancy show a large variation in different studies (15). Why childbirth is such a strong trigger for manic and depressive episodes remains unknown. Several hypotheses are made regarding the role of sleep loss, puerperal hormonal changes, genetic factors and postpartum activation of the immune system (16, 17).

Lithium is the most effective pharmacological treatment for the prevention of both manic and depressive episodes (18). For this reason, lithium is often the pharmacological treatment of choice for individuals with bipolar disorder. It is prescribed to women of childbearing age and it may be continued during pregnancy. It is therefore of high importance to know what the potential consequences are for the unborn child. Prior to this thesis, most research focussed on the risk of congenital malformations associated with lithium use during pregnancy. While this is important, there is also a need for more research on the risk of miscarriage, the effects on fetal growth and birth weight, the risk of neonatal complications and the neurodevelopment of the child.

Aims of this thesis

The research in this thesis was designed with the purpose to close the knowledge gap presented above. For this reason we performed studies that investigated the risk of miscarriage, fetal growth, the rate of neonatal complications and neurodevelopment of the child after intrauterine exposure to lithium. The aim was to expand on the knowledge about the potential consequences of lithium use during pregnancy, in order to support the clinician and patient in their decisions.

To that purpose the following questions will be addressed:

1. Is lithium use during pregnancy associated with an increased risk of miscarriage?
2. Does lithium use during pregnancy influence fetal growth and birth weight?
3. Should it be recommended to lower the lithium dose prior to delivery in order to reduce the risk of neonatal complications?
4. What is known about the long-term neurodevelopmental consequences of prenatal exposure to lithium and antipsychotics?
5. Is prenatal lithium exposure associated with neuropsychological functioning in children later in life?

Study populations

Participants that were included in the studies presented in this thesis originated from one of the following cohorts:

1. *Dutch Bipolar Cohort study*

The Dutch Bipolar Cohort (DBC) study was a collaboration between the University of California in Los Angeles and several Dutch healthcare institutes (University Medical Center Utrecht, Geestelijke gezondheidszorg (GGZ) Altrecht, GGZ inGeest, University Medical Center Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel). Participants in the DBC study were patients with bipolar disorder, aged 18 years and older, between June 2011 and July 2015. The objective of the DBC study was to investigate the genetic and phenotypic information of the participants.

2. *Generation R study*

The Generation R study is a prospective population-based study conducted in Rotterdam. In total 8880 mothers were enrolled during pregnancy with delivery dates from 2002 until 2006. The follow-up of children is currently still ongoing. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development, and health from fetal life until young adulthood.

3. *NP3 study*

The National Postpartum Psychosis Prevention (NP3) study is a clinical cohort study designed to investigate the clinical outcome of pregnancies in women with a history of bipolar disorder and/or postpartum psychosis. Mothers and their children were followed until 3.5 years postpartum. The NP3-study consist of a retrospective cohort (a collaboration between Erasmus Medical Center and Leiden University Medical Center) and a prospective cohort with nationwide inclusion. Inclusion took place from 2013 until 2018.

4. *Image_AL study*

The Image_AL study is a clinical cohort study designed to investigate the neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics. Participants were children aged 6 to 14 years old. Study data were collected during a single research visit in which an MRI scan of the brain was made (including structural and functional images) and neuropsychological tests were performed. The Snijders-Oomen Nonverbal Intelligence Test was used to estimate IQ and the NEPSY-II-NL assessment was used to test neuropsychological functioning on several domains. Additionally, questionnaire information on maternal, paternal and child health and child behaviour were collected. Data collection took place from February 2017 until March 2020.

Outline of this thesis

Chapter 2 provides a review of the literature on lithium use during pregnancy, as available at the start of this PhD trajectory. All published scientific studies on the risks and benefits of lithium use during pregnancy are discussed and clinical recommendations are made.

In part I we focus on the consequences of prenatal lithium exposure on pregnancy outcome, fetal growth and neonatal complications. In **chapter 3** we relate lithium use during pregnancy to an increased risk of miscarriage. We calculate the odds ratio of miscarriage after lithium use during pregnancy in a sample of women with bipolar I disorder that participated in the Dutch Bipolar Cohort study. **Chapter 4** provides information on fetal growth at 20 weeks of gestation and birth weight in a group of lithium-exposed pregnancies and a control group from the Generation R study. We report associations between prenatal lithium exposure and fetal growth. In **chapter 5** we explore the validity of lithium dose adjustment around delivery by investigating lithium blood level changes around delivery and by examining the association between neonatal lithium blood levels at delivery and neonatal outcomes (NP3 study).

In part II of this thesis we focus on the neurodevelopmental consequences of prenatal lithium exposure. **Chapter 6** is a meta-analysis and systematic review of findings from preclinical and clinical studies that examined the neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics. In **chapter 7** we investigate the association between prenatal lithium exposure and neuropsychological functioning in offspring of women with a diagnosis of bipolar spectrum disorder. We present data from a clinical cohort study (Image_AL study) with detailed in person neuropsychological assessments in lithium-exposed and non-exposed children.

Chapter 8 provides a general discussion of the main findings of this thesis and some methodological considerations. Additionally, hypotheses about pathophysiological mechanisms underlying the reported associations are made and clinical implications and recommendations for future research will be discussed.

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CHAPTER 2

LITHIUM DURING PREGNANCY AND AFTER DELIVERY: A REVIEW

Eline M.P. Poels
Hilmar H. Bijma
Megan Galbally
Veerle Bergink

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ABSTRACT

Lithium is an effective treatment in pregnancy and postpartum for the prevention of relapse in bipolar disorder. However, lithium has also been associated with risks during pregnancy for both the mother and the unborn child. Recent large studies have confirmed the association between first trimester lithium exposure and an increased risk of congenital malformations. Importantly, the risk estimates from these studies are lower than previously reported. Tapering of lithium during the first trimester could be considered but should be weighed against the risks of relapse. There seems to be no association between lithium use and pregnancy or delivery related outcomes, but more research is needed to be more conclusive. When lithium is prescribed during pregnancy, lithium blood levels should be monitored more frequently than outside of pregnancy and preferably weekly in the third trimester. We recommend a high-resolution ultrasound with fetal anomaly scanning at 20 weeks. Ideally, delivery should take place in a specialised hospital where psychiatric and obstetric care for the mother is provided and neonatal evaluation and monitoring of the child can take place immediately after birth. When lithium is discontinued during pregnancy, lithium could be restarted immediately after delivery as strategy for relapse prevention postpartum. Given the very high risk of relapse in the postpartum period, a high target therapeutic lithium level is recommended. Most clinical guidelines discourage breastfeeding in women treated with lithium. It is highly important that clinicians inform and advise women about the risks and benefits of remaining on lithium in pregnancy, if possible preconceptionally. In this narrative review we provide an up-to-date overview of the literature on lithium use during pregnancy and after delivery leading to clinical recommendations.

INTRODUCTION

Lithium therapy has a well-established evidence base as a long-term maintenance treatment for bipolar disorder with demonstrated efficacy in reducing both manic and depressive relapse and anti-suicidal properties (1). Bipolar disorder often has its onset before the age of 25 years (2), and as such lithium is frequently prescribed to women of childbearing age. However, there is enormous global variance in prescription patterns of lithium and recommendations for its use during the perinatal period (defined as pregnancy and the first year postpartum). In general, data on the prevalence of lithium use during pregnancy are scarce with the exception of population-based studies from Denmark and the UK. In a recent clinical overview, the Danish author Larsen and colleagues recommended lithium as the first-line mood-stabilizing treatment during pregnancy (3). Despite this recommendation, only 16% (53/336) of women with bipolar disorder redeemed at least one lithium prescription during pregnancy and only 6.3% of women used lithium in the third trimester, indicating that the majority of women discontinued lithium during pregnancy (4). Similarly, in the UK discontinuation rates of lithium during pregnancy is high with a study of pregnant women showing that only 17 out of 52 pregnant women continued lithium use during pregnancy (5). This pattern of discontinuation of lithium before pregnancy is supported by the NICE guideline where it is recommended to "not offer lithium to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective" (6). For most other countries information on lithium use during pregnancy is lacking. In a recent meta-analysis on bipolar disorder in the perinatal period, 5700 bipolar pregnancies (n=37 studies) were included (7). Of these, information on medication use was only available for 445 bipolar pregnancies (60 women with various medication including lithium and 385 women without medication). Most of these lithium users came from the Netherlands, which can be explained by the recommendation in the Dutch guidelines to list lithium as a first line treatment option during pregnancy (8). In the Australian Clinical Practice Guideline on perinatal mental health, no specific recommendation was made to continue or discontinue lithium during pregnancy, but rather proposes care pathways for both situations (9). Altogether, guidelines give inconsistent and highly variable information regarding the safety of lithium use during pregnancy. A comprehensive Canadian review of recommendations for the treatment of bipolar disorder during pregnancy recommended: "Women at risk for new onset or relapse of a mood episode who are not on maintenance treatment should be considered for trial of a mood stabilizer other than valproate, or an atypical antipsychotic drug" (10).

To guide clinicians in their decision making we provide a narrative review of the literature on efficacy of lithium use in the perinatal period and the risks for mother and child.

Lithium during pregnancy

Efficacy

To date the literature on the impact of pregnancy on the course of bipolar disorders is inconsistent. Previous studies suggested that women with bipolar disorder may have a lower risk of relapse during pregnancy, when compared to the period before or after (11). A recent systematic review concluded that based on the literature to date the question of how pregnancy affects the course of bipolar disorder can't be answered (12). Viguera et al. showed that in women who discontinued mood stabilizing treatment including lithium during pregnancy (n=62), the relapse risk was two times increased compared to women who continued treatment (n=27) (13). In the postpartum period there is a high risk of a bipolar episode and hospitalization for psychiatric morbidity (14-16). A perinatal history of affective psychosis or depression is the most important risk factor, as reported in a recent cohort study investigating risk factors for postpartum recurrence in bipolar disorder (17). Unfortunately, this study did not investigate the effect of medication use during pregnancy on the risk of recurrence. A recent meta-analysis showed significantly higher postpartum relapse rates in women without medication during pregnancy (N=385; 66%, 95% CI: 57-75) as compared to women using prophylactic medication (N=60, 23%, 95% CI: 14-37) (7). Of these 60 patients with prophylactic medication during pregnancy, the majority used lithium (18-21). Hence, lithium prophylaxis during pregnancy in women with bipolar disorder might be important not only to maintain mood stability during pregnancy, but also for postpartum relapse prevention.

Interestingly, a recent population based cohort study reported that lamotrigine during pregnancy was not inferior to lithium in the prevention of severe postpartum episodes (22). However, the authors point out the likely influence of confounding by indication since lamotrigine was primarily prescribed to women with a vulnerability for depressive episodes, while lithium was primarily prescribed to women with a history of manic episodes. Therefore, this finding requires replication in studies that can account for diagnosis, variant and severity of illness.

Dosing and monitoring of blood levels during pregnancy and around delivery

Lithium has a narrow therapeutic range of 0.5-1.2 mmol/L and higher levels may lead to toxicity (23). Excretion of lithium is almost exclusively renal, hence blood plasma levels mainly depend on intravascular volume and glomerular filtration rate (GRF) (23, 24). As pregnancy progresses total body water, plasma volume and GFR are increased (25) with GFR rising from as early as 6 weeks gestation up to 50% over non-pregnant women by the end of the first trimester (26). Clinical studies have shown lithium blood levels to decrease significantly during pregnancy (27, 28). An average decrease of 24% in the first trimester, 36% in second trimester and 21% in third trimester was described. Creatinine blood levels

showed a similar longitudinal pattern, showing that indeed changes in lithium blood level reflect changes in renal physiology.

In summary, first and second trimester are characterised by a significant decrease of lithium blood levels with a risk of subtherapeutic levels. In third trimester and the postpartum, lithium levels gradually return to their preconception level which implicates that in this period clinicians need to be aware of the risk of lithium intoxication. Close monitoring and dose adjustment is needed with conditions such as hyperemesis gravidarum, pre-eclampsia, impaired renal function, concomitant medication or acute blood loss occur, as these conditions increased the risk of toxicity (29, 30). Furthermore, as lithium levels in the fetus equal those in the mother, changes in dosing may impact fetal health and increase the risk of complications (31). A multiple day dosing regime has been proposed to minimise fetal risk by minimising peak lithium levels (32). However, multiple day dosing has been associated with an increased risk of renal side effects and as a consequence possible non-adherence (33). Therefore, twice daily dosing seems to be preferred to more frequent administration.

The above described dynamic changes in GFR and maternal haemodynamics during pregnancy necessitate monthly monitoring of lithium blood levels until 34 weeks and weekly monitoring thereafter until delivery (27).

Several authors and guidelines have suggested to decrease or discontinue lithium treatment when in labour in order to minimise lithium side-effects in the neonate (6, 8, 34). However, there is currently no evidence that suggests this strategy decreases the risk of perinatal and infant complications and this strategy has to be weighed against the risk of maternal relapse during a high-risk period. Both Deligiannidis et al. and Wesseloo et al. have recommended careful lithium blood level monitoring instead of discontinuation in all cases (35). Lithium blood levels should be measured before and 24h after delivery and adequate fluid management is important to prevent dehydration. Lithium blood level, as well as thyroid-stimulating hormone (TSH) and free thyroxine (T4) should be evaluated in umbilical cord blood sample (8). Nephrotoxic medication and nonsteroidal anti-inflammatory drugs should be avoided (35). When considering anaesthesia options during delivery, drug interactions with lithium should be taken into account. Lithium potentiates succinylcholine and pancuronium and can be expected to potentiate other depolarising and non-depolarizing muscle relaxants (30). Close monitoring of neuromuscular function is therefore required. Regional anaesthesia is considered to be safe (30).

Obstetric complications

When investigating the effect of lithium exposure on obstetric complications in cohort studies it is important to consider that bipolar disorder, the indication for which lithium is often prescribed, is associated with obstetric complications independent of medication. In specific, women with bipolar disorder are at increased risk of antepartum hemorrhage,

placental abnormalities and caesarean section (36, 37). The mechanism underlying this increased risk for women with bipolar disorder is unclear but psychosocial stress accompanied by high cortisol levels, comorbidity and lifestyle factors might play a role (36). In a recent shared protocol meta-analysis of 727 lithium exposed pregnancies and 21397 pregnancies in disease matched controls lithium use during pregnancy was not associated with preeclampsia, diabetes during pregnancy, fetal distress, postpartum hemorrhage or caesarean section (38). Additionally, in two studies the rates of obstetric complications were not higher in women who continued lithium during pregnancy compared to women who discontinued lithium before or early in pregnancy (39, 40). Table 1 presents an overview of the results from observational cohort studies on obstetric complications of lithium use during pregnancy. Results of these studies should be interpreted considering several methodological limitations, i.e. the sample size of two studies was very small and these studies did not correct for confounding variables and timing, duration or dose of the exposure.

Table 1. Obstetric outcome after lithium treatment during pregnancy: findings from clinical cohort studies

Study	Design	Sample size	Findings
Petersen 2016	Registry-based study	Exposed = 35 Disease matched non-exposed = 84 Controls = 320.853	No difference in the rate of caesarean sections.
Frayne 2017	Cohort study	Exposed = 33	No difference in the rate of obstetric complications between the women that continued (n = 19) or discontinued (n = 14) lithium.
Munk-Olsen 2018	Meta-analysis (6 study sites)	Exposed =727 Disease matched controls= 21,397	No association between lithium exposure *in utero* and preeclampsia (OR 0.97, 95% CI: 0.52-1.80), gestational diabetes (OR 1.20, 95% CI: 0.81-1.78), fetal distress (OR 1.00, 95% CI: 0.76-1.32), postpartum hemorrhage (OR 1.28, 95% CI: 0.64-2.57) and caesarean section (OR 0.94, 95% CI: 0.66-1.33.

OR odds ratio, *CI* confidence interval

Polyhydramnios has not been investigated in observational cohort studies, but has been described in two case reports (41, 42). This warrants further investigation because polyuria is a well-known side effect of lithium and fetal polyuria could lead to polyhydramnios. In summary, while women with bipolar disorder have an increased risk of obstetric complications, there seems no association between lithium use during pregnancy and pregnancy or delivery related outcomes.

Consequences for the developing child

Lithium freely crosses the placental barrier and lithium concentrations equilibrate between maternal and fetal circulation (31). Hence maternal lithium therapy results in fetal lithium exposure. We provide a summary of published results from investigations on the short- and long-term consequences of intrauterine exposure to lithium.

Congenital malformations

The first trimester of pregnancy is crucial to the normal development of the fetus. Since in this period all major body organs are forming, the fetus is susceptible to damage from teratogens and this has raised some concerns about the possible teratogenicity of lithium use during the first trimester. In this review we summarise the results from clinical cohort studies investigating the risk of congenital malformations after lithium use during pregnancy, an overview of these studies is presented in table 2.

Table 2. Findings from clinical cohort investigations on the association between *in utero* exposure to lithium and congenital malformations

Study	Design	Sample size	Findings
Schou 1973	Cohort study	Exposed = 118	Nine children with congenital malformations, of which six with cardiovascular malformations.
Nora 1974	Retrospective cohort study	Teratogenic history obtained in 733 women	Two lithium exposed pregnancies and both children were born with Ebstein anomaly.
Weinstein 1975	Cohort study	Exposed = 143	Cardiovascular abnormalities found in 9.1% of cases of exposure to lithium in 1st trimester.
Kallen 1983	Registry-based study	Exposed = 59 Other drugs = 38 Disease matched non-exposed = 80 Controls = 110	Four children with heart defects after lithium exposure. No cases of Ebstein anomaly.
Jacobson 1992	Prospective cohort study	Exposed = 138 Controls = 148	No difference in the rate of major malformations.
Reis 2008	Registry-based study	Exposed = 79	Eight children with congenital malformations, of which four with cardiac malformations.
Diav-citrin 2014	Prospective cohort study	Exposed = 183 Disease matched non-exposed = 72 Controls = 748	Single center comparison: no difference in major malformations, increased risk of cardiovascular malformations (RR 7.23, 95% CI: 1.97–26.53), not after excluding cases that spontaneously resolved (RR 5.78, 95% CI: 0.82–40.65).
Patorno 2017	Registry-based study	Exposed = 663 Lamotrigine = 1945 Controls = 1,322,955	Increased risk of cardiac malformations after first trimester lithium exposure compared to controls (RR 1.65, 95% CI: 1.02 - 2.68) and lamotrigine-exposed (RR 2.25, 95% CI: 1.17 - 4.34).
Munk-Olsen 2018	Meta-analysis (6 study sites)	Exposed =727 Disease matched controls=21,397	First trimester lithium exposure was statistically significant associated with congenital malformations (OR 1.62, 95% CI: 1.12 – 2.33) but not with cardiac malformations in specific (OR 1.54, 95% CI: 0.64 - 3.70).

RR risk ratio, *OR* odds ratio, *CI* confidence interval

In multiple investigations, lithium treatment during pregnancy has been associated with cardiovascular malformations, including Ebstein anomaly (43-46). Ebstein anomaly is a congenital malformation characterised by an abnormal development of the tricuspid valve and the right ventricle, with highly variable prognosis. The prevalence in the normal population is estimated to be about 1 per 20,000 live births (47). The association with lithium use during pregnancy was first reported in the 1970's investigation on the Register of Lithium Babies (43, 44). Based on the data from the Register of Lithium Babies, Nora et al. estimated a five-fold increase in the risk of congenital heart-disease and about a 400 fold increase in the risk of Ebstein anomaly (45). In contrast, case control studies in children born with Ebstein anomaly or other cardiovascular malformations did not find an association with lithium exposure (48-53). For a comprehensive summary of case-control studies we refer to a review and meta-analysis by McKnight et al. (50). A registry based case control study of 264 Ebstein anomaly cases by Boyle et al. found an association with maternal mental health problems in general but not with lithium use (49).

Two studies on congenital malformations in general have yielded contradicting results, with one study reporting a high rate of congenital malformations after *in utero* exposure to lithium (54) and another study reporting no association between lithium exposure and congenital malformations (55). Additionally, several case reports have been published on congenital diaphragmatic hernia (56), goiter (57, 58), cardiovascular complications (59-62), bilateral hip dislocation (63) and neural-tube defect (55). In general, sample sizes of these clinical investigations are considered too small to study rare congenital malformations.

Recently, three cohort studies with large sample sizes, have provided more evidence on the matter (38, 46, 64). Diav-Citrin et al. compared the rate of congenital abnormalities in lithium exposed pregnancies, disease matched and nonteratogenic-exposed pregnancies (64). The occurrence of cardiovascular anomalies was higher in the lithium-exposed group although this difference was not significant after excluding the anomalies that resolved spontaneously. Patorno et al. used register data from Medicaid in the U.S. to study 1,325,563 pregnancies of which 663 were exposed to lithium and 1945 exposed to lamotrigine (46). They found a dose dependent association between lithium exposure and cardiac malformations, including Ebstein anomaly. The adjusted risk ratio for cardiac malformations was calculated to be 1.65 compared to controls and 2.25 compared to lamotrigine-exposed. The risk of cardiac malformations was estimated to be in the order of one additional case per 100 live births. The same study found no association between lithium exposure and noncardiac malformations. In contrast, in a shared-protocol meta-analysis of six study sites the risk of major malformations (including cardiac malformations) was increased in lithium-exposed pregnancies (OR 1.62, 95% CI: 1.12-2.33) compared to non-exposed pregnancies in mothers with a mood disorder, while there was no statistically significant increase in the risk of cardiac malformations (38).

While this evidence is not conclusive it is recommended that it is discussed with women who seek advice on treatment of bipolar disorder either pre-pregnancy or during pregnancy. One option would be to taper lithium during the first trimester although the risk of relapse needs to weighed if considering this option. In the case of lithium continuation, fetal anomaly ultrasound including detailed fetal cardiac scanning, should be offered at 20 weeks gestational age. This could also be advised at 16 weeks (65). In the case of detection of a cardiac malformation, information, guidance and counselling can be offered as early as possible. Although the pathophysiology of the association between lithium and congenital malformations is unclear, it might be related to lithium's inhibition of the glycogen synthase kinase-3β (GSK3β) (66). GSK3β expression is of importance for the Wnt signaling pathway, which is of influence on cardiac and vascular development in the embryo (67, 68).

Neonatal outcomes

Two studies found an increased risk of preterm birth in women with lithium use during pregnancy when compared to controls (64, 69). In contrast, three studies including the meta-analysis of six studies reported no difference in the rate of preterm birth between lithium exposed pregnancies and controls (34, 38, 55). In addition, most studies do not find differences in birth weight except for one small study in which lithium-exposed neonates had a higher birth weight (34, 38, 55, 64, 69).

Lithium exposure is associated with increased risk of neonatal complications. Newport et al. found an association between high infant lithium concentrations and lower 1-minute Apgar scores, higher rate of central nervous system and neuromuscular complications and longer duration of hospital stays (31). In a cohort of 19 babies exposed to lithium during pregnancy, 8 were admitted to a special care unit post-delivery (40). This high rate of neonatal admissions was confirmed in a large meta-analysis of six study sites (38). Additionally, there are case reports on neonatal lithium toxicity (70-75), nephrogenic diabetes insipidus (76), and jaundice (77). In a review of case reports, Kozma further reports respiratory problems, hypotonia, lethargy, poor drinking ability, thyroid problems, cyanosis, hypoglycemia and polyuria (70). Normal neonatal outcome was reported in the study from Silverman et al (78).

Because of potential problems in the neonatal period after *in utero* exposure to lithium, we recommend that delivery should take place in a specialised hospital with advanced neonatal care available immediately after delivery. In table 3 we present the results of studies on neonatal outcome.

Table 3. Neonatal outcome after lithium treatment during pregnancy: findings from clinical cohort studies

Study	Design	Sample size	Findings
Jacobson 1992	Prospective cohort study	Exposed = 138 Controls = 148	No difference in the rate of preterm birth. Higher birthweight in lithium exposed neonates.
Troyer 1993	Cohort study	Exposed = 60 Disease matched non-exposed = 290	Cohort of manic-depressive women: risk ratio for prematurity of 2.54. No difference in birthweight.
Newport 2005	Cohort study	Exposed = 24	Lower Apgar scores, longer hospital stays and higher rates of CNS and neuromuscular complications in infants with high lithium levels. No statistically significant association with preterm birth or low birth weight.
Diav-citrin 2014	Prospective cohort study	Exposed = 183 Disease matched non-exposed = 72 Controls = 748	2.3 times higher rate of preterm delivery in exposed group (13.7% versus 6.0%). No differences in birth weight.
Frayne 2017	Cohort study	Exposed = 19	8 neonates admitted to a special care unit.
Munk-Olsen 2018	Meta-analysis (6 study sites)	Exposed =727 Disease matched controls=21,397	No association between lithium exposure *in utero* and preterm birth (OR 1.24, 95% CI: 0.83-1.84), low birth weight (OR 0.98, 95% CI: 0.72-1.35) or small for gestational age (OR 0.90, 95% CI: 0.67-1.21). A significant higher rate of neonatal admission (OR 1.62, 95% CI: 1.12-2.33).

OR odds ratio, *CI* confidence interval

Long term developmental outcome

It is assumed that the fetal environment influences lifetime disease risk based on Barker's hypothesis of Developmental Origins of Health and Disease (DOHaD) (79, 80). This hypothesis proposes that exposure during fetal development can result in permanent physiological and metabolic changes, which modify disease risk through life. Prenatal exposure to lithium may therefore have consequences on development and health outcomes well beyond infancy. Indeed, results from preclinical studies in mice, rats and zebrafish show neurodevelopmental deficits (81). Clinical data are scarce, four small clinical cohort studies have investigated long term neurodevelopmental outcomes. The results of these studies are presented in table 4. Schou used data from the Scandinavian Register of Lithium Babies to compare the mothers' subjective retrospective assessment of their children's development in lithium-exposed children (n=60) and their non-exposed siblings (n=57) and found no difference (82). In a prospective multicenter study, there was no difference in the age of attainment of major developmental milestones in lithium-exposed children compared to non-exposed children (55). Another study examined 15 lithium-exposed children at the age of 3-15 years old and used standard validated tests to assess growth, neurological, cognitive and behavioural outcomes (83). Most children scored lower on the performance Block patterns

when compared to the general population although this difference was not statistically significant. Growth and behavioural development was within normal range. One child in this study was diagnosed with minor neurological dysfunction without clinical implications. A recent study compared the intelligence quotient (IQ) in children with *in utero* exposure to lithium (n=20), non-exposed children of mothers with a mood disorder (n=8) and controls (n=11) and reported no difference in total, performance or verbal IQ (84).

Table 4. Neurodevelopmental consequences of intrauterine exposure to lithium: findings from clinical cohort studies

Study	Design	Sample size	Follow-up	Findings
Schou 1976	Prospective cohort study	Exposed = 60 Controls = 57	Mean = 7 years	No difference in development based on questionnaire filled out by the mother.
Jacobson 1992	Prospective cohort study	Exposed = 22 Controls = n.r.	1-9 years, mean = 61 weeks	No difference in attainment of milestones.
vd Lugt 2012	Cohort study	Exposed = 15	3-15 years	Normal developmental milestones (n=15), minor neurological dysfunction (n=1), low verbal + total IQ, normal performance IQ (n=1), subclinical anxiety problems (n=2), subclinical oppositional problems (n=1).
Forsberg 2017	Cohort study	Exposed = 20 Disease matched non-exposed = 8 Controls =11	4-5 years	No differences in total, performance and verbal IQ.

IQ intelligence quotient, *n.r.* not reported

In summary, while preclinical evidence does point to possible developmental effects of perinatal exposure to lithium, this is not found in clinical investigations. Due to methodological weaknesses of the published clinical studies (e.g. small sample sizes, lack of control group and subjective outcome measures) no conclusion can be drawn from these results and more research is needed to provide an estimation of the risk for the developing child.

Lithium use during pregnancy

- *Maintenance of lithium during pregnancy is effective in the prevention of relapse during pregnancy and the postpartum period.*
- *The first and second trimester are characterized by a significant decrease in blood levels for lithium.*
- *Fetal anomaly ultrasound including detailed fetal cardiac scanning, should be offered at 20 weeks gestational age.*
- *In the third trimester, weekly monitoring of lithium blood levels is recommended. Preferably, lithium blood levels should be measured before and 24 hours after delivery.*
- *Lithium blood level, TSH and free T4 should be evaluated in umbilical cord blood sample.*
- *Lithium use during pregnancy has not been associated with obstetric complications. However, the association with preterm birth and birthweight remains uncertain.*
- *Lithium exposure during the first trimester is associated with congenital malformations in several studies, recent studies estimate the risk lower than previously reported. Tapering of lithium during the first trimester should be considered but weighed against the risks of relapse.*
- *Lithium exposure is associated with increased risk of neonatal complications. Lithium-exposed neonates should be observed directly post-delivery.*
- *Little is known about the developmental consequences of intrauterine exposure to lithium.*

Lithium use postpartum

Efficacy

Women with a history of bipolar disorder or postpartum psychosis are at extremely high risk of relapse postpartum. Few clinical studies have investigated the efficacy of pharmacotherapy when it is initiated immediately after delivery, as a prophylactic strategy in women who have not been treated during pregnancy. A meta-analysis showed that patients with bipolar disorder using prophylactic pharmacotherapy during the postpartum period had a lower relapse rate (N=98; 29%, 95% CI: 16-47) compared with those who remained medication free (N=107; 65%, 95% CI: 55- 73) (7). Off these 98 women, thirty-eight started prophylactic treatment during pregnancy while twenty-two were medication free during pregnancy and initiated prophylaxis immediately postpartum. For the remaining women information regarding the timing was unavailable or they were on chronic maintenance treatment. Numbers are very small but in all studies on prophylactic treatment with lithium postpartum, women with bipolar disorder had significantly lower rates of postpartum relapse compared to medication free women (18, 19, 85). In contrast, valproate failed

to demonstrate significant prophylactic benefits (86) and further investigation of second generation antipsychotics is warranted. In our previous work we have recommended distinct perinatal treatment algorithms for women with bipolar disorder and women with a history of psychosis limited to the postpartum period. In women with bipolar disorder, prophylaxis during pregnancy increases the likelihood of maintaining mood stability during pregnancy and preventing postpartum relapse. In women with a history of psychosis limited to the postpartum period, prophylactic treatment immediately after birth is appropriate (87). In this group of women with a history of postpartum psychosis, the established efficacy of lithium makes it the drug of first choice for postpartum prophylaxis.

Dosing and monitoring of blood level

Lithium prophylaxis has demonstrated efficacy in reducing postpartum episodes. However, the dosing and duration of prophylaxis is unknown. We recommend relapse prevention prophylaxis in women with bipolar disorder with a higher lithium target level (for example 0.8 mmol/L) during the first month postpartum. Given that the relapse risk is high particularly in the first month postpartum, we follow the view that the benefits of higher lithium target blood levels in the first month postpartum outweighs the potential risks. We recommend to start lithium on the first evening after delivery and with a dose to target blood level of 0.8-1.0 mmol/L to optimize relapse prevention. In our previous work, we observed that normalization of renal function can take up to a few weeks after delivery as both mean lithium and creatinine blood levels were higher in the postpartum period than in the preconception period (+9% and +7% respectively) (27). Therefore, we recommend twice weekly monitoring of lithium blood levels for the first 2 weeks postpartum. Women with bipolar disorder on maintenance treatment with lithium might want to change to their preconception dose and blood level after one month postpartum. For those women who want to taper their lithium dose (i.e. women with isolated postpartum psychosis/mania in history, or women with bipolar disorder without regular maintenance treatment) we advise to commence tapering after 3 months postpartum.

Breastfeeding

Clinical guidelines generally discourage breastfeeding in women treated with lithium due to the possible risk of lithium toxicity in the newborn (6). Furthermore, the lack of continued sleep during puerperium might also increase the risk of maternal relapse. Lithium is excreted into breast milk and the elimination rate in infants is lower than in adults, which may cause higher exposure levels in infants. However, there is a lack of data from clinical investigations on this topic. In table 5 we present the results of clinical studies on infant lithium exposure through lactation. Some case studies have estimated serum lithium levels to be about one-half of maternal serum lithium levels (88, 89) while others estimated levels closer to one quarter of the mothers' levels (90, 91). The larger study available for lithium and

breastfeeding consists of 11 mother infant pairs with a calculated infant lithium dose as 0 to 30% of the maternal dose per kilogram bodyweight, based on the daily milk intake and lithium levels measured in breast milk (92). Unfortunately, serum lithium levels were only available in two mother-infant pairs. In one pair lithium serum levels of the infant achieved 17 to 20% of the maternal serum level while in the other infant this was calculated to be 50%. No adverse effects were observed in the lithium exposed infants. Viguera et al. measured lithium levels in breast milk, maternal serum and infant serum in ten mother child pairs from eight to 27 weeks postpartum (93). Based on these measurements it was estimated that infant lithium levels in serum were about one quarter of the lithium levels in serum of the mother. This estimation was lower than previous reports (88, 89, 92). Lithium exposure through breastmilk was generally well tolerated by the infants in this study although one infant developed elevated levels of TSH which, normalised after the mother discontinued lithium treatment. Three other infants showed transient elevations in blood urea nitrogen and creatinine levels. In summary, there is a lack of sufficient information on infant lithium levels and the consequences of lithium exposure through breast milk. Due to the lack of information and the possible nephrotoxic effects of lithium in infants, in combination with the vulnerability of the developing neonatal kidneys and the risk of dehydration associated with the neonatal period, breastfeeding while on lithium treatment is discouraged in many national guidelines and individual centers worldwide (94).

Table 5. Summary of the results from clinical studies on infant lithium exposure through lactation

Study	Design	Sample size	Findings
Schou 1973	Case series	8 mother-infant pairs	Infant/maternal serum lithium concentration of 1/2 in first week and 1/3 during the following weeks.
Sykes 1976	Case report	1 mother-infant pair	Breast milk lithium level of 1/4 of maternal serum level, infant had good excretion of lithium into urine.
Moretti 2003	Case series	11 mother-infant pairs	Infant lithium dose of 0-30% of the maternal dose/kg. Infant serum level of 17-50% of maternal serum level.
Viguera 2007	Case series	10 mother-infant pairs	Mean infant serum level of 0.16 meq/L (range= 0.09–0.25). In four infants: transient elevations of TSH, blood urea nitrogen and creatinine.
Bogen 2012	Case series	3 mothers with 4 infants	Infant lithium levels ranged from 10% to 17% of maternal levels at 1 month postpartum.
Frew 2015	Case report	1 mother-infant pair	Infant/maternal serum lithium concentration ratio of 0.58. No adverse events.

Lithium use postpartum

- *When lithium is discontinued during pregnancy, lithium should be restarted immediately after delivery and is an effective strategy for relapse prevention in the immediate postpartum.*
- *For women with an isolated episode of postpartum psychosis or mania in history lithium prophylaxis immediately after delivery is effective for relapse prevention, there is no need to use lithium during pregnancy.*
- *Consider a high target therapeutic lithium level immediately after delivery and during the first month postpartum to optimize relapse prevention (e.g., 0.8-1.0 mmol/L).*
- *Obtain lithium blood levels twice weekly during the first two weeks postpartum.*
- *Breastfeeding while taking lithium is not recommended.*

SUMMARY AND DISCUSSION

The aim of this review was to provide a broad range of information and clinical guidance regarding lithium use during pregnancy and the postpartum period. Since it was our aim to give a broad overview of the literature from a clinical perspective we opted for a narrative review rather than a systematic review or meta-analysis. The clinical recommendations in this review article are suggestions based on the available scientific information and clinical experience of the authors. Readers should note that recommendations were not formulated within the context of a guideline procedure.

Women of childbearing age requiring mood stabilisation should be given the opportunity to weigh the risks and benefits of lithium treatment during pregnancy and the postpartum period, and to develop an individualised treatment plan together with their healthcare providers in a specialised centre (95, 96). Antenatal care should take place in a multidisciplinary setting, with close collaboration between psychiatric and obstetric services. During pregnancy and the postpartum period women with bipolar disorder should be closely monitored. The possible risks for the unborn child, such as the risk of congenital malformations need to be carefully weighed against the risk of maternal relapse. The pros and cons of discontinuation of medication need to be compared with the pros and cons of continuing medication. In this context it is important to note that also relapse of bipolar disorder carries a fetal risk. High maternal stress but also high-risk behaviour, such as alcohol or drug use or lack of compliance to antenatal care are associated with adverse fetal outcomes.

Switching to maintenance therapy with lamotrigine before conception should be considered as the efficacy of lamotrigine in prevention of postpartum relapse is not inferior to lithium (22) and there are no risks of congenital malformations associated with its use

(46). However, the efficacy of lamotrigine in the prevention of postpartum episodes was established in a group of women with a high vulnerability to depressive episodes and lamotrigine is not effective in the prevention of mania. Moreover, the efficacy of lamotrigine in the prevention of relapse during pregnancy is not yet investigated. Maintenance therapy with second generation antipsychotics is an alternate treatment option (6). Importantly, the use of second generation antipsychotics during pregnancy is not associated with an increased risk of congenital malformations (39, 97). However, a recent Medicaid study found an increased risk of gestational diabetes associated with the continuation of quetiapine and olanzapine during pregnancy (98) and there is uncertainty on the long-term impact on neurodevelopment (81). Notably, the efficacy of second generation antipsychotics in relapse prevention during the perinatal period is not yet properly investigated in women with bipolar disorder. Moreover, antipsychotics are known to be less effective than lithium in maintenance treatment for bipolar disorder outside the perinatal period (1).

When providing advice to the individual patient, knowledge about past treatment efficacy should also be taken into account. In women with a history of severe bipolar episodes and a good effect on lithium therapy, continuation of lithium might be preferred in order to prevent relapse. When lithium therapy is continued during pregnancy, regular antenatal visits are warranted for checking lithium blood levels, evaluation of fetal growth, and for monitoring signs of preterm labour. Detailed fetal anomaly scanning, including detailed fetal cardiac scanning should be offered at 20 weeks gestational age or maybe earlier in the future. Furthermore, evaluation of maternal thyroid (TSH and free T4) levels and kidney function is recommended (8). Delivery should take place in a specialised hospital where psychiatric and obstetric care for the mother is provided and neonatal evaluation and monitoring of the child can take place immediately after birth.

More investigations are required on the development of children exposed to lithium *in utero* as the studies that have been published so far provide insufficient information to properly advise women. We recommend against breastfeeding while on lithium treatment given both the paucity and the poor quality of the available clinical reports. However, we are aware of the differences in clinical recommendations between guidelines and authors. For instance, a recent systematic review by Pacchiarotti et al. studied the same literature as reported in this review paper but they concluded that lithium levels in the infant were low and breastfeeding should be permitted through an individualized approach (99). Clinicians that do recommend breastfeeding should publish their findings with comprehensive data on lithium levels in serum and breast milk, as well as infant outcomes including neurological, renal and thyroid function. In this way more knowledge will be available in order to develop evidence based recommendations.

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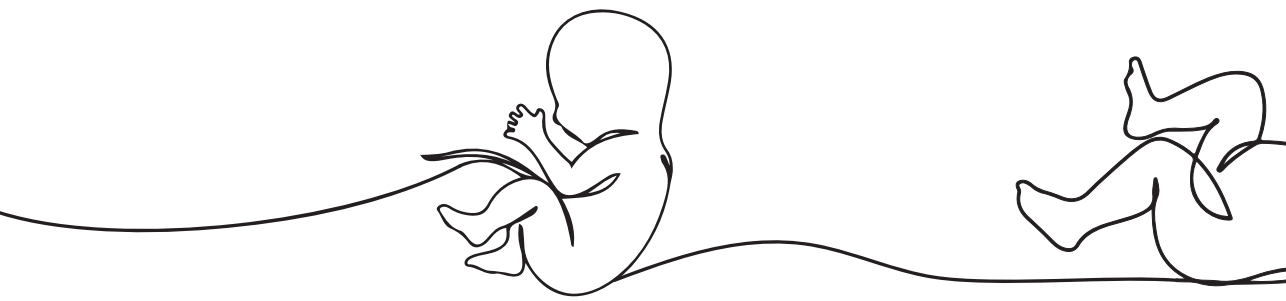
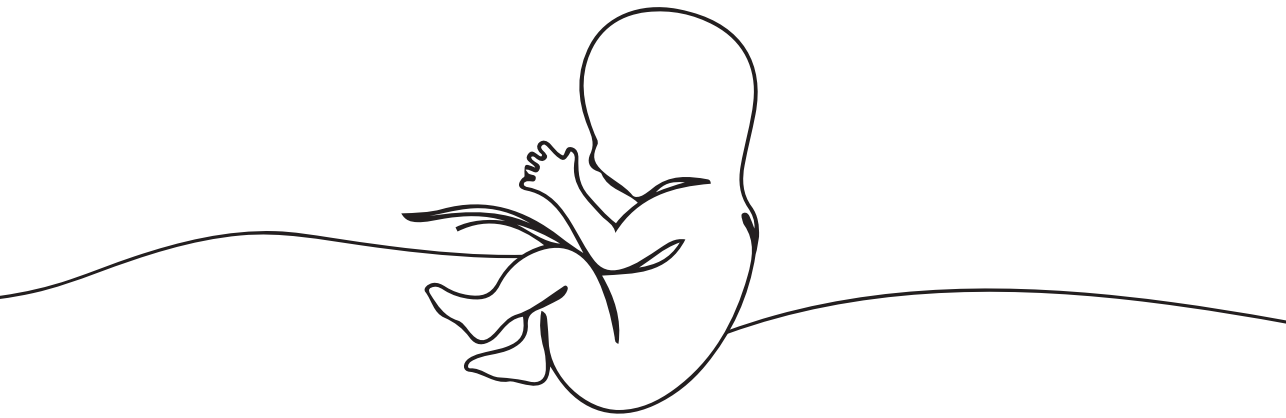


PART I

CONSEQUENCES FOR THE FETUS AND NEONATE



CHAPTER 3

LITHIUM USE DURING PREGNANCY AND THE RISK OF MISCARRIAGE

Eline M.P. Poels
Astrid M. Kamperman
Annabel Vreeker
Janneke Gilden
Marco P. Boks
René S. Kahn
Roel A. Ophoff
Veerle Bergink

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ABSTRACT

Recent studies have provided new data on the teratogenicity of lithium. Less is known about the risk of miscarriage after lithium use during pregnancy. The aim of this study was to investigate the association between lithium use during pregnancy and miscarriage. Participants were women with bipolar I disorder and one or more pregnancies, of which information on medication use and pregnancy outcome was available (n = 443). The unadjusted odds ratios for miscarriage after lithium use during pregnancy was calculated. Multilevel logistic regression was used to calculate the odds ratio, adjusted for the age at conception and the clustering of pregnancies per woman. Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366) (OR = 2.14; 95% CI: 1.13–4.06). The adjusted odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22). Lithium use during pregnancy may increase the risk of miscarriage.

INTRODUCTION

Women with bipolar disorder have a high risk of recurrent episodes in the perinatal period (1). Treatment with mood-stabilizing medication during pregnancy might be necessary to reduce this risk, but this warrants special attention, as these medications may be potentially harmful to the developing fetus. Valproate and carbamazepine are highly teratogenic. Lithium has a well-established evidence base in the prevention of episodes in bipolar disorder (2) and is often prescribed during pregnancy, especially because, in 2012, a meta-analysis concluded that there was not enough evidence to say that lithium is teratogenic (3). However, last year, the two largest studies to date were published, and they both showed the teratogenicity of lithium during the first trimester of pregnancy (4, 5). The first study compared 663 lithium-exposed pregnancies with 1945 lamotrigine-exposed pregnancies, and found a dose-dependent association between first trimester lithium exposure and cardiac malformations (5). The second study reported an increased risk of major malformations (including cardiac malformations) in 727 first trimester lithium-exposed pregnancies, compared with 21,397 unexposed pregnancies in mothers with a mood disorder (OR = 1.62; 95% CI: 1.12–2.33) (4). A few years earlier, a smaller study had found a similar, non-significant effect (6). Interestingly, this study by Diav-Citrin et al. was the first to show an increased risk of miscarriage after first trimester lithium use (OR = 1.94; 95% CI: 1.08–3.48) (6). In this prospective cohort study, 183 lithium-exposed pregnancies of women who had contacted the Israeli Teratology Information Service were followed up and compared with 72 disease-matched and 748 nonteratogenic-exposed pregnancies. Pregnancy outcome was assessed by maternal interview. The rate of miscarriage was 16.4% in lithium-exposed pregnancies, versus 8.3% in the bipolar disorder comparison group, and 5.7% in nonteratogenic-exposed pregnancies. In contrast, another prospective cohort study by Jacobson et al. did not find a difference in the rate of miscarriage between lithium-exposed and control pregnancies (7). In this study, women were also recruited for study participation if they had contacted a teratogen information center, and pregnancy outcome was assessed by telephone interview. The rate of miscarriage was 9% in the lithium-exposed group (*n* = 138), versus 8% in a control group of women who used nonteratogenic drugs during pregnancy (*n* = 148). Other studies did not report on miscarriages, because they were designed to investigate live births only (8). Information on the risk of miscarriage associated with lithium use during pregnancy is relevant for both clinicians and women with bipolar disorder of childbearing age. Based on the magnitude of this risk, further decisions regarding family planning and prevention strategies can be made. In this study, we present new information on miscarriages after lithium use.

METHODS

Study Design and Participants

This retrospective cohort study was part of the Dutch Bipolar Cohort (DBC) study, a collaboration between the University of California in Los Angeles and several Dutch healthcare institutes (University Medical Center Utrecht, Geestelijke gezondheidszorg (GGZ) Altrecht, GGZ inGeest, University Medical Center Groningen, Delta, Dimence, Parnassia (PsyQ) and Reinier van Arkel) (9). Participants in the DBC study were patients with bipolar disorder, aged 18 years and older, between June 2011 and July 2015. The objective of the DBC study was to investigate the genetic and phenotypic information of the participants. The study was approved by the accredited Dutch Medical Ethical Trial Committee (METC 10-285) and all participants provided written informed consent (9). In the current study, we selected a subcohort of women who had experienced one or more pregnancies, with a diagnosis of bipolar I disorder before pregnancy, and for which detailed data on lithium use and pregnancy outcomes were available. Analyses were performed on the total number of pregnancies that ended in live birth or miscarriage.

Data Collection and Procedures

For all patients, bipolar I disorder diagnosis was established using the Structured Clinical Interview (SCID) for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), conducted by at least one well-trained independent rater (9). In a self-report Questionnaire on Postpartum Mood Disorders, developed by one of the authors (V.B.), women were asked about the dates of the abortions, miscarriages, and births of their children. All participants were asked to complete a questionnaire, in which they were asked for detailed information on their current and lifetime medication use. In addition, they filled in a lithium satisfaction questionnaire, with specific questions on both their current and past use of lithium. Both questionnaires were combined to assess their current and past lithium use as accurately as possible and to restrain misclassification.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 24.0, IBM Corp., Armonk, NY, USA). In order to investigate the association between lithium use during pregnancy and miscarriage, the odds of miscarriage were determined for pregnancies with and without lithium use. For our primary analysis, the unadjusted odds ratio for miscarriage after lithium use was calculated using a logistic regression model. Since an underlying maternal medical condition or genetic predisposition could cause multiple miscarriages within the same woman, this is a potential source of bias. In a sensitivity analysis, we adjusted for the occurrence of multiple miscarriages within one woman by means of a multilevel logistic regression analysis taking the clustering of pregnancies per

woman into account. A generalized linear mixed model was defined with age at conception as a covariate in order to calculate the adjusted odds ratio. This generalized linear mixed model analysis was performed on a subgroup of pregnancies without comorbid lifetime valproate and carbamazepine use. Even though these medications are generally not prescribed during pregnancy in the Netherlands, they are teratogenic, and therefore we wanted to exclude any influence these medications might have had on the risk of miscarriage. Odds ratios were reported with their corresponding 95% confidence intervals. A two-sided *p*-value of 0.05 was considered to be statistically significant.

RESULTS

In Table 1, we present the characteristics of our study sample. We analyzed the data of all the pregnancies of the women in the DBC study with a diagnosis of bipolar I disorder before pregnancy (*n* = 509), for which detailed data on lithium exposure and pregnancy outcomes were available (*n* = 443). Of these 443 pregnancies in 241 women, 56 ended in a miscarriage (12.6%; 56/443). The remaining pregnancies ended in a live birth (87.4%; 387/443). Lithium exposure varied over successive pregnancies. In total, 77 pregnancies were exposed to lithium (17.4%; 77/443) and 366 pregnancies were unexposed to lithium (82.6%; 366/443). Lifetime valproate or carbamazepine use was present in 26% of the lithium-exposed pregnancies and in 21% of the pregnancies not exposed to lithium. Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366), (OR = 2.14; 95% CI: 1.13–4.06, $p = 0.018$). After adjusting for the age at conception and the clustering of pregnancies per woman, the odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22, $p < 0.005$).

Table 1. Characteristics of study sample

	Total	Lithium-Exposed	Unexposed
N Pregnancies	443 in 241 women	77 in 50 women	366 in 202 women
N Miscarriages	56 in 41 women	16 in 11 women	40 in 30 women
Age at Conception, Mean (SD)	30.7 (4.9)	33.2 (4.6)	30.1 (4.9)
Age at Onset Bipolar Disorder, Mean (SD)	21.8 (6.3)	21.9 (5.1)	21.7 (6.5)
Lifetime Valproate or Carbamazepine Use *N* (%)	97 (21.8)	20 (26.0)	77 (21.0)

DISCUSSION

In the general population, miscarriage can be expected in 10–15% of pregnancies (10), which is similar to the rate of occurrence of miscarriage in our group of women with bipolar I disorder without lithium exposure. We found the rate of miscarriage to be increased in

lithium-exposed pregnancies. This is consistent with data from the study by Diav-Citrin et al., who also reported the rate of miscarriage to be twice as high in lithium-exposed pregnancies (*n* = 183) when compared with disease-matched unexposed (*n* = 72) (OR = 1.94; 95% CI: 1.08–3.48) (6). When we add the results of the current study to the previously published literature, we can conclude that two out of the three studies show an increased risk of miscarriage in lithium-exposed pregnancies (6, 7). This information warrants attention from clinicians treating women with bipolar I disorder of childbearing age. The risks associated with lithium use should be weighed against the risks of maternal recurrence. Maternal mood stability is also crucial for the wellbeing of mother and child, and the prevention of recurrence is especially important in women with a history of severe mood episodes. Lithium use during pregnancy lowers the risk of recurrence during pregnancy and postpartum for women with bipolar disorder (1, 11), and lithium is less teratogenic than carbamazepine or valproate. Clearly, the risks and benefits of lithium use during pregnancy should always be weighed on an individual basis.

The association between lithium use during pregnancy and miscarriage in this study remained present after adjusting for the age at conception, the clustering of pregnancies per woman, and their lifetime use of valproate and carbamazepine. Importantly, the age at onset (an important indicator of the severity of illness in women with bipolar disorder) was similar in the lithium-exposed and unexposed groups, suggesting that the severity of illness does not explain the increase in miscarriages in the lithium-exposed group. Our results might, therefore, suggest a specific effect of lithium use during pregnancy.

The mechanism of the association between lithium use during pregnancy and miscarriage has not yet been investigated. We would like to propose a hypothetical mechanism of this association. Lithium use has been associated with overt and subclinical hypothyroidism in several studies (12) and (sub)clinical hypothyroidism has been associated with pregnancy loss (13). Thyroid function might, therefore, have a mediating role in the association between lithium use during pregnancy and miscarriage. Unfortunately, thyroid levels during pregnancy were not available in this study. Further research is needed to study this hypothesis.

A few limitations need to be considered. In this study, data on pregnancy outcome and medication use were collected retrospectively by questionnaire and, therefore, recall bias might be present. However, a miscarriage is a major life event, and is likely to be remembered and reported by all women. Due to the fact that lithium use was assessed by questionnaire, we did not have information on lithium level and dosage during pregnancy and were not able to investigate a dose–response relationship. Additionally, information on maternal medical conditions, body mass index, smoking, alcohol and substance use at the time of miscarriage was not available and, therefore, it was not possible to investigate the potential mediating, moderating or confounding influence of these factors on our results.

CONCLUSIONS

Our findings suggest that, in addition or related to its teratogenic effect, lithium may increase the risk of miscarriage. These findings underscore the need for caution, but there is no imminent need to change clinical guidelines for lithium use during pregnancy, as current guidelines already warn against prescribing lithium during the first trimester of pregnancy. The possible risks associated with lithium use during pregnancy, such as the risk of miscarriage and congenital malformations, need to be carefully weighed against the risk of maternal recurrence. The current study provides important information that should be discussed with all women with bipolar disorder of childbearing age.

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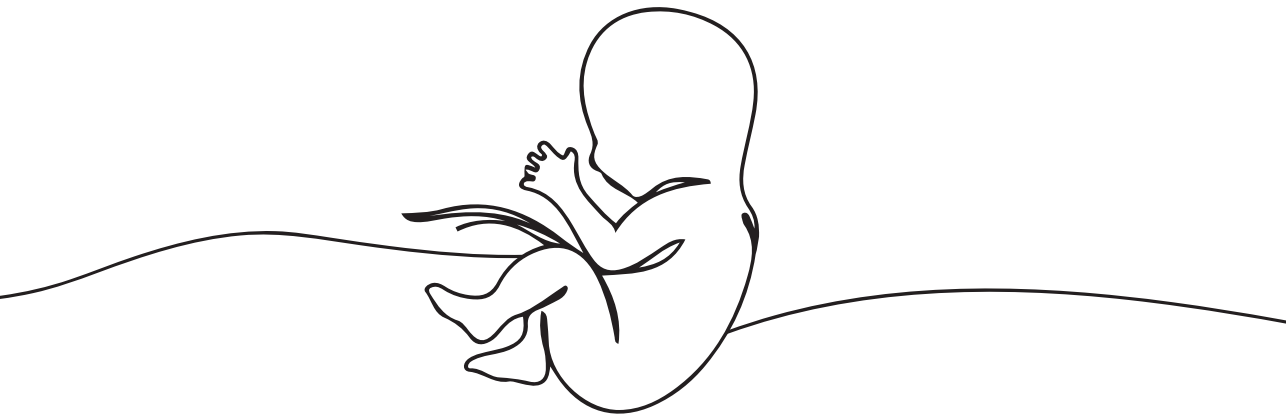

CHAPTER 4

LITHIUM EXPOSURE DURING PREGNANCY INCREASES FETAL GROWTH

Eline M.P. Poels
Karin Sterrenburg
André I. Wierdsma
Richard Wesseloo
Annemerle Beerthuizen
Laura van Dijke
Condon Lau
Witte J.G. Hoogendijk
Hanan E.l. Marroun
Inge L. van Kamp
Hilmar H. Bijma
Veerle Bergink

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ABSTRACT

Background

Lithium is an effective treatment in pregnancy and postpartum for the prevention of relapse in bipolar disorder, but there is lack of knowledge about potential adverse impact on fetal development.

Aims

To investigate the impact of lithium exposure on early fetal growth.

Methods

In this retrospective observational cohort study, we included all singleton pregnancies of women using lithium and referred for advanced fetal ultrasound scanning between 1994 and 2018 to the University Medical Centers in Leiden and Rotterdam, the Netherlands (n=119). The Generation R study, a population-based cohort, served as a non-exposed control population from the same geographic region (n=8184). Fetal head circumference, abdominal circumference, femur length and transcerebellar diameter, were measured by ultrasound at 18-22 weeks of gestation.

Results

Lithium use during pregnancy was associated with an average increase in head circumference of 1.77 mm (95% confidence interval: 0.53, 3.01), in abdominal circumference of 5.54 mm (95% confidence interval: 3.95, 7.12) and in femur length of 0.59 mm (95% confidence interval: 0.22, 0.96) at 18-22 weeks gestation. Furthermore, lithium use during pregnancy was associated with an average increase in birth weight of 142.43 grams (95% confidence interval: 58.01, 226.89), while it was associated with an average decrease of 1.41 weeks in gestational duration (95% confidence interval: -1.78, -1.05).

Conclusions

Lithium use during pregnancy was associated with increased fetal growth parameters at 18-22 weeks gestational age and increased birth weight. Further research is needed to evaluate both short- and long-term implications, as well as the mechanisms driving this difference in growth.

INTRODUCTION

Lithium is currently the most effective drug for relapse prevention and is widely used as a first line treatment in bipolar spectrum disorder (1). It has beneficial treatment effects during both depressive and manic episodes, is associated with a reduction in suicide risk and is highly effective for relapse prevention (2). Since the onset of bipolar disorder often occurs before the age of 25 years (3), lithium is frequently prescribed to women of childbearing age. Women with bipolar disorder who continue lithium use during pregnancy have a lower risk of relapse, both during pregnancy and in the postpartum period (4-6). While lithium has clear beneficial effects for the mother, it may have unintended consequences for the developing fetus. Lithium is known to pass the placenta completely, which means the fetus is exposed to the same level of lithium as the pregnant woman (7). Intrauterine lithium exposure has been associated with increased risks of congenital malformations, but the risk is low (6, 8-11). Moreover, lithium has been associated with spontaneous abortion, preterm birth and increased neonatal birth weight in some studies, while others refuted these findings (7-9, 12). Importantly, to our knowledge no information is available relating maternal lithium therapy during pregnancy to fetal growth patterns. An environmental study showed an effect of lithium exposure through drinking water on fetal growth (13). Studying the effects of intrauterine exposure to lithium on fetal development is especially important since intrauterine environment impacts fetal programming. Even small changes can have a large impact on the development of the child (14). As fetal growth is an important marker for fetal programming, the main aim of the current study is to examine the association of prenatal exposure to lithium on fetal growth and birth weight.

METHODS

Study design and participants

In this retrospective observational cohort study, we collected data from two academic medical centers in the Netherlands; the Erasmus University Medical Center (EMC) and the Leiden University Medical Center (LUMC). Pregnant women using lithium and referred for advanced fetal ultrasound scanning between March 1994 and January 2018 were evaluated for eligibility. In the Netherlands, all pregnant women using lithium are referred for advanced 20 weeks ultrasound scan. All singleton pregnancies were included if there was daily lithium use from conception until 20 weeks of gestation and if data of the advanced 20-weeks ultrasound scan were available (n = 119). As a control population, the Generation R Study, a prospective population-based study conducted in Rotterdam with delivery dates from 2002 until 2006, was used. All participants in the Generation R study provided written informed consent. The Generation R Study is designed to identify early environmental and genetic determinants of growth, development, and health from fetal life until young adulthood (15).

All singleton pregnancies in the Generation R study with information available from the start of pregnancy and data of the 20-weeks ultrasound scan were included as a reference group (n = 8184). None of these pregnancies were lithium exposed. This study was approved by the Institutional Review Board of the Erasmus University Medical Center and conducted and reported in accordance with the STROBE guidelines.

Maternal lithium use and psychiatric history

In the lithium exposed group, information on lithium dose, duration of use, lithium blood levels and use of additional psychotropic medication were extracted from the medical files. Information on psychiatric diagnosis was also collected from the medical files. In the control group, information on psychotropic medication use during pregnancy was collected using two sources of information to minimise misclassification (self-reports in each trimester of pregnancy and pharmacy records) (16). Psychiatric symptoms were assessed by self-reported vignettes in mid-pregnancy (~ 20 weeks of gestation). Within the control group, women were categorized with a bipolar spectrum disorder if they reported at least one depression and (hypo)manic episode in history.

Fetal growth

The records of the 20 week's ultrasound scans were evaluated for fetal growth measurements. The fetal growth measurements used for this study are standardised measurements and measured by well-trained and qualified sonographers in exactly the same way in both patient and control group, according to international quality standards set by the ISUOG (17). In both groups, head circumference (HC), transcerebellar diameter (TCD), abdominal circumference (AC) and femur length (FL) were measured at 18-22 weeks of gestation. In both groups gestational age was assessed earlier, by measuring crown to rump length in the first trimester. TCD is generally considered to be a measure for gestational age in the second trimester of pregnancy. Estimated fetal weight was calculated by means of the Hadlock formula (18). Neonatal birth weight was collected from the medical files.

Covariates

Covariates were maternal age, parity, smoking, psychotropic medication use (other than lithium), body mass index (BMI) (calculated using pre-pregnancy height and weight), gestational age at birth and child sex.

Statistical analyses

Descriptive statistics and statistical analyses were performed using the Statistical Package for the Social Sciences (version 24, IBM). The association of prenatal lithium exposure with fetal growth measurements and birth weight was analyzed using separate multiple linear regression analyses. Models for fetal growth and birth weight were adjusted for the following

covariates: maternal age, maternal BMI, gestational age at the time of measurement, parity, smoking and psychotropic medication use other than lithium (i.e. a combined covariate for the use of drugs for depression, psychosis and insomnia/anxiety). Additionally, the model for birth weight was adjusted for sex of the child. Interactions between the covariates and lithium use were tested for significant improvement of the model fit. Quadratic and cubic terms for gestational age were tested for significant improvement of the model fit. Models for gestational age at birth were adjusted for maternal age, maternal BMI, parity, smoking and psychotropic medication use other than lithium. In order to compare our results to previous studies (9, 19) and to assess clinical relevance, we additionally calculated odds ratios for preterm birth (<37 weeks of gestation) and large for gestational age (LGA) (i.e., a birth weight above the 90th percentile of birth weight by gestational age and sex), using binary logistic regression analyses. Odds ratios were adjusted for the same covariates as described above. All continuous covariates were centered to improve interpretation. Missing data in the covariates were handled using multiple imputations with chained equations. Missing covariate values were imputed based on birth weight, gestational age at time of ultrasound and birth, sex of the child, age of the mother, BMI of the mother, smoking status during pregnancy, psychotropic medication use during pregnancy, gravidity and parity. Ten imputed datasets were generated and analyzed. Pooled effect estimates and their 95% confidence interval were reported. A two-sided p-value of 0.05 was considered to be statistically significant. All analyses were performed per pregnancy, not per mother. By directly comparing the lithium-exposed group to a control group from the normal population one cannot address the effect of confounding by indication, (i.e., the indication for which lithium is most often described, bipolar disorder, can potentially also affect fetal growth independent of lithium exposure). To address this issue, we conducted sensitivity analyses within the control group using a selection of pregnancies in women with a broadly defined bipolar spectrum disorder but no lithium exposure and comparing these to the control pregnancies in women with no bipolar spectrum disorder. Sensitivity analyses were also performed limiting the analysis to one (the first) pregnancy per mother, in order to explore the impact of consecutive pregnancies on our results. In the lithium-exposed cohort, labour was induced as part of regular clinical practice (before 2002) around 38 weeks pregnancy. We therefore removed pregnancies before the year of 2002 in additional sensitivity analyses on gestational duration. Additional sensitivity analyses were performed after excluding pregnancies with gestational diabetes from the lithium group. The aim was to investigate whether associations of lithium with fetal growth were driven by gestational diabetes.

RESULTS

Descriptive statistics

Descriptive characteristics are shown in Table 1. In the lithium group on average 1.4 (range 1-6) pregnancies per woman were included, versus 1.1 (range 1-3) pregnancies per woman in the control group. Maternal age and BMI were on average higher in the lithium group than the control group. Within the lithium-exposed group, most pregnancies were of women diagnosed with a bipolar spectrum disorder (i.e. bipolar I disorder, bipolar II disorder or schizoaffective disorder) (n=110), other diagnoses were postpartum psychosis in history (n=1) and depressive disorder (n=8). Within the control group, 282 pregnancies were from women with a categorized bipolar spectrum disorder, based on self-reported lifetime experience of at least one depressive and one (hypo)manic episode. A higher percentage of women in the control group smoked throughout pregnancy (18.6% vs 6.7%). Gestational diabetes was present in 4.2% of pregnancies in the lithium group and in 1.0% of pregnancies in the control group. Gestational age at ultrasound and sex of the child were comparable in both groups. Notably, the rate of fetal death was 2.5% (n=3) in the lithium group (1. at 22 weeks due to placental insufficiency and early intrauterine growth restriction, 2. at 38 weeks due to a placental maturation problem, 3. at 39 weeks discovered during routine check-up, possibly due to missed signs of impaired fetal condition) and 0.5% (n=37) in the control group. These fetuses were included in the fetal growth parameter analyses but not in the analyses on neonatal birth weight. The mean percentiles of head circumference, abdominal circumference and femur length were higher in the lithium-exposed group while the percentile of TCD was comparable in both groups. In the lithium-exposed group the rates of premature birth and LGA were higher than in the control group.

Lithium use

Different types and various compounds of lithium were used. The most commonly prescribed was lithium carbonate, also known as Camcolit® and Priadel®. Another preparation is lithium citrate, also known as Litarex®. In 60 pregnancies women used lithium carbonate (Camcolit® n=37, Priadel® n=19, and Lithium Carbonate (other brands) n=4); lithium citrate was used in 38 pregnancies; in the remaining 21 pregnancies the prescription of lithium medication was unknown. The average daily lithium dosage during pregnancy was 1007 mg divided over an average of 2.8 doses per day. Lithium citrate dosages (Litarex 564mg = 6mmol lithium) were multiplied by 0.395 in order to calculate lithium carbonate dosage equivalents (400 mg = 10.8 mmol lithium). Maternal lithium plasma level during pregnancy was available for 88 pregnancies. The mean lithium level close to the time of the ultrasound, was 0.44 mmol/L.

Table 1. Descriptive characteristics of the study population[a]

	Lithium-exposed group (N= 119)	Control group (N=8184)
Maternal characteristics, mean (SD)		
Age	34.0 (4.1)	29.7 (5.3)
BMI	26.3 (5.8)	23.6 (4.4)
Bipolar spectrum disorder, %	92.4	3.4
Lithium use, %	100	0.0
Lithium dosage in mg, mean	1007	-
Lithium level in mmol/L, mean	0.44	-
Psychotropic medication use during pregnancy other than lithium, %		
Drugs for depression	16.1	1.5
Drugs for psychosis	22.0	0.1
Drugs for anxiety/insomnia	10.1	1.5
Parity, %		
0	46.2	56.3
≥1	53.8	43.7
Gestational diabetes, %	4.2	1.0
Smoking habits, %		
Never smoked in pregnancy	92.4	72.7
Smoked until pregnancy was known	1.0	8.7
Smoked throughout pregnancy	6.7	18.6
Child characteristics		
Gestational age at ultrasound, mean (SD)	20.2 (1.2)	20.7 (1.2)
Sex of the child, % of girls	54.3	49.4
Intrauterine fetal death, n (%)	3 (2.5)	37 (0.5)
20 weeks fetal parameter percentiles, mean (SD)		
Head circumference	58.4 (28.6)	48.9 (28.9)
Abdominal circumference	70.1 (24.8)	49.9 (28.9)
Femur length	60.9 (27.0)	50.3 (28.9)
Transcerebellar diameter	49.9 (25.2)	49.3 (28.7)
Birth outcome		
Gestational duration in weeks, mean (SD)	38.4 (3.0)	39.8 (1.9)
Premature birth, %	15.5	5.2
Birth weight percentile, mean (SD)	58.7 (29.8)	44.5 (29.6)
Birth weight in grams, mean (range)	3402 (600-4955)	3412 (635-5310)
Large for gestational age, %	19.6	8.1

[a.] In case of missing data, valid means and percentages are presented.
BMI: body mass index.

Fetal growth measurements

In Table 2 we present the associations of lithium exposure with fetal growth characteristics. Lithium use during pregnancy was significantly associated with an average increase in most growth parameters at 20 weeks gestation, including: head circumference of 1.77 mm (95% CI: 0.53, 3.01), abdominal circumference of 5.54 mm (95% CI: 3.95, 7.12), femur length of 0.59 mm (95% CI: 0.22, 0.96) and estimated fetal weight of 21.05 grams (95% CI: 12.29, 29.81). Lithium use during pregnancy showed no association with TCD measurements (β: 0.13, 95% CI: -0.11, 0.36).

Table 2. Associations of maternal lithium use in pregnancy with fetal biometric parameters at 20 weeks gestation

Fetal parameter	β	95% CI	*P*-value
Head circumference (mm)	1.77	0.53, 3.01	.005
Abdominal circumference (mm)	5.54	3.95, 7.12	<.001
Femur length (mm)	0.59	0.22, 0.96	.002
TCD (mm)	0.13	-0.11, 0.36	.28
Estimated Fetal Weight (grams)	21.05	12.29, 29.81	<.001

Models were constructed using multiple linear regression analyses. β represents the difference in fetal growth parameter between the lithium-exposed versus controls. Models are adjusted for: gestational age at time of ultrasound, maternal age and BMI, smoking during pregnancy, psychotropic medication use other than lithium during pregnancy, and parity.
BMI: body mass index; CI: confidence interval; TCD: transcerebellar diameter.

Birth weight and gestational duration

The results of the multiple regression analyses on birth weight and gestational duration are presented in Table 3. Lithium use during pregnancy was significantly associated with an average increase in birth weight of 142.43 grams (95% CI: 58.01, 226.89). Additionally, lithium use during pregnancy was associated with gestational duration, with an average decrease of 1.41 weeks (95% CI: -1.78, -1.05). Results of the binary logistic regression analyses showed that lithium use during pregnancy was associated with LGA (adjusted OR = 1.85, 95% CI: 1.09, 3.12) and premature birth (adjusted OR = 3.26, 95% CI: 1.86, 5.74).

In the sensitivity analyses no association of bipolar spectrum disorder with 20 weeks' fetal growth, birth weight and gestational duration was found (Table 1, Supplementary Material). The results of our analyses did not change when we limited the analyses to one pregnancy per mother, when all pregnancies before the year of 2002 were removed from the analyses, and when pregnancies with gestational diabetes were removed from the lithium group.

Table 3. Associations of maternal lithium use in pregnancy with birth weight and gestational duration

Birth outcome	β	95% CI	*P*-value
Birth weight (grams)[a]	142.43	58.01, 226.89	.001
Gestational duration (weeks)[b]	-1.41	-1.78, -1.05	<.001

Models were constructed using multiple linear regression analyses. β represents the difference in birth weight in grams and pregnancy duration in weeks between the lithium-exposed versus controls.
[a] Adjusted for: gestational age at time of birth, sex of the child, maternal age and BMI, smoking during pregnancy, psychotropic medication use other than lithium during pregnancy, and parity.
[b] Adjusted for: maternal age and BMI, smoking during pregnancy, psychotropic medication use other than lithium during pregnancy, and parity.
BMI: body mass index; CI: confidence interval

DISCUSSION

In this study we examined the association between lithium use during pregnancy and fetal growth parameters. In the lithium-exposed group, we found increased fetal growth at 20 weeks of gestation when compared to the control group. In addition, we found that prenatal lithium exposure was related to increased birth weight, while the average gestational age at birth was lower. Furthermore, lithium use during pregnancy was associated with large for gestational age birth weight and preterm birth. No association of maternal bipolar spectrum disorder and fetal growth was found, which may potentially suggest a specific effect of lithium exposure during pregnancy on fetal growth.

An environmental study by Harari et al. found a non-significant inverse association between lithium exposure during pregnancy and fetal size in the second trimester in a study of 194 pregnancies in the Argentinean Andes (13). In addition, they found a significant association between lithium exposure during pregnancy and birth length but no association with birth weight. In this study lithium exposure was through drinking water in relatively very low concentrations (median 25 µg/L which corresponds to 0.0036 mmol/L, i.e. 122 times lower than the mean lithium blood concentration in our study) which could explain the difference in our findings. It is possible that the increases in fetal growth and birth weight found in our study are not present when lithium blood concentration is low. The association of lithium and higher neonatal birth weight was previously found in a prospective cohort study by Jacobson et al. (12). Three other studies reported no differences in birth weight between lithium exposed and non-exposed neonates (8, 9, 19). Importantly, the largest study on this subject investigated only the association of lithium with low birth weight and small for gestational age (SGA) (<10th percentile) (9). In our study, we found an association of lithium use during pregnancy with an average increase in birth weight of 142 grams and also with LGA. The magnitude of our findings strengthens the clinical relevance of our results. There are several effects of high birth weight on the child, both short-term and long-term. Short-term effects are shoulder dystocia (obstructed delivery of the shoulder

due to mechanical issues), perinatal asphyxia, hypoglycaemia and longer hospital stay (20). Long-term effects are increased risk of obesity from childhood to early adulthood, as well as an increased risk of cardiovascular disease (21).

An increased risk of preterm birth was previously reported in two studies including women with lithium use during pregnancy (8, 19). Our results are consistent with these studies, although the mechanism of this association remains unclear. Our sensitivity analysis on the gestational duration association showed that results remained unchanged after excluding all pregnancies before 2002 (in which labour was induced as part regular clinical practice) from the analysis. This is particularly important because data on the lithium group was collected over a long period of time (between 1994 and 2018) and due to a change in clinical hospital guidelines in this time period the induction of labour around 38 weeks pregnancy became less common after 2002. The association of lithium with pregnancy duration should be interpreted very carefully, as residual confounding by indication is possible as symptom severity of bipolar disorder or side effects from lithium could have influenced healthcare professionals to induce labour prematurely, also after 2002.

Further, our results suggest that lithium use during pregnancy is associated with increased fetal growth, already measurable at around 20 weeks of gestational age. The mechanism of this association should be investigated further, for example in animal models. As an interesting hypothesis in this context we propose the role of brain-derived neurotrophic factor (BDNF). Recent research has indicated that BDNF plays a crucial role in fetal metabolic programming through regulation of energy homeostasis and by regulating glucose metabolism in peripheral tissues (22). Further, it has been shown that placental BDNF gene expression is upregulated in maternal type1 diabetes and gestational diabetes mellitus, and downregulated in neonates with non-diabetic macrosomia, compared with normal birth weight neonates (22). Interestingly, lithium use has been associated with increased BDNF-levels (23, 24). Hence, one of the possible mechanisms underpinning the association between lithium use and increased fetal growth, might be that lithium results in increased maternal serum BDNF, which might subsequently result in altered regulation of placental BDNF. This in turn could alter the regulation of fetal growth by interfering the energy homeostasis and by regulating glucose metabolism. In this scenario, the effect of maternal lithium use on fetal growth most likely reflects altered fetal programming with possible long-term impacts.

Thanks to a collaboration between Erasmus University Medical Center and Leiden University Medical Center, we were able to include a large number of women with bipolar disorder who used lithium during pregnancy. Also, thanks to a collaboration with the Generation R study, we were able to compare this group to a representative sample of the general population, which increased the power of this study. The results of this study need to be interpreted with a few limitations in mind. As in any observational study, we cannot rule out residual confounding, i.e. unmeasured factors associated with both lithium

and fetal growth. For example, we did not have detailed information on education and socioeconomic status in the lithium group and were therefore not able to adjust for these possible confounders. However, it is unlikely that our results are driven by a confounding effect of socioeconomic status. Bipolar disorder is associated with lower socioeconomic status (25) and low socioeconomic status has been associated with lower birth weight (26). In the contrary, we find fetal growth to be increased in the lithium group. Other possible confounding factors of importance might be related to the severity of the psychiatric disease, as well as dosing regimens and serum levels of lithium, glucose metabolism and nutrition. Also, our study was not designed to study trimester specific effects since we assessed fetal growth at one time point during pregnancy. We did have birth weight data, enabling us to conclude that the effect we found at around 20 weeks of gestation was still present at birth. Data from the lithium-exposed group was collected over a longer time period (between 1994 and 2018) while data from the control group was collected between 2002 and 2006. Ideally data would have been collected in the same time period even though we believe that our outcomes of interest (i.e. fetal growth and birth weight) are relatively stable over time. Lastly, we cannot rule out an effect of confounding by indication, even though we did not find an association between fetal growth and unmedicated bipolar spectrum disorder in our control group. In our study, we investigated the influence of bipolar disorder without medication on fetal growth, by running sensitivity analyses on women with self-reported bipolar spectrum disorder (n= 282). However, these women likely have a less severe form of bipolar spectrum disorder compared to the lithium exposed patients since diagnosis is based on self-reported vignettes. Since detailed information on psychiatric history was not available for a large part of the population, sensitivity analysis correcting for illness severity was unfortunately not possible.

Our results are important for the estimation of all effects associated with lithium use during pregnancy. These effects may not only be limited to pregnancy but might also be carried into child development later in life. The theory of Developmental Origins of Health and Disease refers to the concept that early life events could explain an individual's risk for non-communicable disease in later life (27). According to this theory, the intrauterine environment can change fetal programming, that bears an impact on much more than just birth weight, including changes in physiology and metabolism. This means that small prenatal changes, such as the increased fetal growth we found in our study, can have impact in later life (28). As an example, LGA fetuses have an increased risk of developing components of the metabolic syndrome during childhood (29). Only one study investigated the postnatal growth of 15 children exposed to lithium *in utero* and reported outcomes within the normal range (30). Therefore, there is an urgent need for studies with a larger sample size. The rate of fetal death, also before 20 weeks of gestational age, clearly warrants further investigation.

Women of fertile ages who use lithium should be preconceptionally informed about the potential risks and benefits associated with lithium use during pregnancy. Together with their treating physician, women should weigh the benefits of lithium treatment during pregnancy against the risks of adverse fetal and neonatal (long-term) outcomes and compare these risks with those associated with the use of alternative medication.

CONCLUSION

This study investigated the effect of lithium use during pregnancy on fetal growth, as an indicator of fetal programming. We found associations of prenatal lithium exposure and increased fetal growth, which may have health implications in later life. Knowledge of unintended consequences of maternal lithium use during pregnancy is of importance for the establishment of clinical guidelines to optimise the treatment of bipolar disorder during the perinatal period.

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Supplementary Materials

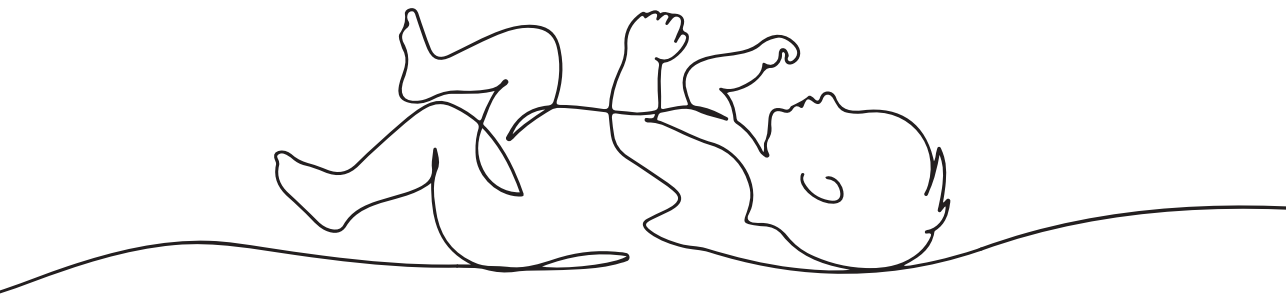
Table 1. Associations of maternal bipolar spectrum disorder with fetal biometric parameters at 20 weeks gestation and birth outcome

Fetal parameter	β	95% CI	*P*-value
Head circumference (mm)	-0.62	-1.37, 0.14	.11
Abdominal circumference (mm)	-0.48	-1.47, 0.51	.34
Femur length (mm)	-0.13	-0.36, 0.10	.25
TCD (mm)	-0.05	-0.19, 0.10	.55
Estimated Fetal Weight (grams)	-4.95	-10.49, 0.59	.08
Birth outcome			
Birth weight (grams)	3.02	-49.04, 55.08	.91
Gestational duration (weeks)[a]	0.20	-0.03, 0.42	.09

Models were constructed using multiple linear regression analyses. β represents the difference in fetal growth parameter between the bipolar spectrum group versus controls. Models are adjusted for: gestational age at time of ultrasound, maternal age and BMI, smoking during pregnancy, psychotropic medication use other than lithium during pregnancy, and parity.

[a] Adjusted for: maternal age and BMI, smoking during pregnancy, psychotropic medication use other than lithium during pregnancy, and parity.

TCD: transcerebellar diameter



CHAPTER 5

MANAGEMENT OF LITHIUM DOSING AROUND DELIVERY: AN OBSERVATIONAL STUDY

Nina M. Molenaar
Eline M. P. Poels
Thalia Robakis
Richard Wesseloo
Veerle Bergink

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ABSTRACT

Objectives

Recommendations on lithium dosing around delivery vary, with several guidelines suggesting that lithium should be discontinued prior to delivery. We aimed to evaluate the validity of these recommendations by investigating 1) maternal lithium blood level changes following delivery, and 2) the association between neonatal lithium blood levels at delivery and neonatal outcomes.

Methods

In this retrospective observational cohort study, we included women with at least one lithium blood level measurement during the final week of pregnancy and the first postpartum week. For aim 2, we included a subcohort of women with neonates for whom neonatal lithium blood levels (obtained from the umbilical cord or a neonatal vein puncture within 24 hours of delivery) were available.

Results

There were a total of 233 maternal lithium blood level measurements; 55 (23.6%) in the week before delivery and 178 (76.4%) in the week after. There was no association between time and lithium blood level/dose ratio (Pearson correlation coefficient −0.03, P = .63). Additionally, we included a total of 29 neonates for whom a lithium measurement was performed within 24 hours postpartum. Maternal and neonatal lithium blood levels were strongly correlated. We observed no associations between neonatal lithium blood levels at delivery and neonatal outcomes.

Conclusion

Based on our findings, we do not recommend lowering the dosage or discontinuation of lithium prior to delivery. Stable dosing can prevent subtherapeutic lithium serum levels, which is especially important in the postpartum period when relapse risks are highest.

INTRODUCTION

Women with bipolar disorder are at high risk of relapse in the postpartum period (1, 2). Especially women without prophylactic pharmacotherapy are at elevated risk of postpartum relapse, with a reported pooled prevalence rate of 66% (2). Effective treatment with pharmacotherapy is therefore of critical importance. Lithium is an effective mood stabilizer and is widely used as a first-line treatment for bipolar disorder (3). Some women choose to start lithium prophylaxis immediately after delivery, but for other women, continuation of lithium during pregnancy is the best option, despite associated risks (4). Lithium use during the first trimester of pregnancy is associated with a dose dependent increased risk of congenital malformations (5, 6). An increased risk could not be found for lithium use during the second and third trimester.

Dosing of lithium can be challenging as a result of normal physiological adaptations of renal function throughout pregnancy (7). Lithium blood levels decrease gradually in the first and second trimester, returning to their preconception level in the third trimester (8, 9). As a consequence, there is a risk of subtherapeutic lithium levels in the first and second trimester, which might lead to an increase in the dose by clinicians. This, in turn, could lead to an increased risk of lithium intoxication in the third trimester and the postpartum period. Frequent monitoring of lithium blood levels during pregnancy is therefore recommended and dosage should be adjusted in order to remain within the therapeutic window (0.5 mmol/L to 1.2 mmol/L) (4, 9-11).

Several reviews and guidelines have provided clinical advice on dosing strategy during pregnancy and the postpartum, including strategies for dosing around delivery to minimize the risk of both maternal and neonatal complications. Some suggest dose reduction by 30%-50% upon first signs of labor or immediately after delivery (8, 12-15), and others recommend to stop lithium prior to delivery (16-18). The underlying rationale is two-fold: 1) blood lithium levels may rise due to a decrease in lithium clearance and vascular volume following delivery, and 2) a previous study found an association between lithium blood levels around delivery and neonatal complications, suggesting that a lower dosage could reduce the complication rate (19).

In the current study we aimed to evaluate the validity of the recommendations around delivery by further investigating maternal lithium blood level changes following delivery (aim 1) and by examining the association between neonatal lithium blood levels at delivery and neonatal outcomes (aim 2).

PATIENTS AND METHODS

This retrospective observational cohort study was part of a larger study for which all women referred to the psychiatric and obstetric out-patient clinics of Erasmus Medical Center and Leiden University Medical Center between January 2003 and May 2018 were eligible (9). Women were included in the current study if they used lithium during pregnancy and at least one lithium blood level measurement was obtained during the final week of pregnancy and the first postpartum week (aim 1). From the medical records, we extracted demographic, psychiatric and obstetric data, lithium blood level measurements, daily lithium dose, dosing alterations, and the dosing frequency. For aim 2, we included a subcohort of women with neonates for whom neonatal lithium blood levels were available. Clinical protocols in the Erasmus Medical Center recommend clinical observation of all lithium exposed neonates during the first 5 days after birth. Neonatal lithium blood levels were obtained from the umbilical cord or a neonatal vein puncture within 24 hours of delivery. From the medical records, we extracted information on neonatal outcomes and complications, including mild and transient complications. Extracted neonatal outcomes included: preterm birth, birth weight, Apgar scores, cord blood pH-values, cord blood Base Excess values, and admission to medium/high care. We extracted information of all reported complications, ranging from mild to severe, and categorized them by organ system: respiratory, circulatory, hematological, gastro-intestinal, metabolic, neurological, and immune system (infections). The study was approved by the medical ethical review board of Erasmus University Medical Centre (MEC-2013-319).

Statistical analysis

For aim 1, we calculated the lithium blood level/dose ratio for each measurement, and visualized (scatterplot) and tested (R-squared) the correlation between time (−7 to +7 days of delivery date) and lithium blood level/dose ratio. Lithium citrate (Litarex 564mg = 6mmol lithium) dosages were multiplied by 0.395 in order to obtain lithium carbonate prescription equivalents (400 mg = 10.8 mmol lithium).

For our second aim, we first visualized (scatterplot) and tested (R-squared) the correlation between maternal and neonatal lithium blood levels surrounding delivery. Sensitivity analyses (two sample t-test and Mann-Whitney U test) were used to assess whether mean neonatal blood levels differed between umbilical cord and neonatal vein puncture measurements. We then used linear and binary logistic univariate regression to examine the association between neonatal lithium blood levels and neonatal outcome measures (preterm birth, birthweight, Apgar scores, cord blood pH- and BE-values, admission to medium/high care, and neonatal complications). No multivariate regression analysis was performed due to the limited number of pregnancies included. The Statistical Package for Social Sciences (SPSS) version 25.0 was used for data analyses and the significance level was set at 0.05, two sided.

RESULTS

Lithium blood level changes following delivery (Aim 1)

We identified 78 women with a total of 100 pregnancies who were referred to the specialized out-patient university clinics of Rotterdam (n = 57) and Leiden (n = 21). The most common psychiatric diagnosis was bipolar spectrum disorder (n = 68, 87.2%), while the remaining women (n = 10, 12.8%) were diagnosed with schizoaffective disorder, depressive disorder, or borderline personality traits. Median parity of all pregnancies was 1 (range 0-6) and mean age at delivery 34.6 years (SD 4.3).

There were a total of 233 lithium blood level measurements: 55 (23.6%) in the week before delivery and 178 (76.4%) in the week after. Mean lithium dosage was 1071 mg (SD 368) in the week before delivery and 1016mg (SD 284) in the week after delivery. Mean lithium blood level was 0.73 mmol/L in the week before delivery and 0.70 mmol/L in the week after delivery. The course of the lithium blood level/dose ratio before and after delivery can be seen in Figure 1. There was no association between time and ratio (Pearson correlation coefficient −0.03, P = .63). Lithium blood levels not normalized to dose can be found in Supplementary Figure 1.

Figure 1. Course of lithium blood level/dose ration around delivery

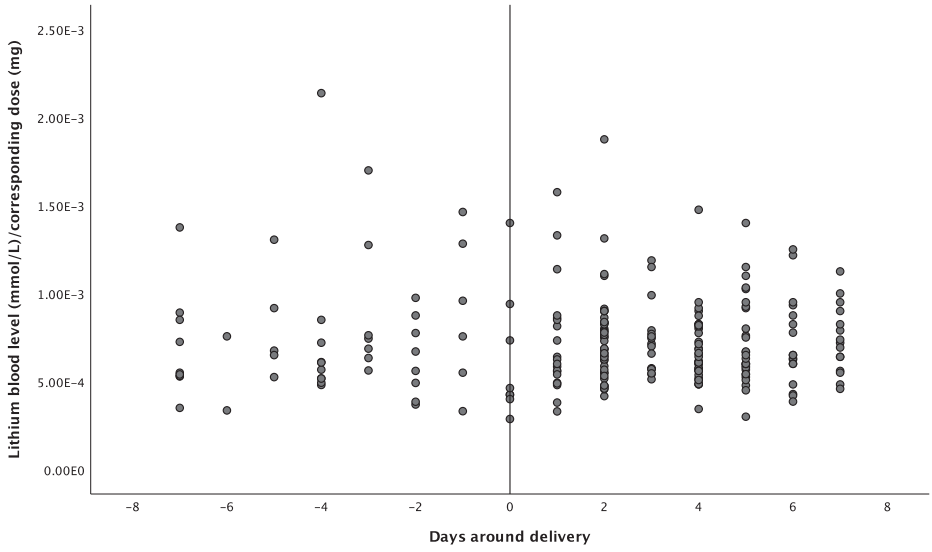


Table 1. Maternal and neonatal characteristics of the subcohort (aim 2)

Maternal characteristics	**All (N = 29)**
Lithium dosage in mg/day, mean (SD)[a]	1142.82 (350.74)
Lithium blood level in mmol/L, mean (SD)	0.67 (0.23)
Complications during delivery, n (%)[b]	16 (55.2)
Neonatal characteristics	
Lithium blood level in mmol/L, mean (SD)	0.61 (0.31)
Preterm (<37 weeks), n (%)	3 (10.3)
Birth weight in grams, mean (SD)	3589.14 (457.16)
Apgar score 1 minute, median (IQR)	8 (2)
Apgar score 5 minutes, median (IQR)	9 (2)
pH-value cord blood, mean (SD)	7.24 (0.10)
Base Excess value cord blood, mean (SD)	-4.50 (5.12)
Admission medium/high care, n (%)	13 (44.8)
Duration admission medium/high care in days, median (IQR)	3 (4)
Any complication (including mild/transient), n (%)[c]	14 (48.3)
Neurological complications, n (%)	5 (17.2)
Respiratory complications, n (%)	5 (17.2)
Circulatory complications, n (%)	1 (3.4)
Gastro-intestinal complications, n (%)	1 (3.4)
Infectious complications, n (%)	4 (13.8)
Hematological complications, n (%)	1 (3.4)
Metabolic complications, n (%)	7 (24.1)

[a] Lithium dosage closest to delivery

[b] Observed complications: fetal distress (n=7), postpartum hemorrhage (n=5), prolonged rupture of the membranes (n=5), increased duration second stage of labor (n=3), preterm birth (n=3), shoulder dystocia (n=1), retained placenta (n=1), meconium amniotic fluid (n=1)

[c] Details of complications: neurological – hypotonia (n=3), tremors (n=1), irritability (n=1); respiratory – asphyxia with no spontaneous breathing after birth (n=1), dyspnea (n=1), cyanosis (n=1), decreased oxygen saturation due to vomiting (n=1), impaired breathing coordination (n=1); circulatory – bradycardia (n=1); gastro-intestinal – cholestasis (n=1); infectious – pneumonia (n=1), observation/treatment for suspected infection (n=3); hematological – disseminated intravascular coagulation (n=1); metabolic – hyperbilirubinemia (n=6), transient abnormal thyroid levels (n=1)

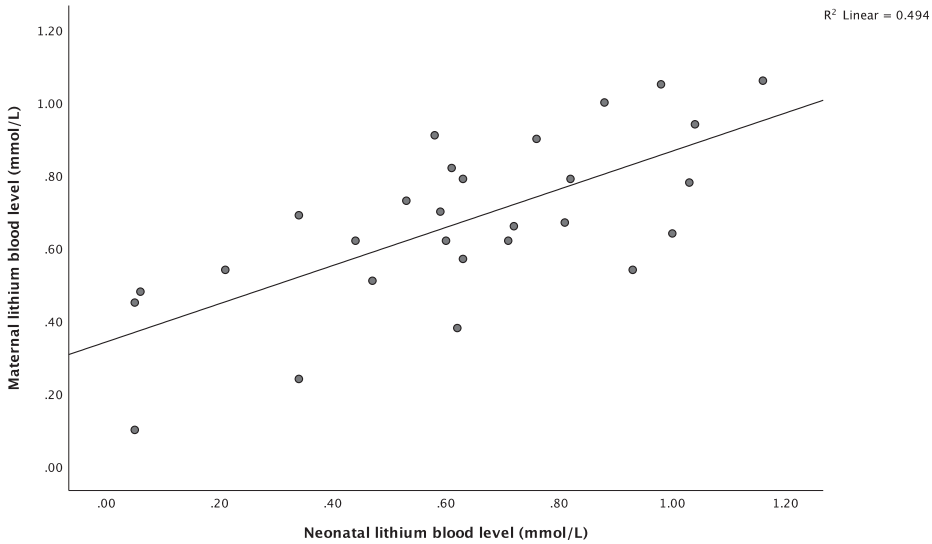
Lithium blood levels and neonatal complications (Aim 2)

We included a total of 29 neonates for which a lithium measurement was performed within 24 hours postpartum (20 umbilical cord, 9 neonatal vein puncture). Cohort characteristics are represented in Table 1. While approximately half of the neonates had a complication, the majority of reported neonatal complications were mild and transient. One term neonate with fetal distress had complications in all seven organ systems, while having

a neonatal lithium blood level of 0.72 mmol/L, and a birth weight of 4360 grams. A full overview of complications per neonate with additional lithium blood level can be found in Supplementary Table 1. All neonates with medium/high care admission were discharged in good medical condition, except for one neonate that was transferred to another hospital for further recovery from a respiratory infection.

There was a strong positive correlation between maternal and neonatal lithium blood levels (Pearson correlation coefficient 0.703, $P < .001$), which is visualized in Figure 2. Sensitivity analyses showed no significant difference in mean neonatal blood levels between umbilical cord and neonatal vein puncture measurements (two sample t-test, $P = .288$; Mann-Whitney U test, $P = .390$).

Figure 2. Correlation between maternal and neonatal lithium blood levels around delivery. Maternal lithium blood levels were obtained between 2 days prior to delivery and 6 days after delivery. Neonatal blood levels were obtained from the umbilical cord (n = 20) or neonatal vein puncture within 24 hours after delivery (n = 9)



Univariate linear and logistic regression analysis showed no associations between neonatal lithium blood levels and complications during delivery (B = 11.8, 95% CI 0.8;181.1, $P = .1$), preterm birth (B = 8.2, 95% CI 0.1;746.7, $P = .4$), birth weight (B = 79.8, 95% CI −496.1;655.7, $P = .8$), Apgar score at 1 minute (B=−1.2, 95% CI −3.9;1.4, $P = .4$) and 5 minutes (B = −0.8, 95% CI −2.8;1.1, $P = .4$), cord blood pH-value (B = −0.1, 95% CI −0.2;0.0, $P = .2$), cord blood BE-value (B = −6.2, 95% CI −12.7;0.4, $P = .1$), admission to medium/high care (B = 1.8, 95% CI 0.2;20.1, $P = .6$), and neonatal complications (B = 1.2, 95% CI 0.1;12.9, $P = .9$).

DISCUSSION

In this retrospective observational cohort study, we found no maternal lithium blood level fluctuations surrounding delivery. Maternal and neonatal lithium blood levels were strongly correlated. We observed no association between neonatal lithium blood levels at delivery and neonatal outcomes.

Several guidelines recommend, out of caution, lowering or discontinuing lithium prior to labor to avoid high plasma lithium levels (12-14, 16-18). Blood levels are assumed to rise due to a decrease in lithium clearance and contraction of fluid volume following delivery, possibly reaching toxic levels. These recommendations are primarily based on reviews and case studies rather than on observational data of the target population, as cohort studies are sparse due to methodological difficulties. Our data indicates that lithium plasma levels do not increase during labor after correcting for the prescribed lithium dose.

A second argument for decreasing or discontinuing lithium treatment just before labor is the belief that a lower neonatal lithium blood level at time of delivery reduces the risks of lithium side-effects in the neonate. This argument is based on the important study by Newport et al (19), in which lithium concentrations and obstetrical outcomes were available for 10 neonates, plus for another 14 neonates identified from published reports. Infants were grouped into a low and high lithium exposure group (cut-off of 0.64 meq/L). They found that the high lithium exposure group had a higher rate of complications compared to the low lithium group, including central nervous system and neuromuscular complications, longer duration of infant hospital stay, and lower 1-minute Apgar scores. In our sample of 29 neonates, we did not find a significant association between neonatal lithium blood levels and neonatal outcomes. A potential explanation for these contrasting findings is that neonatal blood level range differed substantially between our sample and the sample of Newport et al. (19). The high lithium exposure group in Newport's study was predominantly composed of the neonates from previous case reports, who often had a lithium blood level higher than 0.7 and with some neonates classified as being within the toxic range (>1.2 mmol/L). Their low lithium exposure group existed mainly of women who had suspended their lithium treatment before delivery, and lithium levels were mostly subtherapeutic (<0.5 mmol/L). In our sample, most women were within the therapeutic window and no toxic levels were observed. Neonatal lithium levels might be associated with neonatal complication rate only if high (toxic) lithium dosages are used. Moreover, in the Newport paper, the overall complication rate of 100% in the high exposure group was driven by case reports on this topic for which publication bias is likely. Case studies are in origin a tool to disseminate information on unusual clinical syndromes, disease associations, or unusual side effects to therapy (20), and therefore in this case more likely to be published if neonatal complications were present with high lithium levels.

The high rate of neonatal complications (48.3%) in our study sample should be interpreted keeping in mind that lithium use during pregnancy is an indication for neonatal observation during the first five days following birth. Due to this observation period and the knowledge of lithium exposure during pregnancy, several mild complications might have been detected and recorded that otherwise would have gone unnoticed. Fortunately, even though the rate of complications was high, most complications were mild and transient.

This study is not without limitations. Statistical power was limited for examining the association between neonatal lithium levels and neonatal outcomes, even though we report on the largest sample thus far. In addition, neonatal lithium levels are not routinely assessed in clinical settings. Selective sampling might have contributed to relatively high neonatal lithium levels, as well as to a high complication rate.

Lithium dosing during pregnancy can be challenging due to changes in clearance throughout the trimesters. Relapse risk during pregnancy is not elevated and some authors even suggest that pregnancy is protective for relapse (21). Lithium levels in the lower range are often accepted, especially during the first trimester, in which there is a dose dependent increased risk for congenital malformations (22). In general, we recommend to monitor lithium levels frequently until 34 weeks of pregnancy, for example once every three weeks, followed by weekly monitoring until delivery. Lithium levels should not exceed therapeutic levels during pregnancy, as this may cause harm to the pregnant woman and her developing child. Based on the results of this study, we do not recommend to lower the dosage or discontinue lithium prior to delivery when lithium is used within the therapeutic window, unless this is warranted by special circumstances such as severe dehydration or renal dysfunction. Lowering the lithium dosage prior to delivery could lead to a subtherapeutic blood level and, as a consequence, insufficient protection against maternal relapse in the postpartum period, when relapse risks are highest (23). Instead, we recommend to carefully monitor lithium blood levels around delivery, and secure adequate fluid management. After delivery, we recommend lithium blood levels be obtained once at day 2 postpartum, followed again by (bi-)weekly monitoring, and dosage adjustments when necessary. A high target therapeutic lithium blood level (eg 0.8-1.0 mmol/L) immediately after delivery and during the first month postpartum is recommended to optimize relapse prevention.

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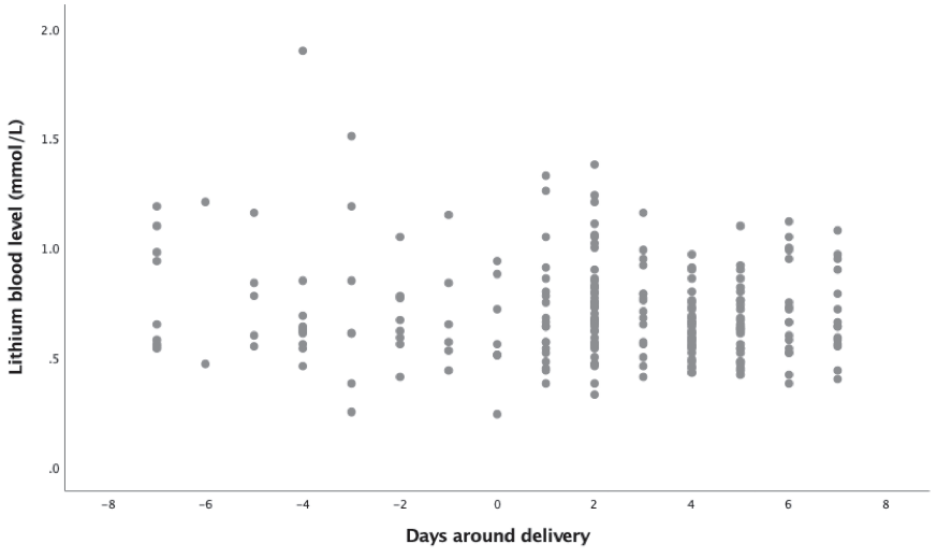
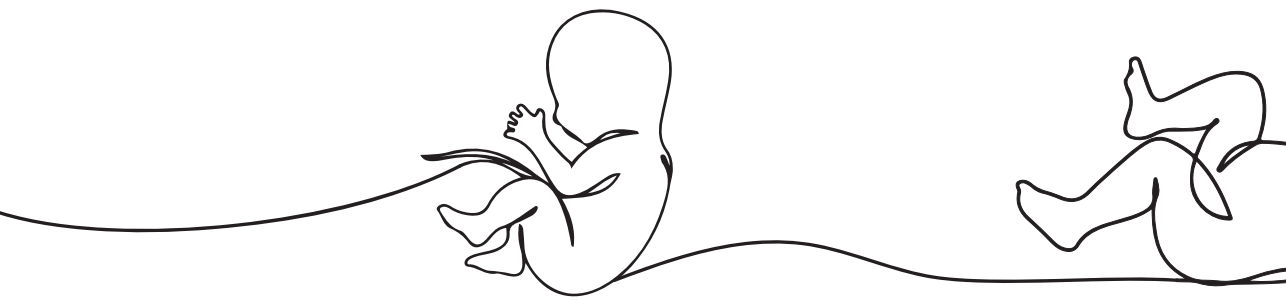
Supplementary Materials

Supplementary Table 1. Neonatal complications per infant

Nr.	Lithium blood level (mmol/L)	Complications
1.	0.05	Hypotonia
2.	0.05	Impaired breathing coordination
3.	0.06	Observation/treatment for suspected infection
4.	0.47	Observation/treatment for suspected infection
5.	0.58	Hyperbilirubinemia, irritability
6.	0.62	Cyanosis
7.	0.63	Transient abnormal thyroid levels
8.	0.63	Hyperbilirubinemia
9.	0.71	Hypotonia, hyperbilirubinemia
10.	0.72	Hypotonia, hyperbilirubinemia, bradycardia, cholestasis, asphyxia with no spontaneous breathing after birth, disseminated intravascular coagulation, pneumonia
11.	0.98	Hyperbilirubinemia
12.	1.00	Decreased oxygen saturation due to vomiting
13.	1.04	Hyperbilirubinemia, dyspnea, observation/treatment for suspected infection
14.	1.16	Tremors

Supplementary Figure 1. Maternal lithium blood levels around delivery not normalized to dose





PART II

NEURODEVELOPMENTAL CONSEQUENCES FOR THE CHILD

CHAPTER 6

LONG-TERM NEURODEVELOPMENTAL CONSEQUENCES OF INTRAUTERINE EXPOSURE TO LITHIUM AND ANTIPSYCHOTICS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Eline M. P. Poels
Lisanne Schrijver
Astrid M. Kamperman
Manon H. J. Hillegers
Witte J. G. Hoogendijk
Steven A. Kushner
Sabine J. Roza

European Child & Adolescent Psychiatry, 2018. 27(9): 1209–1230.

ABSTRACT

Lithium and antipsychotics are often prescribed to treat bipolar disorder or psychotic disorders in women of childbearing age. Little is known about the consequences of these medications during pregnancy for the developing child. The objective of this article is to systematically review findings from preclinical and clinical studies that have examined the neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics. A systematic search was performed in Embase, Medline, Web of Science, PsychINFO, Cochrane, and Google Scholar. Clinical and experimental studies were selected if they investigated neurodevelopment of offspring exposed to lithium or antipsychotics during gestation. Quality of clinical and preclinical studies was assessed by the Newcastle–Ottawa Scale and the SYRCLE's risk of Bias tool, respectively. In total, 73 studies were selected for qualitative synthesis and three studies were selected for quantitative synthesis. Of preclinical studies, 93% found one or more adverse effects of prenatal exposure to antipsychotics or lithium on neurodevelopment or behaviour. Only three clinical cohort studies have investigated the consequences of lithium exposure, all of which reported normal development. In 66% of clinical studies regarding antipsychotic exposure, a transient delay in neurodevelopment was observed. The relative risk for neuromotor deficits after in utero exposure to antipsychotics was estimated to be 1.63 (95% CI 1.22–2.19; I^2 = 0%). Preclinical studies suggest long-term adverse neurodevelopmental consequences of intrauterine exposure to either lithium or antipsychotics. However, there is a lack of high-quality clinical studies. Interpretation is difficult, since most studies have compared exposed children with their peers from the unaffected population, which did not allow correction for potential influences regarding genetic predisposition or parental psychiatric illness.

INTRODUCTION

Patients with bipolar disorder or a psychotic disorder are often treated with lithium and/or antipsychotics in the acute phase of the disease and chronically for relapse prevention (1, 2). As a substantial proportion of patients with bipolar disorder or a psychotic disorder are women of childbearing age, knowledge of the potentially deleterious consequences of intrauterine exposure to lithium and/or antipsychotics is critically important for optimally weighing the risks and benefits of different pharmacotherapy options. Continuation of maintenance treatment during pregnancy is often necessary to maintain symptom stability and prevent relapse, while discontinuation of lithium or antipsychotics is associated with a higher relapse risk (3-5).

The teratogenic, obstetric and neurodevelopmental consequences of intrauterine exposure to lithium and/or antipsychotics have remained poorly defined, largely due to the difficulty of implementing feasible study designs that avoid confounding by indication. Multiple studies have reported a positive association between intrauterine exposure to lithium and the risk of cardiovascular anomalies (6-10). Lithium use during pregnancy has also been associated with an increased rate of miscarriages and preterm delivery (7, 9). Similarly, antipsychotic use during pregnancy has been associated with higher rates of preterm delivery and low birth weight, as well as neonatal withdrawal symptoms, sedation and extrapyramidal side effects (11, 12). However, severe mental illness, the indication for which lithium and antipsychotics are overwhelmingly prescribed during pregnancy, is also associated with increased risk of obstetric and neonatal complications independent of medication (13-15). Therefore, confounding by indication has remained a challenging issue limiting the conclusiveness of previously observed associations between neonatal outcomes and medication exposure during pregnancy.

Further compounding the issue of study design, little is known about the long-term neurodevelopmental consequences of intrauterine exposure to lithium or antipsychotics. It is widely assumed that the fetal environment influences lifetime disease risk based on Barker's hypothesis of 'fetal and infant origins of adult life' (16, 17). Following this reasoning, adverse fetal or neonatal consequences of intrauterine exposure to lithium and/or antipsychotics might be expected to have neurodevelopmental consequences that extend well beyond infancy. Regarding the cellular mechanisms of lithium, a neuroprotective effect is suggested through inhibition of glycogen synthase kinase-3 (GSK-3) (18, 19). Mechanisms of antipsychotic action differ between the different types of antipsychotic medication with dopamine D2 receptor antagonism as the general pharmacodynamic property (20). Several studies have suggested that atypical antipsychotics, but not typical antipsychotics, may also have neuroprotective effects (21). Evidence from clinical neuroimaging studies in adults suggests that the use of lithium or antipsychotic medication can influence brain structure. Structural Magnetic Resonance Imaging (MRI) studies have shown that lithium is associated

with increases or normalization of gray matter volume in fronto-limbic brain structures (22), while antipsychotic medication has been associated with decreased brain volume and increased ventricular size (23). Based on this information one might expect similar, or even larger, effects when not the adult but the fetus is exposed during a crucial stage of neurodevelopment.

The objective of this article is to systematically review and synthesize findings drawn from both preclinical and clinical studies examining long-term neurodevelopmental outcomes following intrauterine exposure to lithium or antipsychotics, in an effort to gain further insight into the risks associated with the use of these medications during pregnancy.

METHODS

Search strategy for systematic review

A systematic search was performed by a trained librarian in the following databases: 1) Embase, 2) Medline, 3) Web of Science, 4) PsychINFO, 5) Cochrane, and 6) Google Scholar, from their respective inceptions through June 8, 2017 to identify studies that investigated the long-term neurodevelopmental consequences of intrauterine exposure to lithium or antipsychotics. The search included the following elements: lithium, antipsychotics, (neuro) development and intrauterine exposure. All elements were transformed into a thesaurus suitable for each specific database. The exact search terms per database are reported in the Supplementary Material (Supplement 1).

Study selection

Studies were considered eligible for inclusion if they were written in the English language and investigated the long-term neurodevelopment, defined as neurodevelopment beyond the newborn period, of offspring exposed to lithium or antipsychotics during gestation. Experimental preclinical investigations and clinical investigations were considered eligible for inclusion. Case reports were also included in this review. Two reviewers (E.P. and L.S.) independently screened the title and abstract of all records identified by our database search. Full text articles were obtained from the studies selected during this first screening step. Both reviewers independently selected the full text articles that met the eligibility criteria. The inclusion of both reviewers was compared and consensus was made on the final inclusion. An additional search was performed on the reference section of relevant studies and review articles to screen for other eligible articles that were otherwise not identified by our structured search.

Data extraction

Two authors (EP and LS) independently extracted data on study design, sample size and characteristics, medication dosage and exposure period, follow-up time, and behavioural,

cognitive and neurological outcome measures. The data were summarized in a data extraction form. Studies were categorized by medication type and study design, and results were reported descriptively in accordance with the PRISMA statement (24).

Assessment of the risk of bias and the quality of studies

Methodological quality and risk of bias was assessed independently for each study by two reviewers (EP and LS). Risk of bias in preclinical studies was assessed with the SYRCLE's Risk of Bias tool (25). This tool was recently developed to assess risk of bias and has been adjusted for specific aspects of animal intervention studies. The Newcastle-Ottawa Scale (NOS) (26) was used for clinical studies. The NOS assesses the risk of bias of observational studies based on selection, comparability and outcome criteria. The NOS rating scale varies from zero to nine; with zero representing the highest risk of bias and nine the lowest risk.

Procedure for meta-analysis

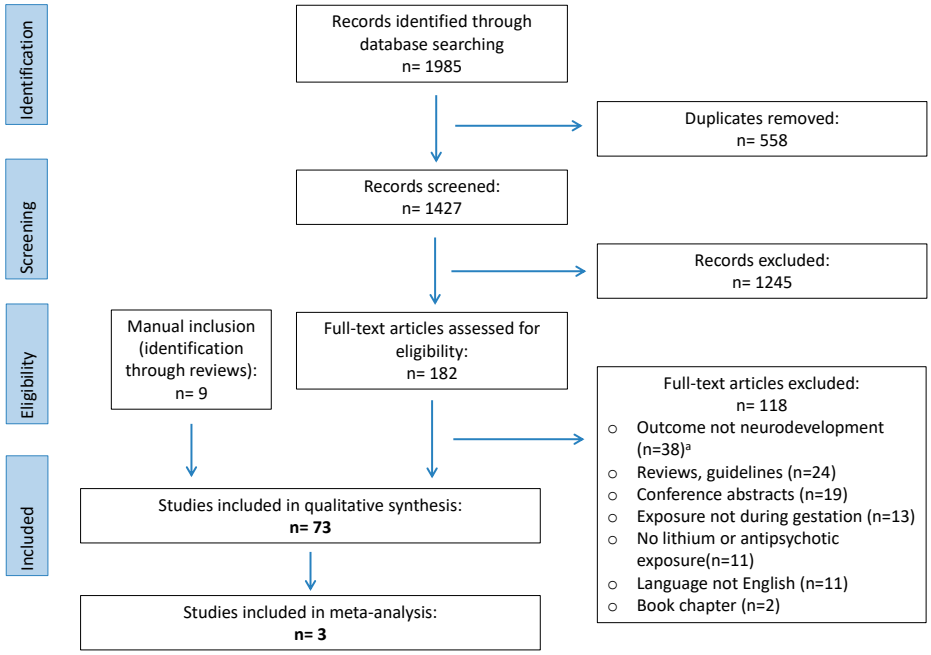
For our meta-analysis, we used the same search strategy as mentioned before. Only clinical investigations were included in the meta-analysis with the goal to enhance further insight into the risks associated with the use of these medications during pregnancy in humans. Pooling was performed per type of neuropsychological outcome and per group of medication exposure (lithium or antipsychotics) over a minimum of two studies. Fixed and random-effect estimation was used. In case of substantial heterogeneity, a random-effect estimation provides more reliable pooled results. Results are plotted in a forest plot. Cochran's Q test, and I^2 statistics were used to quantify heterogeneity across trials. I^2 >40% was considered as substantial heterogeneity. The influence of intrauterine exposure to lithium or antipsychotics on neuropsychological development over time was estimated using random effects meta-regression analysis. Statistical analyses were performed using the 'Metan package' in Stata 15 (27).

RESULTS

Study selection

The study selection process is presented in Fig. 1. Our initial search produced a total of 1985 articles. After duplicates were removed, 1427 articles remained. Based on the screening of title and abstract, 182 full text articles were examined for eligibility, of which 118 were excluded (Fig. 1). In total, 73 studies were included in the qualitative synthesis, of which nine studies were included through manual (non-structured) identification. Additionally, three studies were included in the quantitative synthesis.

Fig.1. Flowchart of the study selection process in this systematic review and meta-analysis



[a] Outcome of the excluded studies: cell development (*n*= 4), teratogenicity (*n*= 5), neonatal outcome only (*n*= 14), obstetric outcome and teratogenicity (*n*= 9), fetal development (*n*= 2), endocrine and cardiologic follow-up (*n*= 1), weight gain and mortality (*n*= 1), treatment choice (*n*= 1), sexual development (*n*= 1).

Study characteristics

The characteristics and results of the preclinical investigations included in the qualitative analysis are summarised in Table 1 and 2. The characteristics and results of the clinical studies can be found in Table 3 and 4. Table 1 and 2 in the Supplementary Material (Supplement 2) present the characteristics and results of case reports.

Table 1. Characteristics and results of preclinical studies on intrauterine exposure to lithium

Author (year)	Species/ strain	Lithium dosage	Control medication	Exposed period	Follow-up time	Measurements	Results
Brain 1986	mice/SW	0.1 or 0.2 mEq s.c.	n.r.	Last 4 days of gestation until PND 4	36 days	Standard Opponent Test: social, defensive, threatening and aggressive behaviour	No difference.
Messiha 1986	mice/SD	Lithium 1mEq solution	Distilled water	G1 until PND 23	37 days	Brain weight	Decrease in brain weight (8,6% female, 8.2% male).
Sechzer 1986	rats/SD	2.0 or 4.0 mEq/ kg/day in orange juice solution	Orange juice solution	G1 until PND 28	4 months	Eye and ear opening, startle response, depth perception, open field activity	Delayed eye and ear opening, startle response and maturation of depth perception. Less spontaneous activity at 4 months.
Rider 1987	rats/n.r.	15 mEq/liter water	Water and low protein diet	During gestation and lactation (days not specified)	4.5 to 5.5 months	T-maze performance, avoidance response	Decreased performance on the T-maze, decreased avoidance response.
Teixeira 1995	rats/W	10mM in tap water	Tap water (restricted) Tap water *ad libitum*	Whole gestation period or G1 until PND 21	21 days	Righting reflex, eye opening, cliff avoidance test, motor coordination (rota-rod test)	Delayed righting reflex and eye opening, decreased cliff avoidance, no difference in motor coordination.
Abu-Taweel 2012	mice/SW	15 or 30 mg/kg/ day in water	Distilled water	G1 until PND 15	22 days	Eye opening. Righting reflex, cliff avoidance, rotating reflex, locomotor activity test	Delayed eye opening. Inhibitory dose dependent effect on sensory motor reflexes and locomotor activity.
Nery 2014	zebrafish/ Danio rerio	0.05mM, 0.5 mM, 5mM	System water	G3	10 days	Locomotor activity	Dose dependent locomotor deficit.

s.c. subcutaneous, *n.r.* not reported, *G* gestation day, *PND* postnatal day, *SW* Swiss Webster, *SD* Sprague–Dawley, *W* Wistar

Table 2. Characteristics and results of preclinical studies on intrauterine exposure to antipsychotics

Author (year)	Species/ strain	Experimental medication (dosage)	Control medication	Exposed period	Follow-up time	Measurements	Results
Jewett 1966	rats/SD	Cpz 2mg/ml or Inj 0.1ml/100g body weight 3 x daily	Distilled water Inj 3x daily or no treatment	G4 - G7	75 days	Spontaneous motor activity (photoelectric cell activity cage), audiogenic seizures	Cpz: decreased motor activity day 30-33; no difference day 23-26. Increased susceptibility to audiogenic seizures.
Ordy 1966	mice/ C57BL/10	Cpz 4 or 16 mg/kg/day orally	Placebo	G6 – PND0	60 days	Open field test, wheel running activity, shock-elicited escape avoidance conditioning	Delayed open field latency to move to middle square. Fewer rotations in wheel running. Fewer avoidances in conditioning.
Hoffeld 1968	rats/SD	Cpz 6.0mg/kg/day	Distilled water	G5-G8 (I) G11-G14 (II) G17-G20(III)	97 days	Rotary activity wheel, emotionality testing (faecal boluses), stress reaction (stomach ulcers)	Increased activity. More activity in 2nd and 3rd than in 1st trimester exposed pups. No difference in emotionality and stress response.
Clark 1970	rats/SD	Cpz 3 mg/kg/day s.c.	Vehicle	G12 - G15	60 days	Open field test, T-maze, mother-goal maze, operant conditioning	Locomotor activity reduced on day 13 but enhanced on day 18. Maze learning: shorter latencies, higher error scores in mother-goal maze; no differences in T-maze. Operant conditioning: 1 more session needed to acquire bar-press response.
Robertson 1979	rats/CR	Cpz 1, 3 or 9 mg/kg/ day by gavage	Vehicle	G6 - G 15	13 weeks	Open field test in week 3,7,13, brain weight in week 15	Increased open field activity and decreased latency time in week 3 and 13 in the 3 and 9 mg group. No difference in brain weight.

Table 2. (Continued)

Author (year)	Species/ strain	Experimental medication (dosage)	Control medication	Exposed period	Follow-up time	Measurements	Results
Spear 1980	rats/SD	Hal 0.25mg/kg/cc in water	Distilled water	G1 - PND21	54 days	Open field test, open field hole-poking, response to amphetamine and haloperidol	Increased locomotor activity, hole-poking and response to amphetamine. Accentuated response to haloperidol in early life and young adulthood but not in adolescence.
Umemura 1983	rats/SD	Cpz 2 or 8 mg/kg/day s.c.	Saline	G17 - PND21	15 weeks	Spontaneous motor activity (magnatic field activity counter) and light-dark discrimination learning test	No difference in spontaneous activity. Impairment of reversal learning.
Hull 1984	rats/LE	Hal 2.5mg/kg/d i.p.	Saline i.p. (4 groups with Hal and saline pre- and postnatally)	G7- PND21	79 days	Open field test, eye opening, haloperidol-induced catalepsy	No difference in open field ambulation, eye opening or haloperidol-induced catalepsy.
Szkilnik 1987	rats/W	Cpz 1 or 5mg/kg/d s.c.	Saline 1ml/kg/day s.c.	G1 – PND21	3 months	Lats' test, open field test, hole test, chlorpromazine-induced catalepsy, conditional avoidance learning	No difference in Lats' test. Lower number of trespassings and lookings outside. Increased excitability. Fewer dippings in hole test. Increased catalepsy. No difference in conditional avoidance learning.
Bruses 1989	rats/SD	Hal 2.5mg/kg/day i.p.	Saline 200µl i.p.	G5 – G20	38 days	Surface righting reflex, negative stereotaxis test, T-maze spatial learning, circling training	Delayed surface righting reflex, fewer turns on circling training, no difference in T-maze spatial learning test.

Table 2. (Continued)

Author (year)	Species/ strain	Experimental medication (dosage)	Control medication	Exposed period	Follow-up time	Measurements	Results
Scalzo 1989	rats/SD	Hal 2,5 or 5 mg/kg/ day s.c.	Vehicle	G6 - G20	62 days	Milk induced behavioural activation (day 6), SPWC (day 9,11,13,15,17), stimulant induced behavioral stereotypies (SIBS) (day 30), duration of barbiturate anesthesia (day 34, 62)	SPWC duration reduced on day 9+11 but not later. Reduced total anesthesia duration at day 62 in 5mg group. No difference in milk induced behavior or SIBS.
Myslivecek 1991	rats/W	Cpz 2.5mg/kg/day Inj	Saline Inj	G15, 18, 20	4 months	Eye opening, righting reflexes, hanging, passive avoidance learning paradigms (neonatal, 2 months, 4 months)	No difference in eye opening. Delayed righting reflexes. Impaired hanging. Impaired passive avoidance learning.
Archer 1992	rats/n.r.	Hal 2.5 µmol/kg/ day by gavage	Vehicle	G6 – G21	25 days	Radial arm maze and circular swim maze. Response to low dose d-amphetamine	Increased locomotion, rearing, and total activity. Rearing behavior reduced 90 min after d-amphetamine, potentiation after 120 min. Potentiation of stimulatory effect of d-amphetamine on locomotion. Retardation of spatial learning.
Williams 1992	rats/SD	Hal 5 mg/kg/d s.c.	Vehicle	G6 – G20	100 days	Brain weight	Decreased brain weight

Table 2. (Continued)

Author (year)	Species/ strain	Experimental medication (dosage)	Control medication	Exposed period	Follow-up time	Measurements	Results
Singh 1997	rats/CF	Hal 0.1 mg/kg/day i.p.	Vehicle	G13 - G20	7-8 weeks	Open field test, tunnel-entry test, elevated zero maze test, elevated plus-maze test	Increased ambulation and rearing. Decreased scratching, licking and washing behavior in open field. Tunnel: decreased time in centre of cage. Zero-maze: less time in open arms. Plus maze: fewer entries and less time in open arms.
Singh 1998	rats/n.r.	Hal 0.1mg/kg/d i.p.	Vehicle	G13 - G21	8 weeks	Foot shock induced aggressive behaviour test	Increased number of fighting bouts. No difference in fighting latency.
Rosengarten 2002	rats/SD	Hal 2mg Qtp 10mg Olz 2mg Ris 1mg /kg/day in water	Vehicle	G8 - G18	2 months	Radial arm maze: spatial learning and short term retention	Hal,Ris,Qtp: impaired spatial learning, Hal, Ris: impaired short-term retention, Olz: no differences in spatial learning or short-term retention.
Singh 2002	rats/CF	Hal 2.5mg/kg/day i.p.	Vehicle	G12 - G20	56 days	Open field test, elevated plus-maze test, zero-maze test (anxiety patterns)	Increased ambulation, rearing and defecation. Plus-maze: fewer entries and less time in open arms, more entries and time in closed arms. Zero-maze: fewer head dips and stretch attend postures.
Wolansky 2004	rats/SD	Hal 2.5 mg/kg i.p.	Vehicle	G5 - G18	90 days	Circling training test	Decreased circling activity, but effect disappeared when exposure was continued during lactation.

Table 2. (Continued)

Author (year)	Species/ strain	Experimental medication (dosage)	Control medication	Exposed period	Follow-up time	Measurements	Results
Zuo 2007	rats/SD	Ris 2mg/kg, Sul 200mg/kg in water	Saline in drinking water	G6 - G18	60 days	Righting reflex, Open field test, Morris water maze	Ris: increased rearing. No difference in water maze tests or righting reflex. Sul: impaired cue response in visual task performance (Morris water maze). Reduction in spontaneous activity. No difference in righting reflex.
Singh 2015	rats/W	Qtp 55 or 80 mg/kg/ day orally	Vehicle	G6 - G21	70 days	Morris water maze; passive avoidance learning task	Impaired (dose-dependent) spatial learning. Impaired retention capability.
Singh 2016	rats/W	Ris 0.8mg/kg/day; 1.0mg/kg/day; 2.0mg/kg/day in water	Saline	G6 – G21	10 weeks	Open field test, elevated plus-maze, brain weight	Increased ambulation and rearing. Anxiety like exploratory behavior. Dose dependent reduction in brain weight.

SD Sprague–Dawley, *W* Wistar, *CF* Charles–Foster, *LE* Long–Evans, *CR* Charles–River, *n.r.* not reported, *Cpz* Chlorpromazine, *Hal* haloperidol, *Ris* Risperidone, *Qtp* Quetiapine, *Sul* Sulpiride, *Olz* Olanzapine, *SIBS* stimulant induced behavioral stereotypes, *s.c.* subcutaneous, *i.p.* intraperitoneal, *G* gestation day, *PND* postnatal day, *Inj* injection, *SPWC* shock precipitated wall climbing

Table 3. Characteristics of clinical studies on neurodevelopmental outcome after intrauterine exposure to lithium

Author (year)	Study design	Sample size	Lithium daily dosage	Treatment indication	Follow-up time	Measurements	Results	NOS
Schou 1976	Prospective cohort study	Exposed = 60 Controls = 57	n.r.	n.r.	Mean: 7 years	Developmental questionnaire[a]	No difference in rate of abnormal development.	7
Jacobson 1992	Prospective cohort study	Exposed = 22 Controls = n.r.	Mean: 927mg	Major affective disorders	Mean: 61 weeks, range: 1-9 years	Telephone interview on the attainment of developmental milestones	No difference.	3
vd Lugt 2012	Cohort study	Exposed = 15 No controls	n.r.	Bipolar disorder	3-15 years	- Development questionnaire[a] - IQ by BSID or WPPSI/WISC - Hempel or Touwen neurological examination - Child Behavior Checklist*	- MND (n=1). - Low V-IQ + T-IQ normal P-IQ (n=1). - Subclinical anxiety problems (n=2). - Subclinical oppositional problems (n=1).	6

n.r. not reported, *BSID* Bayley Scale of Infant Development, *WPPSI* Wechsler Preschool and Primary Scale of Intelligence, *WISC* Wechsler Intelligence Scale for Children, *MND* minor neurologic dysfunction; NOS: Newcastle–Ottawa Scale

[a]parent report

Table 4. Characteristics of clinical studies on neurodevelopmental outcome after intrauterine exposure to antipsychotics

Author (year)	Study design	Sample size	Medication (daily dosage)	Treatment indication	Follow-up time	Measurements	Results	NOS
Slone 1977	Prospective cohort study	Exposed = 2141 Controls = 26.217	Phenothiazine antipsychotics (n.r.)	n.r.	4 years	IQ scores	No difference.	5
Platt 1989	Prospective cohort study	Exposed = 192 D+Med- = 116	Antipsychotic neuroleptics (n.r.)	Psychotic neurotic disorders	7 years	Motor development in newborn period, at 8 months, 4 and 7 years	Newborn: increased abnormal motor activity; 8 months: trend towards more failures on BSID (not sign.).	6
Stika 1990	Cohort study	Exposed = 66 Controls = 66	Chlorpromazine (10-25mg) or chlorprotixene (5mg)	n.r.	10 years	Teacher questionnaire	No difference in behavioural score.	5
Auerbach 1992	Cohort study	Exposed = 14 Controls = 26 D+Med- = 18	Phenothiazine antipsychotics (varied)	SMI	14 days	NBAS at day 3 and day 14	Reduced autonomic stability and higher abstinence score.	8
Mortensen 2003	Register study	Exposed = 63 Controls = 755	Neuroleptics (n.r.)	n.r.	7-10 months	Boel test	Adjusted OR abnormal Boel test in exposed children = 4.1 (95% CI: 1.3–13.0).	7
Johnson 2012	Prospective cohort study	Exposed = 21 Controls = 78 ADD exposed = 183	Antipsychotics combined (n.r.)	Anxiety and Mood Disorders	6 months	INFANIB	Lower INFANIB scores after exposure to antipsychotics.	7
Peng 2013	Prospective cohort study	Exposed = 76 Controls = 76	33 Clz (178mg), 16 Ris (2mg), 13 Sul (461mg), 8 Olz (8mg), 6 Qtp (550mg)	Schizophrenia	12 months	BSID at 2, 6, 12 months	2months: lower on cognitive, motor, social-emotional and adaptive behavior scale, 6months: lower on social-emotional and adaptive behavior scale, 12months: no difference.	7

Table 4. (Continued)

Author (year)	Study design	Sample size	Medication (daily dosage)	Treatment indication	Follow-up time	Measurements	Results	NOS
Shao 2015[a]	Post-hoc analysis (Peng 2013)	Exposed = 63	33 Clz (178mg), 30 other AP (16 Ris (2mg), 8 Olz (8mg), 6 Qtp (550mg))	Schizophrenia	12 months	BSID at 2, 6, 12 months	2 and 6 months: lower adaptive behavior scores for Clz exposed children compared to other AP, 12 months: no difference.	
Hurault-Delarue 2016	Register study	Exposed = 70 Controls = 32.303	Neuroleptics (n.r.)	n.r.	24 months	Pediatric examination	9 months: higher prevalence of motor deficits, no difference in mental development, 24 months: no difference.	7
Petersen 2016	Register study	Exposed = 290 Controls = 210.966 D+Med- = 492	Antipsychotics (n.r.)	SMI	9 months to 5 years	NDBD reported in health record	No difference in relative risk of NDBD after adjustment for confounders (RRR 1.22 (95% CI: 0.80 to 1.84)).	8

n.r. not reported; *D+ Med−* control group of women with comparable treatment indication but no medication use during pregnancy, *SMI* severe mental illness, *NDBD* neurodevelopment disorders and behavioural disorders, *BSID* Bayley Scale of Infant and Toddler Development, *ADD* antidepressant drugs, *INFANIB* infant neurological international battery, *NBAS* Neonatal Brazelton Assessment Scale, *Clz* clozapine, *Ris* risperidone, *Sul* sulpride, *Qtp* quetiapine, *AP* antipsychotics, *OR* odds ratio, *RRR* relative risk ratio, *NOS* Newcastle–Ottawa scale

[a]post hoc analysis on subsample of cohort study by Peng 2013

Of the 73 studies included in the qualitative analysis, 29 were preclinical investigations of which seven examined lithium exposure and 22 examined antipsychotics exposure. Most preclinical studies were performed in rats, some in mice and one study on lithium exposure used zebrafish. There is a large variety of the measurements used to assess neurodevelopment in animal models (Table 1,2). The exposed period was generally during gestation, although several studies also investigated the effect of exposure during lactation. Postnatal brain development in rodents up to postnatal day 10 is considered analogous to prenatal brain development in humans(28).

In total, we found thirteen clinical cohort studies of which three involved lithium exposure and ten involved antipsychotics exposure (Table 3,4). Study samples varied from 14 to 2141 exposed subjects. Mean follow-up duration ranged from 1 to 15 years in studies involving lithium exposure and from 14 days to 5 years in studies involving antipsychotic exposure. Assessment of neurodevelopment varied between cohort studies. Out of the three clinical studies involving lithium exposure, one used standardized assessments while the other two relied on an unvalidated questionnaire or telephone interview. Most studies involving antipsychotic exposure used standardized objective assessments, but some studies relied solely on invalidated questionnaires or interview. Additionally, 31 case studies were included, of which 5 involved intrauterine lithium exposure and 26 involved intrauterine antipsychotics exposure (Supplement 2).

Lithium

Preclinical investigations

Sechzer et al. investigated the long-term developmental consequences of prenatal and early postnatal lithium exposure in rats (29). Female rats were treated with lithium during pregnancy and lactation. Development of the startle response and depth perception in the offspring were delayed. At the age of 4 months, pups exhibited lower spontaneous activity during open field activity testing. A similar study investigated the neurodevelopmental effect of lithium exposure from day 1 of pregnancy until postnatal day 15 (30). Decreased locomotor activity and delayed development of sensory motor reflexes were observed in lithium-exposed mice. Whether these developmental delays were caused by prenatal or early postnatal exposure to lithium could not be determined. Nery et al. studied the behavioural effects of lithium exposure on the development of zebrafish embryos and reported decreased locomotion compared to non-exposed embryos (31). Additionally, several studies have replicated a delay in eye opening (29, 30, 32) and decreased avoidance behaviour (32, 33) in mice and rats exposed to lithium during gestation and/or lactation. One study found impaired performance on the T-maze test (33). Messiha et al. found lower brain weights in lithium exposed offspring at the age of 37 days (34). No changes in social, defensive, threatening or aggressive behaviour was observed in lithium-exposed mice (35).

In summary, preclinical studies suggest a deleterious effect of lithium on motor activity, developmental milestones and reflexes, spatial memory and brain weight.

Clinical investigations

Neurodevelopment of 97 children with in utero exposure to lithium has been investigated in clinical cohort studies. Overall, most children were reported to have typical neurodevelopmental trajectories. Schou analysed data from the Scandinavian Register of Lithium Babies to compare neurodevelopmental outcomes in lithium-exposed children (n=60) with their non-exposed siblings (n=57) (average age, 7 years) (36). Outcomes were assessed by questionnaire and based solely on mothers' subjective retrospective assessment of their children's developmental milestones. No significant differences were observed between the lithium-exposed children and their siblings.

In a prospective multicenter study, major developmental milestones were examined between a sample of 22 lithium-exposed children with non-exposed children (37). Subjects were screened for study inclusion from among mothers who contacted the public teratogen information services to discuss the potential risks of prescription medication use during pregnancy. Data was collected by telephone interview. No differences were observed between lithium-exposed versus non-exposed children in the age at which they achieved major developmental milestones.

In an observational cohort study, 15 lithium-exposed children between 3 and 15 years old were investigated (38). Standardized validated tests were used to assess growth, neurological, cognitive and behavioural outcomes. When compared to norms from the general population, most lithium-exposed children scored lower on the Block patterns subtest of the Wechsler Intelligence Scale for Children (WISC-III-NL). In contrast, no differences in growth or behavioural outcomes were observed. One child in this study exhibited subclinical neurological findings. Importantly however, the conclusiveness of this study was hampered by the lack of a matched non-exposed control group ascertained in parallel with the lithium-exposed group, but rather relied upon an independently collected general population cohort dataset.

In summary, there is a paucity of clinical data on the neurodevelopment of children with in utero exposure to lithium. The three clinical studies published in the literature report normal neurodevelopment.

Case reports

Neurodevelopmental delay after intrauterine exposure to lithium was reported in four case studies, encompassing a total of 8 children (39-42). Kozma et al. reported on a neonate with neurodevelopmental deficits, including decreased muscle tone, depressed reflexes and diminished social response, during the 2.5 months after birth (43). However by 13 months of age, no deficits were observed using the Bayley Scale of Infant Development.

Morrel et al. described a case of lithium toxicity at 35 weeks of gestation (lithium blood level: 2.6 mmol/L) (40). The baby was born with primary cardiac muscle dysfunction and treated with isoprenaline at birth. At 12 months of age, cardiac function had normalized but there was evidence of delayed motor development and a concomitant strabismus. Delayed gross motor function was also reported in two cases with prenatal lithium exposure that did not involve lithium intoxication (41, 42). One case report reported normal psychomotor development (44).

Antipsychotics

Preclinical investigations

Eleven studies have investigated the long-term neurodevelopmental consequences of prenatal haloperidol exposure in rats. Emergence of the surface righting reflex was found to be delayed (45). Two studies found deficits in a circling training test (45, 46), a measure of motor performance and associative learning. Impairments in spatial learning were also found (45, 47, 48) using the Morris water maze, T-maze and radial arm maze. Moreover, the open field test revealed increased rearing, ambulation and general activity (47, 49-51). One study reported finding no difference in ambulation on the open field test (52). Notably, since behaviour in the open field test is influenced not only by locomotor activity, but also by anxiety and exploratory behaviour (53), additional studies have been performed to further differentiate these phenotypes. Indeed, consistent with an increase in anxiety, rats made fewer entries and spent less time in open arms during elevated zero and plus-maze tests (49, 51). Moreover, aggressive behaviour was also increased (54). Duration of shock-precipitated wall climbing was reduced on postnatal days 9 and 11, and there were no differences in stimulant induced behavioural stereotypies (55). Lastly, from a neuroanatomical perspective, rats with intrauterine exposure to haloperidol exhibited significantly lower brain weight in adulthood (56).

Eight studies have investigated the long-term neurodevelopmental effects of intrauterine exposure to chlorpromazine in rats. One study systematically investigated the onset of neurodevelopmental milestones (57). They found no difference in onset of eye opening, but emergence of the righting reflex was delayed. Studies investigating motor development found both increases (58) and decreases (59) in wheel running activity and impairments in a hanging task (57). In the open field test, latency time was decreased (59, 60) and locomotor activity was increased (60, 61). Similarly, spontaneous activity was normal in one study (62), but decreased in another (63). Spatial memory was found to be impaired in a mother-goal maze task, whereas no differences were found in a T-maze task (61). Studies focusing on other types of learning have reported impaired avoidance conditioning (57, 59), reversal learning (62) and operant conditioning (61). Avoidance conditioning was observed to be normal (64). A study investigating exploratory behaviour found that rats made fewer hole dippings (64). Hoffeld et al. did not find changes in emotionality testing (58). Susceptibility to

audiogenic seizures was increased (63). Brain weights did not differ between chlorpromazine and placebo exposed groups (60).

Several other antipsychotics were examined for neurodevelopmental effects. Rosengarten et al. (65) investigated the possible sequelae of intrauterine exposure to quetiapine, risperidone or olanzapine and found impaired spatial learning in a radial arm maze task for both risperidone and quetiapine, and disrupted short-term retention for quetiapine. Intrauterine exposure to olanzapine did not affect learning or retention. A recently published study also found impaired spatial learning and retention capability in rats with prenatal exposure to quetiapine (66). Two studies investigated the effects of risperidone exposure during gestation. Singh et al. reported increased ambulation and rearing in the open field test, and increased anxiety-like exploratory behavior in the elevated plus maze test (67). Intrauterine exposure to risperidone led to a dose-dependent reduction of adult brain weight. Zuo et al. also found increased ambulation (68), while righting reflexes and spatial memory were normal. In the same study, rats with prenatal exposure to sulpiride exhibited an impaired cue response in a visual task performance and reduced spontaneous activity, while righting reflexes and spatial memory were normal.

In summary, most preclinical studies found a deleterious effect of antipsychotics on motor activity, developmental milestones and reflexes and spatial memory. Additionally, exposure to either haloperidol or risperidone led to decreased brain weight.

Clinical investigations

In total, neurodevelopmental data of 2934 children with *in utero* exposure to antipsychotics have been published involving nine clinical cohort studies. Six studies reported neurodevelopmental delays or deficits after prenatal exposure to antipsychotics (69-74), while three studies reported normal developmental outcomes (75-77). Most studies reported antipsychotic exposure on the basis of a single broad category, which combined a wide variety of antipsychotics. The initial report of abnormalities of motor development in children with intrauterine exposure to antipsychotic was authored by Platt in a cohort of 192 children exposed to antipsychotic neuroleptics and 116 children of women with a history of psychiatric disorders described as psychotic/neurotic but without antipsychotic treatment. Notably, deficits at the neonatal assessment of motor activity were more severe than at 8 months of age, when there was a non-significant trend towards more failures based on the Bayley gross motor assessment (73). Another study examined 21 children with prenatal antipsychotic exposure, 183 children with prenatal antidepressant exposure and 78 non-exposed children at six months of age (78). Children with prenatal exposure to antipsychotics had lower scores on the Infant Neurological International Battery (INFANIB) compared to children with prenatal antidepressant exposure or non-exposed children. Comparable results were found in a recent register-based study in France (74). Psychomotor development, assessed by pediatric examination, was compared between 70 children with

prenatal neuroleptic exposure and 32.303 non-exposed controls. A higher prevalence of motor deficits was reported in exposed children at 9 months of age, a difference that was no longer present at 24 months of age. No differences in cognitive development were observed. A Danish general population register-based study reported an association between drug prescriptions during pregnancy and results on the Boel test, a psychomotor development test assessed at 7-10 months of age (71). Specifically, the odds ratio for an abnormal Boel test was 4.1 (95% CI: 1.3–13.0) among children with intrauterine exposure to neuroleptic medication after adjustment for several confounders including gestational age, birth weight and breastfeeding. In contrast, Stika et al. reported finding no discernible adverse behavioural outcomes based on evaluations made by their classroom teachers in 10-year-old children with prenatal neuroleptic exposure (76).

Using data from two large electronic primary care databases in the UK, Petersen et al. investigated the risks and benefits of psychotropic medication during pregnancy. They compared the prevalence of neurodevelopmental and behavioural disorders in children with prenatal exposure to antipsychotics, children with no antipsychotic exposure whose mothers discontinued antipsychotic treatment before pregnancy and non-exposed children whose mother was not prescribed antipsychotic treatment in the 24 months before pregnancy. They found an increased risk of neurodevelopmental and behavioural disorders in children exposed to antipsychotics with a relative risk ratio (RRR) of 1.58 (95% CI 1.04-2.40). However after adjustment for possible confounders, these differences were no longer statistically significant (RRR 1.22, 95% CI 0.80-1.84) (75). An earlier study, focused specifically on phenothiazine antipsychotics, similarly reported no difference in intelligence quotient scores among 4 year-old children, of which 2141 had prenatal exposure and 26 217 were non-exposed (77). Notably however, a higher burden of neonatal withdrawal symptoms and autonomic instability was reported 14 days after birth in neonates with intrauterine exposure to phenothiazine antipsychotics (69).

More recent studies have also focused on the long-term developmental consequences of intrauterine exposure to atypical antipsychotics. Peng et al. prospectively investigated 76 children with intrauterine exposure to atypical antipsychotics and 76 non-exposed controls, from birth until 12 months of age (79). Neurobehavioural development was assessed by the Bayley Scales of Infant and Toddler Development (BSID) at 2, 6 and 12 months of age. At 2 months of age, antipsychotic-exposed children exhibited significantly lower scores regarding cognitive, motor, social-emotional, and adaptive behavioural functioning. At 6 months of age, scores regarding social-emotional and adaptive behavioural functioning were still lower, but not significantly different between groups in cognitive or motor scores. In contrast, by 12 months of age none of these effects persisted. A post-hoc analysis revealed that children prenatally exposed to clozapine had lower scores on the BSID adaptive behavior scale at the ages of 2 and 6 months compared to children exposed to other atypical antipsychotics (80). However, this difference was also no longer present at 12 months of age.

Although studies varied in measurements and follow-up time, five cohort studies (70, 71, 74, 81-83) investigated motor development of children with *in utero* exposure to antipsychotics. These studies consistently showed a deficit in motor functioning in the first 9 months of life, but which appeared to spontaneously resolve based on subsequent follow-up assessments.

Case reports

Overall, case studies on intrauterine exposure to first generation antipsychotics have largely reported normal neurodevelopment (84-91). Additionally, although most case studies involving prenatal exposure to second generation antipsychotics have also reported normal infant and child development (84, 91-104), several case reports have found neurodevelopmental delays or deficits. Two cases reported speech delay, one involving risperidone and the other clozapine (105, 106). One case reported abnormal behavioral development following prenatal exposure to risperidone and ziprasidone (106). Impaired motor development has been reported following exposure to olanzapine, clozapine or risperidone (107-109).

Risk of bias and quality of the included studies

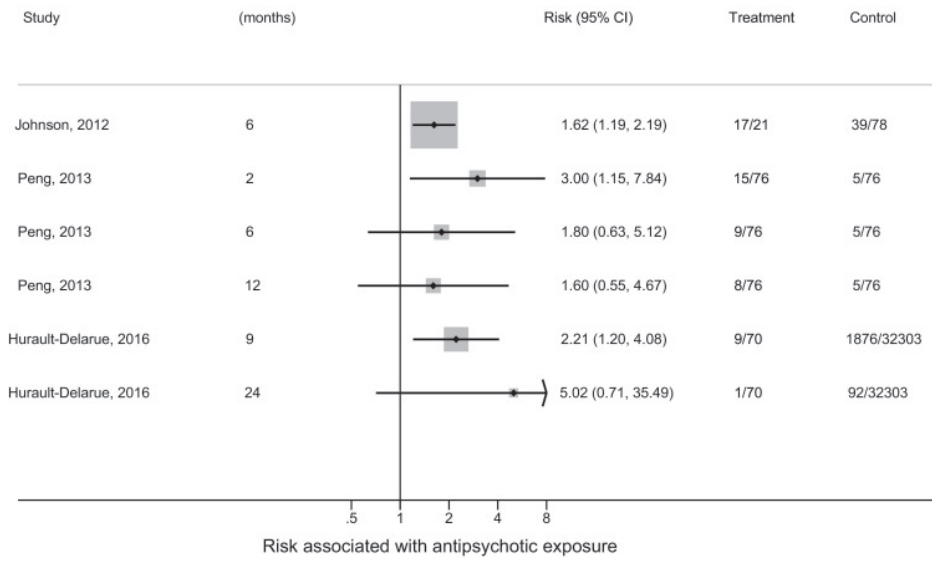
The risk of bias for the included preclinical studies is presented in the Supplementary Material (Supplement 3). Notably, many lack descriptions of the assessed domains, thereby making the risk of bias unclear (e.g., selection bias, performance bias, detection bias or attrition bias). In 34% of the preclinical studies, cross-fostering after birth was applied in order to control for medication-induced changes in maternal care.

NOS scores of clinical cohort studies varied between three and eight points (Table 3 and 4). Only three cohort studies properly controlled for maternal mental illness, widely considered the most important confounder in studies of intrauterine exposure to prescription psychotropic medication. In the other studies, neurodevelopment was compared between children with prenatal exposure to lithium or antipsychotics versus unaffected children, thereby leaving unaddressed the risk of confounding by indication. Moreover, few clinical studies controlled for additional confounders such as maternal age, congenital malformations, preterm birth, or smoking and alcohol use during pregnancy, often because information on these factors was not available. In most studies of antipsychotic exposure, developmental assessments were standardized and validated, although some studies based their results on non-validated questionnaires or information obtained exclusively from medical records. The quality of the included studies on lithium exposure is poor, as only one cohort study used validated measurements of neurodevelopment. Unfortunately, this study did not compare their findings with a formal control group. Regarding case studies, their quality is generally considered low with a high risk of publication bias. Indeed, most case studies did not assess neurodevelopment using validated objective measures.

Meta-analysis

Three out of five studies that investigated neuromotor deficits in children with *in utero* exposure to antipsychotics provided sufficient data and were included in a meta-analysis (70, 72, 74). Figure 2 shows the relative risk of neuromotor deficits for antipsychotic exposure for all reported follow-up assessments (6 effect sizes). Pooled relative risk calculated using fixed effect estimation was 1.97 (95%CI 1.47-2.62; *Z* value: 4.59, P<0.001) with absence of heterogeneity (I^2:0%, p=0.622). Since studies reported multiple follow-up outcomes, this pooled estimate should be interpreted with care.

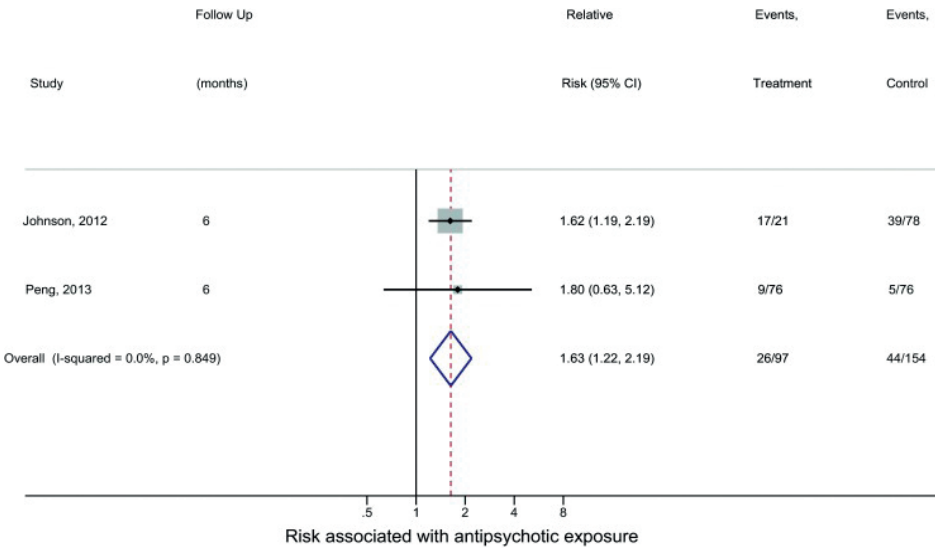
Fig. 2. Relative risk estimates including the 95% confidence interval limits of neuromotor deficits for antipsychotic exposure for all reported follow-up assessments



Two studies (70, 72) reported follow-up outcomes at 6 months. The pooled relative risk was 1.63 (95% CI 1.22–2.19; *Z* value = 3.29; p=0.001, fixed effect) with absence of heterogeneity (I^2 = 0%, p=0.849), indicating a 63% increased risk for neuromotor deficits at 6 months (Fig. 3).

Next we performed a random effects meta-regression analysis to study the longitudinal influence of intrauterine exposure to antipsychotics on motor development. For each study, we included the initial follow-up assessment. The direction of the regression coefficient suggested a decrease of the impact of intrauterine exposure to antipsychotics on neuromotor deficits over time. However, there was no statistically significant effect (-0.03; 95% CI -1.26 to 1.20; p= 0.80). Residual heterogeneity was substantial (I^2=49%). In conclusion, in this meta-analysis we were able to partially confirm the negative effect of antipsychotic exposure on motor development. However, we were not able to confirm the transient nature of the neuromotor deficits.

Fig. 3. Relative risk estimates including the 95% confidence interval of neuromotor deficits for antipsychotic exposure at 6 months of follow-up. The pooled relative risk was estimated using a fixed-effects estimation



DISCUSSION

In this systematic review article and meta-analysis, we present an overview of the current literature regarding long-term neurodevelopmental effects of lithium and antipsychotics. Towards this goal, we included both preclinical and clinical studies. Preclinical studies have the potential to investigate the effect of medication exposure using more optimal study designs in which important biases in clinical studies, such as confounding by indication, can be directly addressed. Notably, although preclinical findings may not always be translatable into clinical practice, they have the potential to provide mechanistic insights and reveal indications of possible risks in situations for which well-controlled high-quality clinical studies are lacking. Undoubtedly however, disproportionate weight should be given to evidence discerned from relevant clinical studies when helping women to consider the risks and benefits of their perinatal treatment options.

Overall, findings from preclinical studies suggest a deleterious effect of lithium on locomotor activity and delayed development of eye opening and righting reflexes. Additionally, brain weight was found to be lower in lithium-exposed offspring. Clinical studies of offspring neurodevelopment after intrauterine exposure to lithium generally reported normal development. However, two out of the three studies based their results exclusively on retrospective maternal reports, while the third study lacked a formal control group. The lack of clinical studies on the risks of lithium use during pregnancy might be due

to the fact that lithium is a naturally occurring element that was never patented. Another explanation for the knowledge gap on long-term neurodevelopmental effects of lithium exposure might be the (earlier recognized) association with cardiac malformations. This association was first reported in the 1970's by Schou et al. and a recent study by Patorno et al. confirmed this association although the authors report that the risk was lower than previously suggested (10, 110). These findings have influenced treatment guidelines in the United Stated and the United Kingdom, where lithium use during pregnancy is discouraged (111, 112), and possibly also influenced research to focus on congenital malformations rather than on neurodevelopment.

Despite the many differences in methodology, preclinical studies consistently reported adverse neurodevelopmental and behavioural effects of prenatal exposure to antipsychotics. Antipsychotics seem to increase locomotor activity and anxiety, as well as impair cognition, in exposed offspring. Lastly, and of important consideration for clinical translational potential, brain weight was found to be lower in offspring with intrauterine exposure to haloperidol and risperidone. Most studies of antipsychotics involved haloperidol and chlorpromazine, while a much smaller number focused on varied atypical antipsychotics. At present, there is insufficient evidence to conclude whether the neurodevelopmental impact of prenatal exposure to antipsychotics is dependent upon the specific type or class. Findings from clinical studies of antipsychotic exposure are inconsistent and difficult to interpret due to the considerable differences in methodology and follow-up period. Several studies reported a delay in neurodevelopment among infants with intrauterine exposure to antipsychotics. However, these early neurodevelopmental delays were frequently transient, having resolved on subsequent longitudinal follow-up assessments. The most consistent finding was a transient delay in motor development. This was confirmed in our meta-analysis with a relative risk of 1.36 for neuromotor deficits after in utero exposure to antipsychotics at 6 months of follow-up. However, this estimate was based on only two studies. More studies are needed to provide a more robust estimate and to study the course of motor development over time. Most studies had a follow-up period of less than two years, for which later-onset neurodevelopmental sequelae cannot be excluded. Based on the currently available reports, no distinction between the various types of antipsychotics can be made as most studies combined different types and classes of antipsychotics into a single broad category, presumably to increase statistical power.

Clinical findings might have been affected by confounding by indication, since most studies compared exposed children to non-exposed children of mothers with no history of psychiatric illness. Therefore, studies have not been able to adequately adjust for genetic predisposition, psychiatric illness during pregnancy, or parenting, all of which would be expected to independently influence child development (113-115). Regardless of medication exposure, offspring of patients with schizophrenia and bipolar disorder have an increased risk to develop any mental illness (116) and experience more cognitive impairments (117-

119). A recent study found impairment of motor function among children with a familial risk of schizophrenia (120). Additionally, studies using structural MRI have reported decreased white and gray matter volume in offspring of parents with bipolar disorder or schizophrenia (121-124). It is therefore of particular importance for future studies to compare psychotropic medication-exposed children to non-exposed children of mothers with similar psychopathology.

Our findings may have been influenced by publication bias, since studies without significant results are less likely to be published (125). This is particularly the case for preclinical studies. As a result, the rate and severity of neurodevelopmental deficits presented in this review might be an overestimation. However, the paucity of evidence regarding the long-term effects of intrauterine exposure to lithium or antipsychotics may also lead to a blunted motivation to invest in studies of the potential adverse neurodevelopmental consequences and consequent underreporting of associations. Undoubtedly more studies of higher quality will be required in order to address these questions with greater certainty.

Our results show a discrepancy between findings from preclinical and clinical studies, with preclinical studies reporting more discernible neurodevelopmental deficits. As mentioned above, publication bias might be part of the explanation. In addition, many preclinical studies used high dosages of medications, exceeding 80% occupancy of the D2-receptor causing more side-effects (126). Lastly, species differences cannot be disregarded as a potential source of discrepancy between pharmacological studies in animals and humans.

High quality clinical studies will be required in order to properly assess the risk of adverse neurodevelopmental effects of intrauterine exposure to lithium and antipsychotics. Randomized controlled trials are often considered the best approach to studying causal inference. However, there is broad consensus that randomized assignment for the purpose of studying medication side effects is unethical (127). Furthermore, placebo-controlled randomization of women with mental health indications for lithium or antipsychotics is also considered unethical when treatment is medically indicated, but also regarding exposure of the fetus when treatment is not medically indicated. Future studies of neurodevelopmental outcome in children with intrauterine exposure to psychotropic medication will therefore have to continue to rely upon clinical cohort studies, for which non-randomized designs can be well suited for studying unintended pharmacological effects (128). However, cohort studies should ideally have a prospective design with extended follow-up periods utilizing validated standardized neurodevelopmental outcome measures. Moreover, in an effort to reduce confounding by indication, the primary comparison group for exposed children should involve non-exposed children of mothers with similar psychopathology. Since it is unlikely that medicated and non-medicated pregnant women have the same disease severity, cohort studies should also consider designs in which pregnant women treated

with lithium or antipsychotics are compared to pregnant women with the same psychiatric disorder but other pharmacological treatments.

The decision for pharmacological treatment during pregnancy should always be decided through a patient-centered discussion with their healthcare provider by carefully weighing the risks and benefits of various treatment options and by developing an individualised treatment plan.

CONCLUSION

Prenatal exposure to lithium or antipsychotics has an adverse effect on neurodevelopment and behaviour in mice and rats, but the precise mechanisms remain unclear. In humans, the existence and nature of any effects remains poorly determined. At present, there is insufficient evidence to estimate the neurodevelopmental effects of intrauterine exposure to lithium. Although several studies have reported a transient neurodevelopmental delay following intrauterine exposure to antipsychotics, the current lack of high quality clinical investigations substantially limits the conclusiveness of the available evidence. In particular, improved clinical studies will require prospective designs with longer follow-up periods and more extensive assessments including validated measures of child development, in order to offer more substantiated evidence-based advice to women with bipolar disorder or psychotic disorders regarding the risks and benefits of pharmacotherapy during pregnancy.

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SUPPLEMENTARY MATERIALS

Supplementary Material 1. Search terms per database:

Embase.com

(lithium/exp OR 'lithium acetate'/exp OR 'lithium carbonate'/exp OR 'lithium chloride'/exp OR 'lithium citrate'/exp OR 'lithium derivative'/exp OR 'lithium fluoride'/exp OR 'lithium gluconate'/exp OR 'lithium hydroxybutyrate'/exp OR 'lithium salt'/exp OR 'lithium sulfate'/exp OR 'neuroleptic agent'/exp OR psychosis/exp/dm_dt OR 'bipolar disorder'/exp/dm_dt OR (lithium* OR carbolit* OR lithane* OR lithonate* OR lithionate* OR antipsychot* OR neuroleptic* OR (major NEXT/1 tranquilizer*) OR aripiprazole* OR bromperidol* OR Chlorpromazine* OR Clozapine* OR Flupenthixol* OR Fluphenazine* OR Haloperidol* OR olanzapine* OR Penfluridol* OR Perazine* OR Perphenazine* OR Pimozide* OR pipamperone* OR Promazine* OR quetiapine* OR Risperidone* OR Sulpiride* OR 'Tiapride Hydrochloride'):ab,ti) AND ('prenatal drug exposure'/exp OR 'prenatal exposure'/exp OR pregnancy/exp OR 'pregnant woman'/exp OR embryotoxicity/exp OR (((prenatal* OR intrauterine* OR maternal OR mother* OR fetal OR foetal OR intra-uterine OR in-utero OR embryo* OR offspring* OR gestation*) NEAR/6 (expos* OR use OR toxic* OR safet* OR medication* OR drug* OR antipsychotic* OR lithium)) OR pregnan* OR embryotoxic*):ab,ti) AND ('child development'/exp OR 'child behavior'/exp OR 'human development'/exp OR behavior/de OR 'animal behavior'/de OR 'adaptive behavior'/exp OR 'adjustment disorder'/exp OR 'adolescent behavior'/exp OR 'coping behavior'/exp OR emotion/exp OR cognition/de OR 'motor activity'/exp OR 'social behavior'/exp OR 'mental development'/exp OR 'behavior disorder'/de OR 'abnormal behavior'/exp OR 'disruptive behavior'/exp OR 'psychomotor disorder'/exp OR 'psychosocial disorder'/exp OR (development* OR neurodevelop* OR behav* OR psychomotor* OR psychosocial* OR emotion* OR fear* OR anxiet* OR well-being):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR 'pediatric nursing'/exp OR (adolescen* OR infan* OR baby OR babies OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

MEDLINE (Ovid)

(lithium/ OR exp "lithium carbonate"/ OR exp "lithium chloride"/ OR exp "lithium Compounds"/ OR exp "Antipsychotic Agents"/ OR exp "Psychotic Disorders"/dt OR "bipolar disorder"/dt OR (lithium* OR carbolit* OR lithane* OR lithonate* OR lithionate* OR antipsychot* OR neuroleptic* OR (major ADJ tranquilizer*) OR aripiprazole* OR bromperidol* OR Chlorpromazine* OR Clozapine* OR Flupenthixol* OR Fluphenazine* OR Haloperidol* OR olanzapine* OR Penfluridol* OR Perazine* OR Perphenazine* OR Pimozide* OR pipamperone* OR Promazine* OR quetiapine* OR Risperidone* OR Sulpiride* OR "Tiapride Hydrochloride"). ab,ti.) AND ("Prenatal Exposure Delayed Effects"/ OR exp "Maternal Exposure"/ OR exp pregnancy/ OR

"pregnant women"/ OR (((prenatal* OR intrauterine* OR maternal OR mother* OR fetal OR foetal OR intra-uterine OR in-utero OR embryo* OR offspring* OR gestation*) ADJ6 (expos* OR "use" OR toxic* OR safet* OR medication* OR drug* OR antipsychotic* OR lithium)) OR pregnan* OR embryotoxic*).ab,ti.) AND ("Growth and Development"/ OR exp "Human Development"/ OR exp "child behavior"/ OR exp "Child Behavior Disorders"/ OR behavior/ OR "Behavior, Animal"/ OR exp "adaptive behavior"/ OR "adolescent behavior"/ OR "Adaptation, Psychological"/ OR exp emotions/ OR "motor activity"/ OR exp "social behavior"/ OR exp "Social Behavior Disorders"/ OR exp "Neurobehavioral Manifestations"/ OR "Mental Disorders Diagnosed in Childhood"/ OR exp "psychomotor disorders"/ OR "Adjustment Disorders"/ OR (development* OR neurodevelop* OR behav* OR psychomotor* OR psychosocial* OR emotion* OR fear* OR anxiet* OR well-being).ab,ti.) AND (exp child/ OR exp infant/ OR adolescent/ OR exp pediatrics/ OR exp Child Health Services/ OR Hospitals, Pediatric/ OR (adolescen* OR infan* OR baby OR babies OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.)

PsycINFO (Ovid)

(lithium/ OR exp "lithium carbonate"/ OR exp "Neuroleptic Drugs"/ OR exp "Psychosis"/dt OR "bipolar disorder"/dt OR (lithium* OR carbolit* OR lithane* OR lithonate* OR lithionate* OR antipsychot* OR neuroleptic* OR (major ADJ tranquilizer*) OR aripiprazole* OR bromperidol* OR Chlorpromazine* OR Clozapine* OR Flupenthixol* OR Fluphenazine* OR Haloperidol* OR olanzapine* OR Penfluridol* OR Perazine* OR Perphenazine* OR Pimozide* OR pipamperone* OR Promazine* OR quetiapine* OR Risperidone* OR Sulpiride* OR "Tiapride Hydrochloride").ab,ti.) AND ("Prenatal Exposure"/ OR exp exp pregnancy/ OR (((prenatal* OR intrauterine* OR maternal OR mother* OR fetal OR foetal OR intra-uterine OR in-utero OR embryo* OR offspring* OR gestation*) ADJ6 (expos* OR "use" OR toxic* OR safet* OR medication* OR drug* OR antipsychotic* OR lithium)) OR pregnan* OR embryotoxic*).ab,ti.) AND ("Development"/ OR "Animal Development"/ OR exp "Delayed Development"/ OR exp "Human Development"/ OR exp "Psychological Development"/ OR exp "Behavior Problems"/ OR behavior/ OR "Adaptive Behavior"/ OR "Attachment Behavior"/ OR "Classroom Behavior"/ OR "Coping Behavior"/ OR exp "Exploratory Behavior"/ OR exp "Social Behavior"/ OR exp emotions/ OR exp "Motor Performance"/ OR "Behavior Disorders"/ OR exp "Psychomotor Development"/ OR "Adjustment Disorders"/ OR (development* OR neurodevelop* OR behav* OR psychomotor* OR psychosocial* OR emotion* OR fear* OR anxiet* OR well-being).ab,ti.) AND (140.ag. OR 160.ag. OR 180.ag. OR 200.ag. OR exp pediatrics/ OR exp Hospitals, Pediatric/ OR (adolescen* OR infan* OR baby OR babies OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.)

Cochrane

((lithium* OR carbolit* OR lithane* OR lithonate* OR lithionate* OR antipsychot* OR neuroleptic* OR (major NEXT/1 tranquilizer*) OR aripiprazole* OR bromperidol* OR Chlorpromazine* OR Clozapine*

OR Flupenthixol* OR Fluphenazine* OR Haloperidol* OR olanzapine* OR Penfluridol* OR Perazine* OR Perphenazine* OR Pimozide* OR pipamperone* OR Promazine* OR quetiapine* OR Risperidone* OR Sulpiride* OR 'Tiapride Hydrochloride'):ab,ti) AND ((((prenatal* OR intrauterine* OR maternal OR mother* OR fetal OR foetal OR intra-uterine OR in-utero OR embryo* OR offspring* OR gestation*) NEAR/6 (expos* OR use OR toxic* OR safet* OR medication* OR drug* OR antipsychotic* OR lithium)) OR pregnan* OR embryotoxic*):ab,ti) AND ((development* OR neurodevelop* OR behav* OR psychomotor* OR psychosocial* OR emotion* OR fear* OR anxiet* OR well-being):ab,ti) AND ((adolescen* OR infan* OR baby OR babies OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

Web of Science

TS=(((lithium* OR carbolit* OR lithane* OR lithonate* OR lithionate* OR antipsychot* OR neuroleptic* OR (major NEAR/1 tranquilizer*) OR aripiprazole* OR bromperidol* OR Chlorpromazine* OR Clozapine* OR Flupenthixol* OR Fluphenazine* OR Haloperidol* OR olanzapine* OR Penfluridol* OR Perazine* OR Perphenazine* OR Pimozide* OR pipamperone* OR Promazine* OR quetiapine* OR Risperidone* OR Sulpiride* OR "Tiapride Hydrochloride")) AND ((((prenatal* OR intrauterine* OR maternal OR mother* OR fetal OR foetal OR intra-uterine OR in-utero OR embryo* OR offspring* OR gestation*) NEAR/6 (expos* OR use OR toxic* OR safet* OR medication* OR drug* OR antipsychotic* OR lithium)) OR pregnan* OR embryotoxic*)) AND ((development* OR neurodevelop* OR behav* OR psychomotor* OR psychosocial* OR emotion* OR fear* OR anxiet* OR well-being)) AND ((adolescen* OR infan* OR baby OR babies OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*)))

Google Scholar

lithium|antipsychotic|antipsychotics|neuroleptic|neuroleptics
"prenatal|intrauterine|fetal|foetal|uterine|uteroexposure"
development|neurodevelopment|behavior|psychomotor|psychosocial|emotions|fear|anxiety
adolescent|infant|infants|child|children

Supplementary material 2

Table 1. Characteristics of case studies on the neurodevelopmental outcome after intrauterine exposure to lithium

Author (year)	Sample size	Medication (daily dosage)	Treatment indication	Follow-up time	Results
Morrel (1983)	1	Lithium (1200mg) + chlorpromazine (50mg)	Bipolar disorder	1 year	Delayed motor development and a concomitant squint.
Frassetto (2002)	1	Lithium, Cyamemazine, Olanzapine, Venlafaxine (n.r.)	Bipolar disorder	3.5 months	Normal psychomotor development.
Kozma (2005)	1	Lithium (900-1350mg)	Bipolar disorder	13 months	At 3 weeks: hypotonic, decreased neonatal reflexes, decreased social interaction. At 13 months: normal scores on the BSID, slightly decreased muscle tone.
Burt (2010)	1	Lithium (1125-1350mg), Olanzapine (10-20mg), Fluoxetine (40-60mg)	Bipolar disorder	29 months	Delay of gross motor development up to the age of 29 months.
Bogen (2012)	4	Lithium (varied)	Bipolar disorder	4 months – 1 year	One child with gross and fine motor delay in the first year.

n.r. not reported, *BSID* Bayley Scale of Infant Development

Table 2. Characteristics of case studies on the neurodevelopmental outcome after intrauterine exposure to antipsychotics

Author (year)	Sample size	Medication (daily dosage)	Treatment indication	Follow-up time	Results
Hammond (1970)	1	Chlorpromazine (1800 mg)	Schizoaffective disorder	6 months	Normal development.
O'Connor (1981)	1	Chlorpromazine (1200mg), Fluphenazine (100mg)	Schizophrenia	15 months	First months: high irritability and motor deficits, 15 months: normal development.
Tanaka (1990)	2	Haloperidol (1.5-2.5mg)	Psychotic disorders	2 – 5 months	Normal physical and mental development.
Barnas (1994)	1	Clozapine (50-100mg)	Schizophrenia	6 months	Normal psychomotor development.
Stingl (2000)	1	Olanzapine (10mg)	Schizophrenia	11 months	Impaired motor development at 7 months, normal development at 11 months.
Ratnayake (2002)	2	Risperidone (2-6 mg)	Schizophrenia	9 – 12 months	No developmental abnormalities.
Tenyi (2002)	1	Quetiapine (150-300mg)	Schizophrenia	6 months	Normal development.
Karakula (2004)	1	Clozapine (200mg)	Schizophrenia	7 months	Encephalopathy after birth with convulsions and floppy infant syndrome, at 7 months delayed development.
Dabbert (2006)	1	LAI risperidone (25mg/2weeks)	Schizophrenia	2,5 years	Minor retardation in motor development at 2 years but within normal range.
Mendhekar (2006)	1	Aripiprazole (10mg)	Schizoaffective disorder	6 months	Normal achievement of milestones.
Cabuk (2007)	1	Quetiapine (1200mg), Haloperidol (15mg)	Bipolar disorder	80 days	Normal development.
Kim (2007)	1	Risperidone (25mg/2weeks)	Schizophrenia	8 months	Normal development reported.
Klier (2007)	1	Quetiapine (300 mg), Venlafaxine (75 mg), Trazodone (150 mg)	Bipolar disorder	1 year	Normal achievement of milestones.
Mendhekar (2007)	1	Clozapine (100mg)	Schizophrenia	5 years	Delayed speech up until 5 years of age.
Aichhorn (2008)	1	Olanzapine (15 mg)	Schizophrenia	6 months	Normal development.
Mendhekar (2008)	2 (1 mother)	Risperidone (2-3 mg)	Schizophrenia	18 – 36 months	No evidence of neurodevelopmental delay.

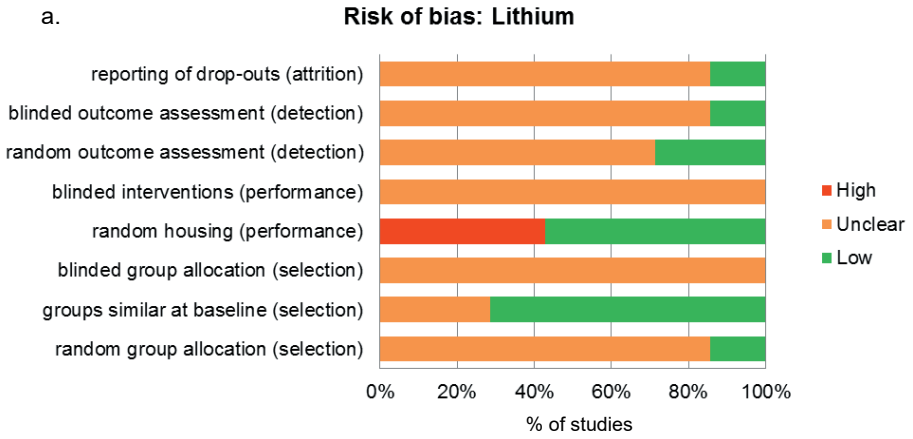
Table 2. (Continued)

Author (year)	Sample size	Medication (daily dosage)	Treatment indication	Follow-up time	Results
Mendhekar (2011)	3 (1 mother)	1st+2nd pregnancy: haloperidol (7,5-10 mg), 3rd pregnancy: haloperidol (15 mg) + risperidone (2mg)	Schizophrenia	16 months – 8 years	Normal developmental milestones and educational attainments.
Werremeyer (2009)	1	Ziprasidone (40mg) Citalopram (60mg)	Psychotic depression	6 months	Normal development.
Wichman (2009)	16	Atypical antipsychotics (varied)	Schizophrenia, schizoaffective disorder, MDD, bipolar disorder	3 years	Two infants with behavioral concerns. One infant with speech delay.
Rowe (2012)	1	Olanzapine (15-20mg), Promethazine (100mg), Lithium (1600mg), Diazepam (5mg)	Bipolar disorder	5 months	Normal development.
Janjic (2013)	2 (1 mother)	LAI zuclopentixol (1st pregnancy: 400mg/2weeks, 2nd pregnancy: 200mg/month)	Schizophrenia	6months - 3years	Normal development.
Stiegler (2014)	1	Olanzapine (15mg)	Schizophrenia	20 months	Normal development.
Gentile (2015)	1	Quetiapine (400 mg), Trazodone (200 mg) Lorazepam (7.5 mg) Mirtazapine(30 mg) Flurazepam (30 mg)	Borderline personality disorder	4 months	No developmental delay.
Kenar (2015)	1	Olanzapine (10 mg) Sertraline (100 mg) Quetiapine (400 mg) Chlorpromazine (100mg)	Generalized anxiety disorder	2 years	Normal motor and mental development.
Rodriguez (2017)	1	LAI paliperidone (100mg/4weeks)	Schizoaffective disorder	1 year	Normal psychomotor development.
McCauley (2014)	5	Olanzapine, Risperidone, Quetiapine, Haloperidol (n.r.)	Serious mental illness	1 year	4 children with normal development. One child had delayed motor development.

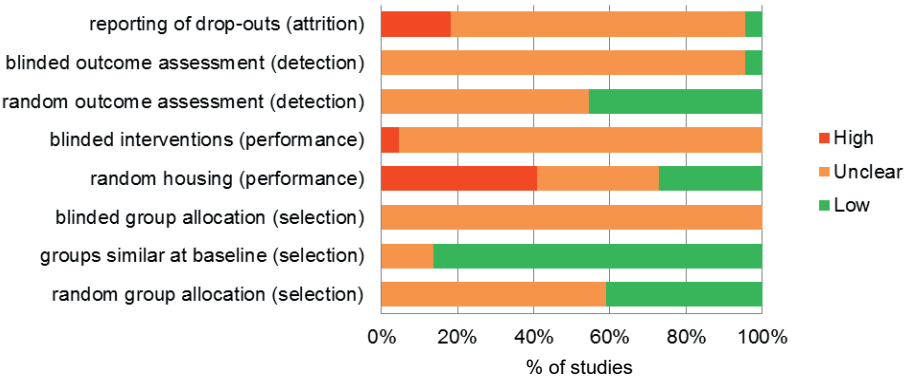
MDD major depressive disorder, *n.r.* not reported, *LAI* long acting injectable

Supplementary Material 3

a.



b.



CHAPTER 7

THE EFFECT OF PRENATAL LITHIUM EXPOSURE ON THE NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD

Eline M.P. Poels*
Lisanne Schrijver*
Tonya J.H. White
Sabine Roza
Milan G. Zarchev
Hilmar Bijma
Adriaan Honig
Inge L. van Kamp
Witte J.G. Hoogendijk
Astrid M. Kamperman**
Veerle Bergink**

** Should be considered joint first author, ** Should be considered joint last author*
Bipolar Disorders, 2021. Online ahead of print.

ABSTRACT

Objectives

Lithium is an effective treatment for bipolar disorder, also during pregnancy to prevent the recurrence of episodes in the perinatal period. Little is known about the neuropsychological development of lithium-exposed offspring. The current study was designed to investigate neuropsychological functioning in lithium-exposed children with the aim to provide further knowledge on the long-term effects of lithium use during pregnancy.

Methods

Participants were offspring of women with a diagnosis of bipolar spectrum disorder, aged 6 to 14 years. In total 99 children participated in the study, 56 were exposed to lithium *in utero* and 43 were not exposed to lithium. Neuropsychological tests were administered, including the Snijders-Oomen Nonverbal Intelligence Test and the NEPSY-II-NL assessment. Linear and Negative Binomial regression models were used to investigate the association between prenatal lithium exposure and neuropsychological functioning. In secondary analyses, the association between lithium blood level during pregnancy and neuropsychological functioning was assessed. Additionally, norm scores and percentiles for task outcomes were calculated.

Results

Lithium use during pregnancy was associated with the total number of mistakes made on the Auditory Attention task, but not statistically significant after full adjustment for potential confounding factors. No association between prenatal lithium exposure and IQ was found. Also, no relationship between lithium blood level during pregnancy and neuropsychological functioning was found after adjustment for potential confounders. Task outcomes in both groups were comparable to the general population.

Conclusion

In this study we found no evidence for significantly altered neuropsychological functioning of lithium-exposed children at the age of 6 to 14 years, when compared to non-lithium-exposed controls.

INTRODUCTION

Bipolar disorder is a severe psychiatric disorder characterized by episodes of depression and (hypo)mania. Lithium is the most effective maintenance treatment and is also well-established during the acute phase of the disease (1). As the onset of bipolar disorder is often in early adulthood, lithium is frequently prescribed to women of childbearing age and may be continued during pregnancy. An important reason to continue lithium treatment during pregnancy is that it reduces the risk of a recurrent mood episode during both pregnancy and the postpartum period (2, 3). However, lithium crosses the placenta freely, resulting in fetal serum levels equaling that of the mother (4). For well-informed balanced decision-making more information on the potential fetal impact is needed.

Most research has focused on the teratogenicity of lithium, investigating the incidence of congenital malformations in lithium-exposed infants. Recently, two large studies have confirmed the results of previous smaller studies and reported that lithium use during pregnancy was associated with an increased risk of congenital malformations, including cardiac malformations, but this effect was smaller than previously estimated (5, 6). Some other studies have reported an increased risk of miscarriage, preterm birth, increased birth weight and neonatal admissions (5, 7-9).

Much less is known about the development of the child after birth. In a previously published systematic review and meta-analysis, we investigated long-term neurodevelopmental effects of prenatal exposure to lithium in both clinical and preclinical studies (10). Pre-clinical studies suggested a detrimental effect of prenatal lithium exposure on motor activity, developmental milestones and reflexes, spatial memory and brain weight. Four clinical studies found normal neurodevelopment in general in lithium-exposed children. The first study compared 60 lithium-exposed children with 57 non-exposed siblings (11). Based on the mothers' retrospective assessment of their children's developmental milestones, assessed by questionnaire, no differences were found. A second study prospectively compared developmental milestones between 22 lithium-exposed children and non-exposed children, assessed by phone interview (12). Also no differences were found in this study. Van der Lugt et al. (2012) performed an observational cohort study, including 15 lithium-exposed children, using standardised validated tests to assess neurological, cognitive and behavioral outcomes. Outcomes were compared to norm scores from the general population; there was no matched non-exposed control group. In this study, most lithium-exposed children scored lower on the Block patterns subtests of the WISC-III-NL, compared to norm scores. No other differences were found (13). The fourth study systematically evaluated in a small cohort whether maternal mood disorders and lithium exposure during pregnancy influenced cognition of children aged four to five years. They compared 20 children exposed to lithium and maternal major mood disorder, 8 children exposed to maternal mood disorder but not to lithium, and 11 children not exposed to mood disorder or lithium. No differences

in intelligence quotients (IQ) were found between groups(14). These studies are of great importance to the field. However, sample size and methodological limitations hamper the interpretation of the results.

In this largest prospective cohort study thus far, validated and systematic measurements controlled for maternal disease severity were used to investigated the effect of lithium exposure *in utero* on the neuropsychological functioning of children aged 6 to 14 years. The aim of the study was to provide further knowledge on the long-term effects of lithium use during pregnancy, that may enable women with bipolar disorder to make more well-informed decisions regarding their treatment during pregnancy.

PATIENTS AND METHODS

Study design and participants

The current study is a clinical cohort study designed to investigate the influence of fetal lithium-exposure on long-term neuropsychological development of the child. Participants were recruited from three Dutch medical centers that provide specialised healthcare for perinatal psychiatry (Erasmus Medical Center Rotterdam, Leiden University Medical Center, Onze Lieve Vrouwe Gasthuis Amsterdam). A structured screening was performed of the electronic medical files for all women who consulted one of the perinatal psychiatry centers and gave birth to a living child between 2003 and 2011. The screening and inclusion process is depicted in the diagram in Appendix 1. The offspring of these women were selected for the lithium-exposed group, if lithium was used during pregnancy. Offspring were selected for the disease matched unexposed group if the mother did not use lithium during pregnancy but did have a diagnosis of bipolar spectrum disorder (bipolar I, bipolar II and mania/affective psychosis limited to the postpartum period). Mothers and their offspring aged 6 to 14 years were invited to participate during a single research visit. If the mother was unable to accompany the child, the father was invited instead. Oral and written study information was provided to all parents and their offspring (from the age of 12 years) before inclusion, and all provided signed, informed consent forms regarding participation in the study. During the research visit, two subtests from the Snijders-Oomen Nonverbal Intelligence Test, Revision (SON-R 6-40) were administered, followed by a selection of subtests from the NEPSY-II-NL. The SON-R 6-40 took about 30–45 min to administer and the NEPSY-II-NL about 60 min. There was a break between the two tests. If indicated, an additional short break could be added in between the SON-R 6-40 Mosaics and Categories subtests.Data collection took place from February 2017 until March 2020. This study was approved by the Institutional Review Board of the Erasmus University Medical Center (MEC 2016-288).

Maternal lithium exposure and psychiatric history

Information on lithium exposure during pregnancy, including dose, duration of use and lithium blood level, were extracted from the mother's medical file. Information on maternal medical history, other medication use and the psychiatric diagnosis during pregnancy were also extracted from the mother's medical file. The mother's current psychiatric diagnosis and status of psychiatric treatment and the number of maternal lifetime episodes were assessed by questionnaire at inclusion in the study.

Offspring characteristics

Information on the child's demographics, health, family situation and socioeconomic status was collected by questionnaire at inclusion in the study. Information on gestational age at birth and birth weight was extracted from the mother's obstetric file.

Outcome assessment

IQ

The Snijders-Oomen Nonverbal Intelligence Test, Revision (SON-R 6-40), is a nonverbal intelligence test for children and adults aged 2,5 years to forty years. The SON-R 6-40 has been validated and correlates highly (r = 0.55-0.83) with several other intelligence tests (WISC, WAIS, WNV, NIO) and has a high reliability with Cronbach's α = 0.95 (15, 16). The test consists of four subtests and we used two subtests: Mosaics and Categories. In the Mosaics subtest, the subject has to copy a spatial figure from an example picture, by placing red and white square tiles in a frame. The test consists of two series of 13 items. In the Categories subtest, three images are shown on the left page and five images on the right page. The subject needs to recognize the common feature of the left images and select two images from the right page that match them. The tests consists of three series of 12 items. The raw scores on the Categories and Mosaics subtests were taken together to compute an IQ-score, using the SON-R 6-40 computer program. The IQ test was performed in both the offspring and their biological parent. The offspring IQ was an outcome variable and the IQ of the parent was collected as a covariate in order to correct for the association between parental and offspring IQ.

Neuropsychological assessment

Neuropsychological development of the offspring was examined using a selection of subtests from the NEPSY-II-NL assessment. The NEPSY-II-NL is an official and validated Dutch translation and adaptation of the North American NEPSY-II (17). Acceptable to good reliability and validity have been reported for the NEPSY-II (18). It consists of 34 subtests in six different cognitive domains: attention and executive functioning, language, memory and learning, sensorimotor, social perception and visuospatial processing. A selection of subtests can be used and gives valid subscores. To limit the time constraint on our participating

children we selected nine subtests covering all six cognitive domains. The selected subtests and corresponding outcome values were: Auditory Attention and Response Set (total number mistakes, i.e. a combined measure of commission, omission and inhibition mistakes), Affect Recognition (total score), Memory for Faces (total score), Memory for Faces delayed (total score), Narrative Memory (total score for free and cued recall combined), Geometric Puzzles (total score), Inhibition (total number of mistakes and total completion time in seconds), Visuomotor Precision (total number of mistakes and total completion time in seconds) and Word Production (total number of correct words in semantic subtest). Rules of the NEPSY-II manual were closely followed (19). It took about 60 minutes to administer this selection of subtests. In Appendix 2 a full description of the NEPSY subtests is provided. For the Inhibition and Visuomotor precision subtest, the number of mistakes and total time were inverse Z-transformed (using the mean of all subjects combined) and the average of both outcomes was calculated per subject. This created a 'combined mistakes and time' variable for which high scores represented high performance, i.e. low number of mistakes and a low completion time.

Covariates

Selected covariates were sex and age of the offspring, gestational age at birth, maternal smoking and alcohol use during pregnancy, maternal folic acid use, maternal use of psychotropic medications other than lithium during pregnancy, maternal education, number of maternal lifetime mood episodes, parental IQ, and household income. Since gestational age at birth was included as a covariate in our analyses, birth weight and premature birth were not included to avoid collinearity.

Statistical analyses

Descriptive statistics and statistical analyses were performed using the Statistical Package for the Social Sciences (version 24, IBM). In our primary analyses separate multivariate regression models were used to investigate the association between prenatal lithium exposure and neuropsychological functioning. The association between prenatal lithium exposure and IQ was investigated using multivariate linear regression models. The association between prenatal lithium exposure and NEPSY outcome was investigated using multivariate linear regression models if the outcomes followed a normal distribution (Affect Recognition, Memory for Faces, Narrative Memory, Geometric puzzles, Inhibition total time, Visuomotor precision total time) or multivariate Negative Binomial regression models if the outcome was count data and followed a Negative Binomial distribution (Auditory Attention, Response Set, Inhibition total mistakes, Visuomotor precision total mistakes, Word production). A square root transformation was used to normalise the Visuomotor precision total completion time outcome. Linear regression models were used to investigate the association between prenatal lithium exposure and the 'combined mistakes and time'

outcomes. In the first step of our analyses, we defined simple models with prenatal lithium exposure as a dichotomous independent variable. IQ and NEPSY subtest scores were used as dependent variables and age and sex were added as covariates in the NEPSY analyses for Model I. In Model II, we added the maternal number of lifetime episodes as a covariate to the model in an attempt to eliminate the influence of confounding by indication to our results. This because a potential association between prenatal lithium exposure and neuropsychological outcome might be confounded by the disease severity of the mother. In this second step, IQ of the parent was also added to the model with IQ of the child as dependent variable. For Model III, we fully adjusted the model for the maternal number of lifetime episodes, IQ of the parent (in the model with offspring IQ as independent variable), gestational age at birth, household income, maternal education level (except for the IQ model since parental IQ was already included), folic acid use during pregnancy, smoking and alcohol use during pregnancy and the use of other psychotropic medication during pregnancy. In a previous paper, we found that maternal bipolar disorder and lithium use during pregnancy was associated with lower gestational age at birth, possibly partly due to a higher rate of induced labour (7), leading to the hypothesis that gestational age at birth could be a mediating factor in the relationship between lithium exposure during pregnancy and neuropsychological development. Therefore, the role of gestational age at birth as a mediator in the association between lithium use and IQ and NEPSY scores was explored. All continuous covariates were mean centered to improve interpretation. Since there were very few missing values for the covariates (2%), the missing values were imputed with the population mean. The unexposed group included some offspring (n=18) of which the mother was diagnosed with mania or affective psychosis in the postpartum period, which might be a less severe bipolar spectrum disorder (20). Therefore, sensitivity analyses were performed excluding these offspring from the analyses, in order to investigate whether the results of our analyses were influenced by the imbalance in maternal diagnosis between the exposed and unexposed groups. Sensitivity analyses were also performed limiting the analyses to one child (the first) per family in order to explore the influence of genetic predisposition and lifestyle factors within families. In our primary analyses, we chose negative binominal regression models because they are conservative in handling outliers. However, all of our outcome values included in this study were true test outcomes. Hence, we performed sensitivity analyses using Poisson models to study the effect of lithium use during pregnancy on neuropsychological test outcome with a more sensitive statistical approach. In our secondary analyses we explored whether there was a dose-response relationship by investigating the association between lithium blood levels during pregnancy and IQ, and NEPSY subtest outcomes. For this aim regression models as described above were repeated with the independent variable being the average weighted lithium blood level during pregnancy. The average weighted lithium blood levels were calculated as follows: 1) each registered lithium blood level was multiplied by the number of days between that measurement and the previous measurement, 2) the last known lithium level was also multiplied with the number

of days between this measurement and the date of delivery, 3) a cumulative lithium level was calculated and divided by the total number of days of pregnancy. Additionally, in order to explore how our exposed and unexposed children compared to the general population, we calculated percentile and norm scores for all outcomes using the SON-R 6-40 computer program for IQ (15) and the psychometric norms provided in the NEPSY-II manual (18). For NEPSY-II percentiles, calculations were not exact but calculated into categories. Therefore, we report the percentage of children with a percentile of 50 or lower, which in the general population would be approximately 50%. For normally distributed data NEPSY-II provided norm scores instead of percentiles, a norm score of 10 (SD = 3) is considered average. Since we performed analyses on 15 neuropsychological outcomes, the chance of a Type-I error was increased. To control for Type-I error we applied a false discovery rate (FDR) correction (21). Notably, because of the small sample size the risk of a Type-II error was increased after FDR correction. Since the aim of the study was to investigate the potential adverse effect of prenatal lithium exposure on neurodevelopment we would rather be on the safe side and not dismiss any potential effect. Therefore, the models original p-values are presented and test outcomes were considered statistically significant if the original p-value was <0.05. Additionally, test outcomes that remained significant after FDR correction were marked.

RESULTS

Descriptive Characteristics

Table 1 shows the child, maternal and paternal characteristics of all subjects that participated in this study.

Table 1. Demographic and Clinical Characteristics of the Participants

	Exposed to lithium	Not-exposed to lithium
N	56	43
Child characteristics		
Age (years), mean (SD)	9.0 (2.2)	10.6 (2.4)
Sex, % female	60.7	48.8
Country of birth both parents Netherlands, %	78.6	86.0
Psychiatric disorder[a], N (%)	11 (19.6%)	5 (11.6%)
Use of psychotropic medication[b], N (%)	3 (5.4%)	1 (2.3%)
Learning disability, N (%)	12 (22.2%)	5 (11.6%)
Birth weight (g), mean (SD)	3290 (729)	3541 (509)
Premature birth (<37 wk), N (%)	14 (26.4%)	3 (7.9%)
Gestational age at birth in weeks, mean (SD)	37.6 (3.4)	39.6 (1.9)
Pregnancy characteristics		
Average maternal lithium dosage (mg), mean (SD)	926 (257)	

Table 1. (Continued)

	Exposed to lithium	Not-exposed to lithium
Period of lithium use (N)		
1st trimester only	2	
1st + 2nd trimester	1	
2nd + 3rd trimester	4	
1st + 2nd + 3rd trimester	48	
Unknown	1	
Lithium level weighted average (mmol/l), mean (SD)		
Whole pregnancy	0.53 (0.12)	
1st trimester	0.47 (0.12)	
2nd trimester	0.51 (0.15)	
3rd trimester	0.57 (0.17)	
Use of any other psychiatric medication, N (%)[c]	17 (30.4%)	5 (11.6%)
Antidepressants	14 (25%)	3 (7.0%)
Antipsychotics	8 (14.3%)	3 (7.0%)
Benzodiazepines	1 (1.8%)	5 (11.6%)
Use of alcohol, N (%)	1 (1.9%)	6 (14%)
Use of recreational drugs, N (%)	1 (1.8%)	0 (0%)
Smoking, N (%)	4 (7.1%)	4 (9.3%)
Folate use, N (%)	49 (92.5%)	37 (90.2%)
Maternal characteristics		
Main diagnosis, N (%)		
Bipolar I disorder	45 (80.4%)	23 (53.5%)
Bipolar II disorder	8 (14.3%)	1 (2.3%)
Postpartum mania/affective psychosis[d]	0 (0.0%)	18 (41.9%)
Schizoaffective disorder	1 (1.8%)	0 (0.0%)
Major depressive disorder (MDD)	2 (3.6%)	1 (2.3%)
Time of diagnosis, N (%)		
Before pregnancy	56 (100%)	20 (46.5%)
During pregnancy	0 (0%)	1 (2.3%)
After pregnancy	0 (0%)	22 (51.2%)
Number of lifetime episodes, median (IQR)	5.5 (3-8)	2 (1-5)
Episode during pregnancy, N (%)	10 (20.8%)	2 (4.8%)
Mean age of onset mood disorder, mean (SD)	23 (6.0)	30 (4.4)
Household income in euro's per month, N (%)		
< 2400	14 (25.9%)	10 (25.6%)
> 2400	40 (74.1%)	29 (74.4%)
Higher education, N (%)	33 (58.9%)	26 (60.5%)
Paternal characteristics		
Lifetime psychiatric disorder, N (%)	14 (25.9%)	11 (25.6%)
Higher education, N (%)	34 (63%)	25 (62.5%)

In case of missingness valid means and percentages are presented.

[a] Exposed group: ADHD/ADD N = 3, Autism Spectrum Disorder (ASD) N = 5, Tourette's syndrome N= 1, Developmental Coordination Disorder N = 1, other behavioral disorder N = 1. Non-exposed group: ADHD/ADD N = 2, ASD N = 1, ADHD and ASD N = 1, Tourette's syndrome N = 1.

[b] Exposed group: methylphenidate N = 2, lamotrigine N = 1. Non-exposed group: methylphenidate N = 1.

[c] Use of any other psychotropic medication than lithium at some point during pregnancy, also subdivided by medication group. Some women used more than one additional type of medication.

[d] These mothers have not experienced episodes outside of the postpartum period.

A total of 99 children from 67 different families participated in the study. The number of participating children per family varied from one to three children (the latter being the case for two families). Three twin pairs participated in the study, all were lithium exposed. For all covariates, there were 2% missing values.

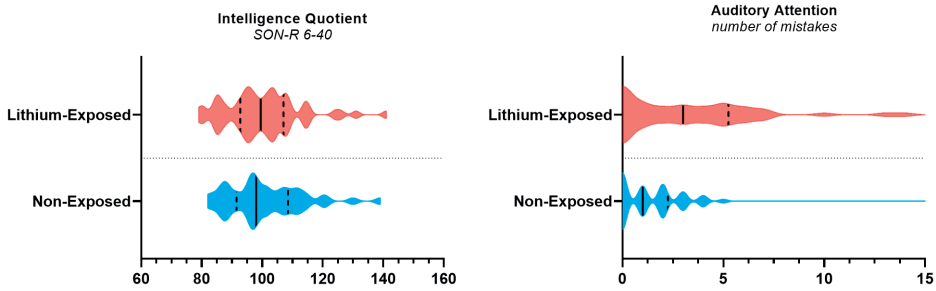
Lithium use

Different types and compounds of lithium were used during pregnancy. In 24 pregnancies mothers used lithium carbonate (Camcolit® n = 13 , Priadel® n = 5, lithium carbonate (other brands) n = 6). Lithium citrate, also known as Litarex®, was used in 19 pregnancies. In 13 pregnancies the type of lithium medication was unknown. Lithium citrate dosages (Litarex 564mg = 6mmol lithium) were multiplied by 0.395 to calculate lithium carbonate dosage equivalents (400mg = 8 mmol lithium), in order to calculate the average lithium dosage in the lithium-exposed group of 926mg/day. For 34 children, information on the maternal lithium blood level during whole pregnancy was available. On average there were 6.5 serum level measurements per pregnancy with a range of 1 to 22 measurements. There was no correlation between the number of serum level measurements and the average weighted lithium level (data not shown).

Neuropsychological tests

IQ tests were performed in 96 children (54 exposed and 42 non-exposed). NEPSY tests were performed in 99 children (56 exposed and 43 non-exposed). The distribution of IQ outcome of the offspring is presented in Figure 1. The mean IQ was 100.4 in the lithium-exposed group and 101.0 in the non-exposed group. Also presented in Figure 1 is the distribution of number of mistakes made on the Auditory Attention NEPSY subtest. The distribution of all NEPSY subtest outcomes are presented in Appendix 3. Visual inspection of the violin plots showed a comparable distribution shape in the lithium-exposed and non-exposed groups for IQ. The distribution shapes of Auditory Attention, Response Set, Inhibition and Visuomotor Precision (number of mistakes) show that in the lithium-exposed group more children have a relatively high number of mistakes, when compared to the non-exposed group. Additionally, more lithium-exposed children have lower scores on the Geometric Puzzles and Affect recognition.

Figure 1. Distribution of IQ and Auditory Attention total mistakes in lithium-exposed and non-exposed offspring. Solid lines represent median and striped lines represent interquartile range[a]



[a] Violin plot: a kernel density estimation of the distribution shape of the IQ and Auditory Attention data. Distribution shapes are presented for the non-exposed and lithium-exposed groups separately. Wide sections of the violin plot represent a higher probability that offspring within this group will take on the given value while narrow sections represent a lower probability.

In table 2 the results of the multivariate regression analyses are presented. An association between prenatal lithium exposure and the number of total mistakes made on the Auditory Attention subtest was found after correction for age, sex and maternal number of lifetime episodes (Incidence Rate Ratio (IRR)= 2.09, 95% CI: 1.30, 3.38). This association was no longer statistically significant in the fully adjusted analysis. In the sensitivity analysis excluding offspring from mothers with mania or affective psychosis limited to the postpartum period no association between lithium use during pregnancy and Auditory Attention total mistakes was found. Sensitivity analyses with Poisson regression models showed an association between lithium use during pregnancy and Auditory Attention total mistakes and additionally with Visuomotor Precision total mistakes (fully adjusted model: IRR = 1.26, 95% CI: 1.07, 3.49). Other associations between prenatal lithium exposure and neuropsychological subtest outcomes were not found.

Table 2. Associations between prenatal lithium exposure and neuropsychological test outcome[a]

	Model I[b]		Model II[c]		Model III[d]	
Outcome	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
SON-IQ (L)	-0.03 (-5.82, 4.52)	0.80	-0.02 (-5.57, 4.78)	0.88	0.06 (-4.35, 7.52)	0.60
Auditory Attention, total mistakes (NB)	1.99 (1.25, 3.12)	0.003**	2.09 (1.30, 3.38)	0.002**	1.76 (0.96, 3.21)	0.07
Response Set, total mistakes (NB)	1.08 (0.66, 1.79)	0.75	1.12 (0,68, 1.86)	0.65	1.02 (0.58, 1.78)	0.95
Affect Recognition, total score (L)	-0.06 (-2.49, 1.24)	0.51	-0.04 (-2.31, 1.48)	0.67	-0.05 (-2.58, 1.50)	0.60
Memory for Faces, total score (L)	0.003 (-1.08, 1.11)	0.98	-0.04 (-1.30, 0.89)	0.71	-0.04 (-1.40, 1.03)	0.76
Memory for Faces Delayed, total score (L)	-0. 04 (-1.47, 0.97)	0.68	-0.09 (-1.72, 0.71)	0.41	-0.07 (-1.73, 0.96)	0.57
Narrative Memory, total free and cued recall (L)	0.02 (-1.69, 2.14)	0.81	0.03 (-1.56, 2.33)	0.70	0.05 (-1.58, 2.74)	0.59
Geometric Puzzles, total score (L)	-0.07 (-2.41, 0.96)	0.40	-0.09 (-2.56, 0.88)	0.33	-0.06 (-2.47, 1.27)	0.53
Inhibition mistakes (NB)	0.86 (0.55, 1.34)	0.50	0.85 (0.54, 1.35)	0.49	0.85 (0.52, 1.40)	0.53
Inhibition time (L)	0.09 (-13.10, 31.54)	0.41	0.06 (-15.74, 29.54)	0.55	0.03 (-21.77, 27.54)	0.82
Inhibition combined mistakes and time (L)	-0.01 (-0.36, 0.32)	0.90	0.00 (-0.34, 0.34)	0.99	0.02 (-0.35, 0.41)	0.89
Visuomotor Precision time (L)	-0.02 (-1.01, 0.82)	0.84	-0.02 (-1.04, 0.83)	0.83	-0.07 (-1.37, 0.71)	0.53
Visuomotor Precision mistakes (NB)	1.22 (0.77, 1.94)	0.39	1.21 (0.75, 1.96)	0.42	1.10 (0.65, 1.85)	0.73
Visuomotor Precision combined mistakes and time (L)	-0.09 (-0.32, 0.10)	0.30	-0.09 (-0.32, 0.10)	0.30	-0.04 (-0.28, 0.18)	0.68
Semantic word Production, total correct words (NB)	0.96 (0.63, 1.48)	0.86	0.96 (0.62, 1.49)	0.87	0.97 (0.61, 1.57)	0.92

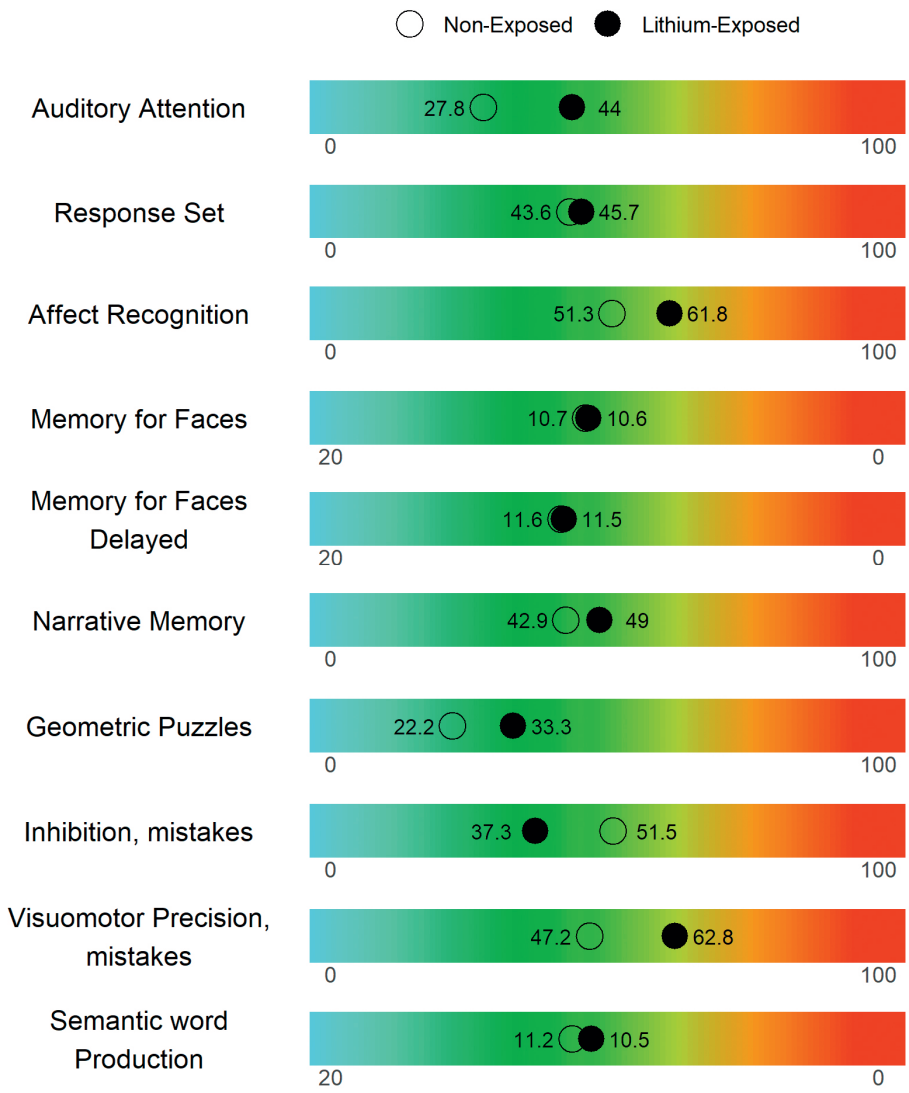
[a] Results from multivariate regression models. Coefficients: for linear regression models (L) the standardised beta and for Negative Binomial regression models (NB) the exponent of the beta (incident rate ratio) are reported. Original p-values (before FDR correction) are presented.
[b] Adjusted for: age and sex in the models on NEPSY subtest outcomes.
[c] Adjusted for: age, sex (NEPSY models), IQ parent (IQ model) and maternal number of lifetime episodes.
[d] Additionally adjusted for: gestational age at birth, household income, maternal education level, folic acid use during pregnancy, smoking and alcohol use during pregnancy, other psychotropic medication used during pregnancy.
* Statistically significant with a an original p-value < 0.05.
** Statistically significant after Benjamini-Hochberg correction.

Table 3. Associations between weighted lithium levels during pregnancy and neuropsychological test outcome [a]

	Model I [b]		Model II [c]		Model III[d]	
Outcome	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
SON-IQ (L)	-0.35 (-81.61, 0.23)	0.051	-0.35 (-81.57, -0.43)	0.048*	-0.18 (-71.84,29.70)	0.40
Auditory Attention, total mistakes (NB)	0.15 (0.004, 6.29)	0.32	0.14 (0.003, 6.21)	0.31	0.30 (0.003, 27.36)	0.60
Response Set, total mistakes (NB)	15.06 (0.32, 706,82)	0.17	13.52 (0.27, 672.50)	0.19	3.03 (0.02, 493.24)	0.67
Affect Recognition, total score (L)	0.14 (-7.69, 23.37)	0.31	0.13 (-8.01, 23.28)	0.33	0.12 (-14.27, 28.38)	0.50
Memory for Faces, total score (L)	0.16 (-4.38, 11.84)	0.36	0.18 (-3.79, 11.91)	0.30	0.27 (-4.89, 17.10)	0.26
Memory for Faces Delayed, total score (L)	0.09 (-7.74, 12.29)	0.65	0.10 (-7.09, 12.42)	0.58	0.08 (-10.61, 14.83)	0.73
Narrative Memory, total free and cued recall (L)	-0.06 (-17.60, 11.20)	0.65	-0.06 (-17.88, 11.49)	0.66	-0.09 (-25.21, 15.98)	0.65
Geometric Puzzles, total score (L)	0.13 (-5.55, 18.23)	0.29	0.14 (-5.47, 18.57)	0.27	0.18 (-7.48, 24.51)	0.28
Inhibition mistakes (NB)	2.80 (0.10, 82.31)	0.55	2.57 (0.08, 79.53)	0.59	5.42 (0.08, 350.69)	0.43
Inhibition time (L)	0.25 (-54.94, 287.88)	0.18	0.25 (-56.22, 292.44)	0.18	0.01 (-213.15, 221,15)	0.97
Inhibition combined mistakes and time (L)	-0.26 (-3.85, 0.54)	0.14	-0.26 (-3.86, 0.60)	0.15	-0.17 (-3.82, 1.63)	0.41
Visuomotor Precision time (L)	0.05 (-5.70, 7.54)	0.78	0.05 (-5.84, 7.66)	0.78	-0.18 (-11.45, 5.08)	0.43
Visuomotor Precision mistakes (NB)	0.81 (0.02, 32.25)	0.91	0.82 (0.02, 33.06)	0.92	1.79 (0.02, 137.03)	0.79
Visuomotor Precision combined mistakes and time (L)	0.03 (-1.58, 1.89)	0.86	0.03 (-1.60, 1.93)	0.85	0.28 (-0.57, 3.61)	0.15
Semantic word Production, total correct words (NB)	0.80 (0.04, 16.27)	0.89	0.79 (0.04, 16.29)	0.88	0.68 (0.01, 35.04)	0.85

[a] Results from multivariate regression models. Coefficients: for linear regression models (L) the standardised beta and for Negative Binomial regression models (NB) the exponent of the beta (incident rate ratio) are reported. Original p-values (before FDR correction) are presented. Data derived from 34 children.
[b] Adjusted for: age and sex in the models on NEPSY subtest outcomes.
[c] Adjusted for: age, sex (NEPSY models), IQ parent (IQ model) and maternal number of lifetime episodes.
[d] Additionally adjusted for: gestational age at birth, household income, maternal education level, folic acid use during pregnancy, smoking and alcohol use during pregnancy, other psychotropic medication used during pregnancy.
* Statistically significant with a p-value < 0.05.
** Statistically significant after Benjamini-Hochberg correction.

Figure 2. NEPSY-II-NL percentile and norm scores for the lithium-exposed and non-exposed groups[a]



[a] The black circle represents the lithium-exposed group and the open circle represents the non-exposed group. The percentage of offspring with a percentile < 50 is presented on a scale from 0 to 100 %. The mean norm scores are presented on a scale from 20 to 0. A colour range is used to depict how norms and percentages relate to the normal population (green = average/expected, blue = above average/better than expected, red = below average/worse than expected).

Dose-response

The results of the secondary analyses on the association between lithium blood level during pregnancy and neuropsychological test outcomes are presented in Table 3. Weighted lithium blood levels were associated with offspring IQ after adjustment for parental IQ and maternal number of lifetime episodes (β= -0.35, 95% CI: -81.57, -0.43) but no longer statistically significant in the fully adjusted model. No other associations between lithium blood level during pregnancy and neuropsychological test outcomes were found.

Percentile and norm scores

In the lithium-exposed group and the non-exposed group the mean percentiles for IQ were 49.3 and 50.6 respectively. For the NEPSY subtest outcomes, the percentages of lithium-exposed offspring with a percentile of 50 or lower and the mean norm scores are depicted in Figure 2. As shown in figure 2, most norm and percentile values lie within the average or above average range, except for Affect Recognition and Visuomotor Precision (mistakes) in the lithium-exposed group.

DISCUSSION

In this clinical cohort study the influence of prenatal exposure to lithium on the neuropsychological functioning of offspring was investigated. Multiple neuropsychological domains were investigated with the aim to provide knowledge of the effects of prenatal lithium exposure on neuropsychological functioning. Lithium-exposed offspring did not significantly differ from non-exposed offspring in IQ and neurodevelopmental NEPSY tasks, after correction for potential confounding variables. Additionally, we did not find a relationship between lithium blood level during pregnancy and neuropsychological test outcomes. When compared to the norm scores of both the SON-R 6-40 and NEPSY-II NL subtests, both the lithium-exposed and non-exposed groups did not show meaningful deviations from scores expected in the normal population.

Even though the fully adjusted analyses did not reveal any statistically significant associations between lithium use during pregnancy and neuropsychological test outcomes, there are some results that need further elaboration. The association with Auditory Attention total mistakes was present after adjustment for age and sex of the offspring and maternal lifetime number of episodes, but no longer statistically significant after correction for potential confounders and in a sensitivity analysis excluding offspring of mothers with mania or affective psychosis limited to the postpartum period. Additionally, using the conservative negative binominal models no association with Visuomotor Precision total mistakes was found while with Poisson models this association was present, and did not disappear after correction for confounding factors or in the sensitivity analyses. Notably, when visually inspecting the violin plots we saw that lithium-exposed children make more

mistakes on several NEPSY subtests. While these performances could be outliers driving our results, we want to emphasize that all values were true test outcome values. It is important to conclude that by using conservative statistical models and after correction for confounders we do not find a statistically significant effect of prenatal lithium exposure on neuropsychological functioning of the child. Additionally, it is also important to consider the possibility of a small effect in some of the children (as depicted by our true outliers) that could not be detected in our study due to lack of statistical power. It remains difficult to interpret the minor differences that we found between groups. It is likely that mothers from the lithium group had more psychiatric symptoms in the years after delivery. This more stressful postnatal environment also has the potential to influence neuropsychological functioning. Low scores in the Auditory Attention subtest are associated with problems in selective and sustained attention. The Auditory Attention subtest and especially the Response Set subtest are sensitive for ADHD. Also children with autism, language and calculation disorders tend to have lower scores on both tasks. Notably, we did not find an association between prenatal lithium use and outcome on the Response Set task. Low scores for Auditory Attention and normal scores for Response Set may imply that the child is more alert or motivated in a more challenging task than in a more monotonous task. Problems in the Visuomotor Precision subtest are usually associated with problems in coordination of fine motor hand movements, or in the speed of hand movements. However, in this task the number of mistakes and the time to finish are related. Personal style of the child can be of influence; hyperactive or impulsive children may try to finish the task quickly, thereby sacrificing accuracy. To address this matter, we created a 'combined mistakes and time' variable. We found no association with time to finish the task or with the combined variable. This suggests that combined visuomotor precision is not impaired and that a high number of mistakes is often compensated with a low completion time. Importantly, none of the lithium-exposed children had any clinical motor problems (data from questionnaires, not shown). Interestingly, children within the lithium-exposed group did appear to have a higher percentage of psychiatric disorders (19.6% vs 11.6%) and learning disabilities (22.2% vs 11.6%). Since this was outside the scope of this study, no statistical tests were performed to analyse these differences. Overall, we found no evidence for significant alterations in neuropsychological functioning after prenatal lithium exposure for children aged 6 to 14 years.

The findings of this study are consistent with existing literature from previous clinical studies. Forsberg et al. did not find a difference in full scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) between lithium-exposed and non-exposed children, using the Wechsler Preschool and Primary Scale of Intelligence 3rd edition(14). Children exposed to major mood disorder during pregnancy, with or without lithium exposure, had significantly lower scores on the processing speed quotient (PSQ). Van der Lugt et al. found no abnormalities in Verbal Intelligence Quotient, Performance Intelligence Quotient and Total Intelligence Quotient (Wechsler Preschool and

Primary Scale of Intelligence or the Wechsler Intelligence Scale for Children), by comparing outcomes of lithium-exposed children with norm scores (13). For two children aged between 16 and 30 months, no abnormalities were found in the Bayley Scales of Infant Development. The authors note, however, that many children had (non-significant) lower scores on the performance tests, especially on the subtest Block patterns. The block patterns subtest mainly measures spatial visualization ability and also requires visuomotor coordination. Two other clinical studies did not find an effect of lithium on development, but they did not use systematic tests (11, 12). To our understanding, no other study has used the NEPSY-II NL or a comparable test battery to systematically assess different domains of neuropsychological functioning in addition to IQ in lithium-exposed children. We investigated the cognitive domains attention and executive functioning, language, memory and learning, sensorimotor, social perception and visuospatial processing. Some preclinical studies have suggested detrimental effects of gestational lithium exposure in rodents and zebrafish on locomotor activity, developmental milestones and reflexes, spatial memory and brain weight (22-26). However, these preclinical studies had substantial methodological limitations and may not be directly translatable to the clinical practice.

Lithium serum level during pregnancy did not affect neuropsychological outcome in our study. An effect of lithium blood level on IQ was found after correction for parental IQ and maternal lifetime number of episodes, but not present after correction for multiple potential confounders. Importantly, lithium has a small therapeutic range that is usually closely monitored during pregnancy. As a result of the small range, a possible effect of serum level may not become apparent in our relatively small subsample. It should also be noted that serum lithium levels during pregnancy were only available in 61% of lithium-exposed pregnancies and that we found wide confidence intervals with our model estimates. Hence, the results of these analyses should be interpreted with caution as they were likely underpowered.

The current study has several strengths and limitations. Firstly, this is the largest prospective cohort study on this topic thus far. Another strength of this study is the use of validated tests for the assessment of IQ and neuropsychological functioning. Although we did not study every aspect of neuropsychological functioning, we did provide information on IQ and six different cognitive domains. Because we recruited our participants via specialised centers for perinatal psychiatry, detailed information during pregnancy was available and this made it possible to define the exposure with large certainty and correct for the most relevant confounding factors. Also, by including a non-exposed control group in which the maternal psychiatric diagnosis was matched to the exposed group, we addressed the issue of confounding by indication in the best way possible for a cohort study. Severity of disease is likely to be higher for women that choose to continue lithium treatment during pregnancy. This also follows from the higher number of lifetime mood episodes and the younger age of onset in the lithium-exposed group in our study. The non-exposed group contained a larger

group of women that were diagnosed with postpartum psychosis only, which is generally considered to have a better prognosis than bipolar disorder (20). We addressed this issue by performing a sensitivity analysis and by correcting for maternal lifetime number of mood episodes. The association between lithium use during pregnancy and Auditory Attention total mistakes was present after correction for maternal lifetime number of episodes. For all the other tests no significant association was found. The latter could be seen as an argument for the safety of lithium on eventual neuropsychological functioning and IQ of the offspring or even a neuroprotective effect of lithium. This because one would expect that maternal disease severity would negatively impact neuropsychological development of the child (27). Thanks to the collaboration between Erasmus MC, Leiden University Medical Center and Onze Lieve Vrouwe Gasthuis we were able to include a large number of participants in this study. This enabled us to study neuropsychological functioning with more power.

Limitations of the current study are the fact that lithium serum levels were not available for all women and that the analyses on the association between lithium blood level and neuropsychological function were, as a consequence, underpowered. Also, most children had Dutch parents, limiting the ethnic variety in our sample. Neuropsychological functioning is a result of many factors such as genetic make-up, brain development, parental education, parenting strategies and life events. Since it would be relevant to find out if prenatal lithium exposure does affect brain structure in the offspring, brain MRI studies might provide further elucidation of this question.

Knowledge of long-term consequences of maternal lithium use during pregnancy for the offspring has so far been limited, but is essential for women with bipolar disorder to make informed decisions regarding their treatment during the perinatal period. Our findings reveal no evidence for significantly altered neuropsychological functioning for children exposed to lithium *in utero*. Several smaller differences in neuropsychological functioning may need further investigation. Since the collection of data in this specific group of children is challenging and sample sizes are generally small, we propose data sharing as a mean to create more power. Overall, the current and previous studies on this topic point towards a clinical neurodevelopment within the normal range for lithium-exposed offspring. When counseling women with bipolar disorder on treatment options in the perinatal period, this information should preferably be integrated in the knowledge of all potential consequences of maternal lithium use during pregnancy.

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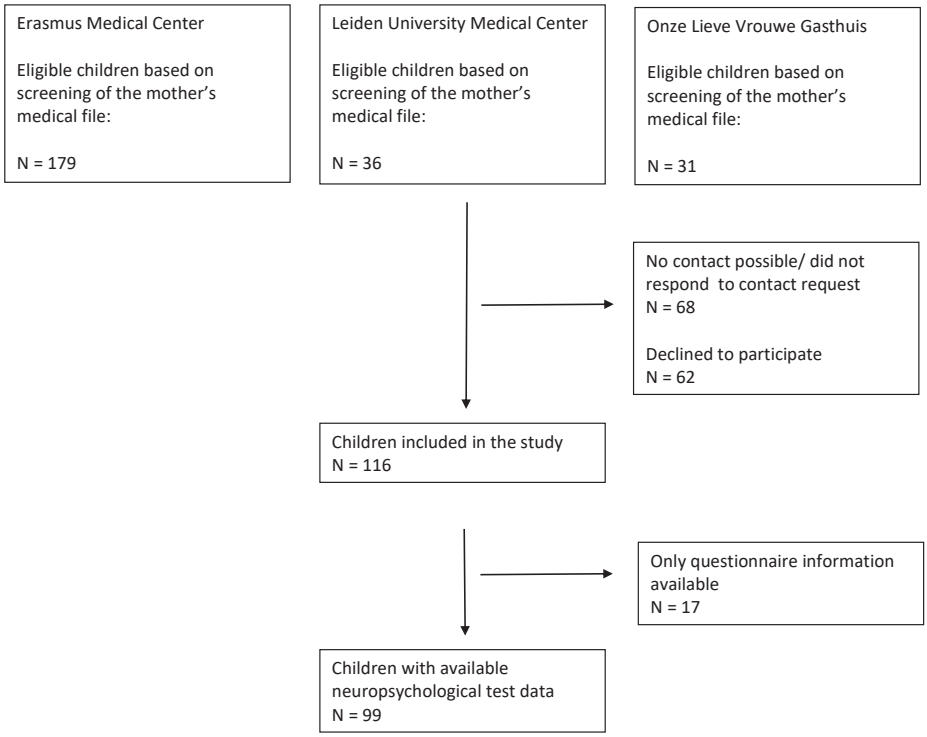
Supplementary materials

Appendix 1. Consort Diagram



Appendix 2. Description of NEPSY subtests

Auditory Attention and Response Set

These subtests are part of the attention and executive function domain. In the first subtest, auditory attention, the child listens to a recording of color words and other words. Their task was to respond to the word 'red' by touching a red circle on the sheet in front of them. The sheet contains also circles in blue, black and yellow, which had to be ignored. A response was considered correct if the child touched the red circle within 2 seconds after hearing the word 'red'. In the second subtest, response set, the child received a new task. It had to respond to the word 'red' by touching the yellow circle and respond to the word 'yellow' by touching the red circle. At the word 'blue' it had to touch the blue circle. Auditory attention is designed to assess selective and sustained attention and response set assesses the ability to shift and maintain a new and complex set involving both inhibition of previously learned responses and correctly responding to matching or contrasting stimuli.

Affect Recognition

This subtest is part of the social perception domain. This subtest was designed to assess the ability to recognize affect (happy, sad, anger, fear, disgust, and neutral) from photographs of children's faces. The child had to decide whether or not two faces showed the same affect and he or she had to select photographs of faces with the same affect.

Memory for Faces

The memory for faces task is part of the memory and learning domain. It investigates immediate and delayed memory for faces and the ability to recognize and distinguish different faces. The child was presented with a series of pictures of children's faces (with neutral facial expression) which were presented for 5 seconds each. After this, three pictures were shown each time and the child had to select the face that it had already seen. A delayed task, assessed 15 to 25 minutes after the first task, investigated long-term memory for faces.

Narrative Memory

The narrative memory task is part of the memory and learning domain. The child was told a short story and then asked to reproduce as many aspects of the story as it could remember (free recall). After this, specific questions about the story were asked (cued recall). Finally, yes and no questions were asked about the story (recognition). This subtest was designed to assess memory for organised verbal material under free recall, cued recall, and recognition conditions.

Geometric Puzzles

The geometric puzzles task is part of the visuospatial processing domain. The child was presented with a set of geometric figures on a grid. It had to identify the two figures that

correspond to the two figures outside of the grid. Corresponding figures had the same shape, but may have been rotated. This task required mental rotation, visuospatial analysis and attention to detail.

Inhibition

The inhibition subtest is part of the attention and executive functioning domain. The child was presented with black and white shapes or arrows. It was asked to name the shape or direction of the arrow, or an alternate response, depending on the colour of the shape or arrow. The task required the ability to inhibit an automatic response and the flexibility to switch between different responses.

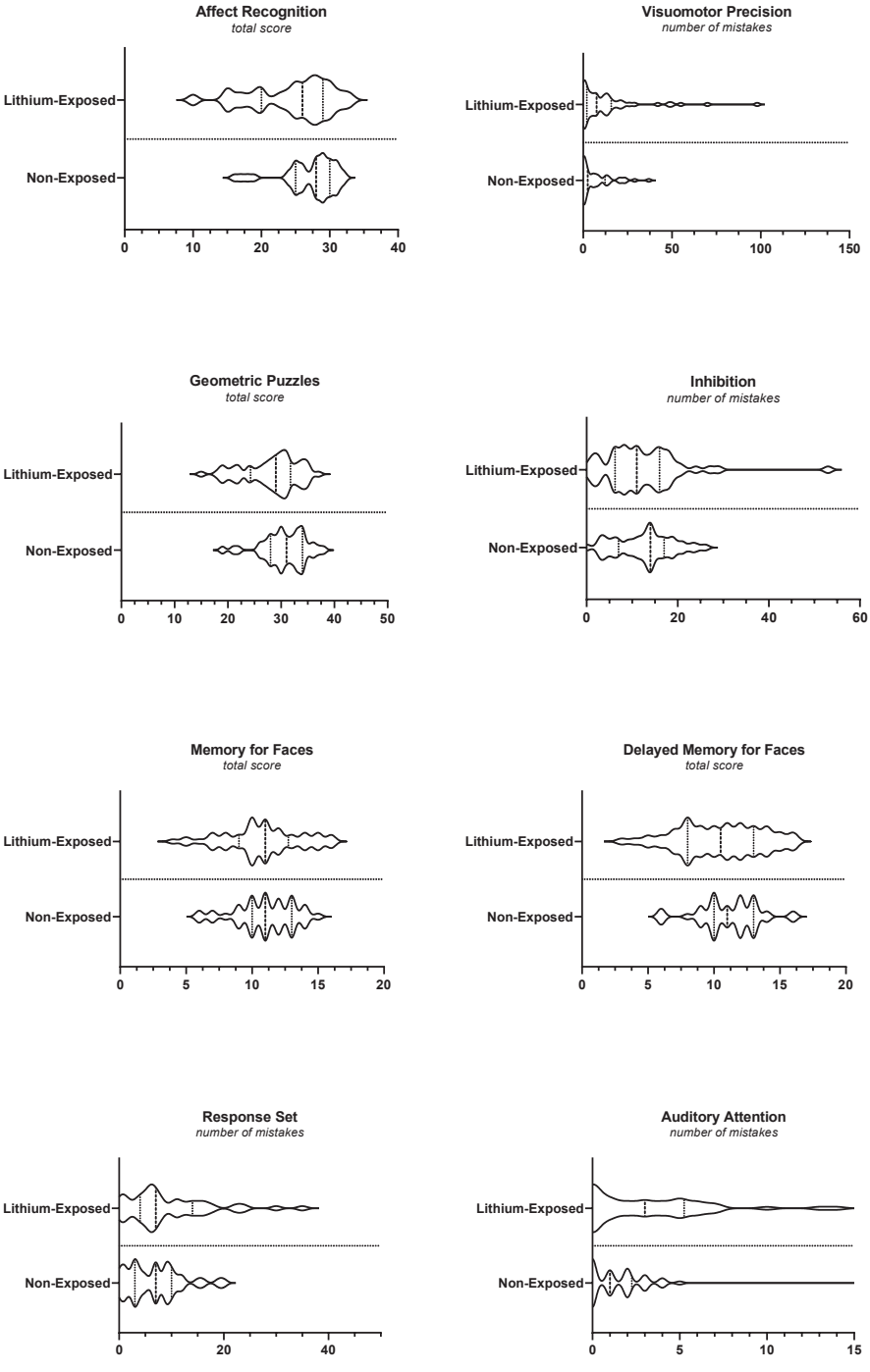
Visuomotor Precision

This subtest is part of the sensorimotor domain. In this pen-and-paper task the child had to draw a line by following a given paper path. The path consisted of parallel lines that were curved in different directions. The child was given the instruction to perform the task as fast as possible, but without crossing the parallel lines and without lifting the pencil from the paper. The task measured coordination of fine motor skills by assessing graphomotor speed and accuracy.

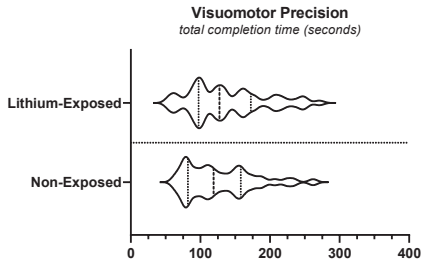
Semantic Word Production

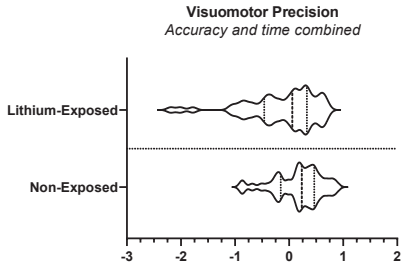
This subtest is part of the language domain. The child had to generate as many words as possible within 60 seconds. It it had to name words from two different categories; first animals, then food or drinks. This subtest investigated the verbal productivity through the ability to generate words.

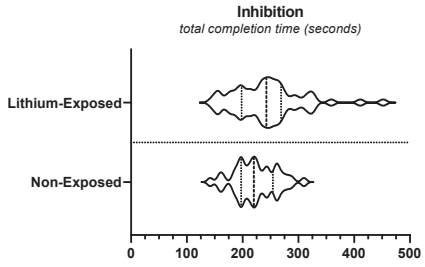
Appendix 3. Distribution of NEPSY-II-NL subtest scores for lithium-exposed and non-exposed children. Dotted lines represent median and interquartile range

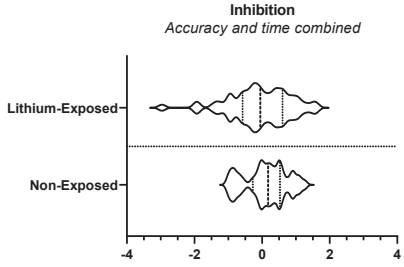


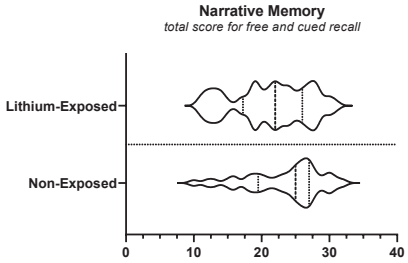
Appendix 3. Distribution of NEPSY-II-NL subtest scores for lithium-exposed and non-exposed children. Dotted lines represent median and interquartile range *(continued)*

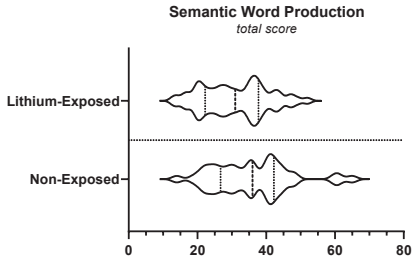


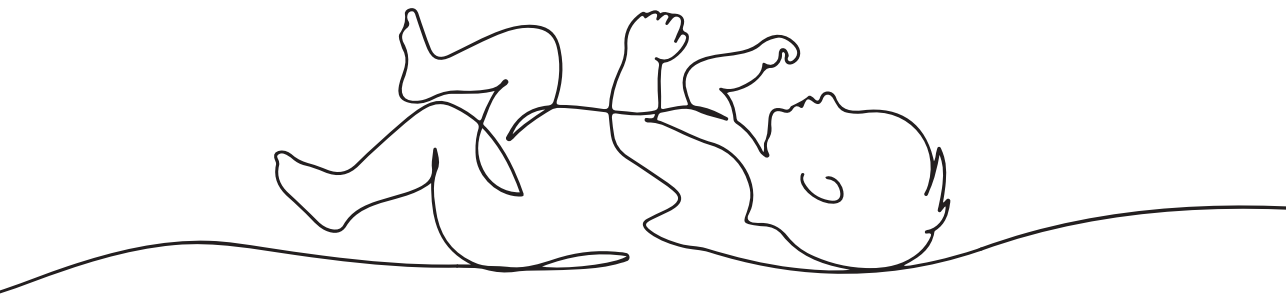












CHAPTER 8

GENERAL DISCUSSION

The aim of this thesis was to expand the knowledge about the potential consequences of lithium use during pregnancy. As shown in **chapter 2** most previous studies on this topic mainly investigated the teratogenicity of lithium and showed an increased risk of congenital malformations, including cardiac malformations. The focus of this thesis was on other potential adverse effects of lithium use during pregnancy. Namely, the risk of miscarriage, consequences for fetal growth and birth weight, the risk of neonatal complications, and the neurodevelopmental consequences for the child.

We investigated the risk of miscarriage related to ongoing lithium exposure and the influence of intrauterine exposure to lithium on fetal growth and birth weight. Also, we investigated the evidence behind lithium dose adjustment prior to delivery by studying lithium blood level changes around delivery and by investigating the association between neonatal lithium blood levels and neonatal outcome. A meta-analysis and systematic review of the literature on the neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics was performed. Lastly, we presented the first results of the Image_AL study, a clinical cohort study designed to investigate the neurodevelopmental consequences of prenatal lithium exposure in children aged 6 to 14 years.

This chapter will provide a general discussion of all main findings including several methodological considerations. Additionally, a hypothesis about the pathophysiological mechanism underlying these findings is proposed and recommendations for clinical practice and for future research are made.

MAIN FINDINGS

1. *Is lithium use during pregnancy associated with an increased risk of miscarriage?*

In **chapter 3** we investigated the risk of miscarriage in 443 pregnancies of women with bipolar I disorder who participated in the Dutch Bipolar Cohort study. Self-reported information was used to assess whether lithium was used during pregnancy and whether a miscarriage occurred. Our study showed that the risk of miscarriage was higher in lithium-exposed pregnancies when compared to unexposed pregnancies (20.8% versus 10.9% respectively). After adjustment for the age at conception and the clustering of pregnancies per woman the adjusted odds ratio for miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22).

2. *Does lithium use during pregnancy influence fetal growth and birth weight?*

Lithium completely passes through the placenta and therefore has the potential to influence fetal development (1). Studying the effect of lithium on fetal development is especially important because even small changes in the intrauterine environment can have consequences for the development of the child later in life (2). In **chapter 4** we investigated the effect of prenatal lithium exposure on fetal growth parameters at 20 weeks of gestation and birth weight. This study compared lithium-exposed pregnancies (N = 199) from women referred for advanced fetal ultrasound scanning to the University Medical Centers in Leiden and Rotterdam, with unexposed pregnancies (N = 8148) from the Generation R study. Lithium use during pregnancy was associated with increased fetal growth at 20 weeks of gestation and increased birth weight, while the average duration of pregnancy was shorter. In sensitivity analyses within the Generation R cohort, maternal bipolar spectrum disorder was not associated with fetal growth, which may suggest a more specific effect of lithium.

3. *Should it be recommended to lower the lithium dose prior to delivery in order to reduce the risk of neonatal complications?*

Lithium blood levels fluctuate during pregnancy due to normal physiological changes in renal function and vascular volume (3, 4). Delivery causes a significant decrease in vascular volume and renal clearance. Based on this, several reviews and guidelines have recommended to discontinue lithium or reduce its dose at the start of delivery, in order to prevent an increase in lithium blood level with potential negative consequences for the neonate (5-8). In **chapter 5** we explored the validity of these recommendations by investigating lithium blood level changes around delivery and by examining the association between neonatal lithium blood level and neonatal outcome and complications. In our cohort of 100 lithium-exposed pregnancies (from 78 women), a total of 223 lithium blood level measurements were available around delivery (in the last week of pregnancy and the first week postpartum). We found no association between time and lithium blood level/dose ratio (Pearson correlation coefficient −0.03, P = .63). Information on neonatal blood lithium level within 24 hours after birth was available in 29 neonates. We found no association between neonatal lithium blood level and neonatal outcome or complications. Based on these findings, we do not recommend to lower the lithium dose prior to delivery.

4. *What is known about the long-term neurodevelopmental consequences of prenatal exposure to lithium and antipsychotics?*

In a systematic review article and meta-analysis (**chapter 6**), we presented an overview of the literature regarding long-term neurodevelopmental effects of lithium and

antipsychotics. Both preclinical and clinical studies were included. Overall, findings from preclinical studies suggest a deleterious effect of lithium on neurodevelopment in offspring. Only three clinical studies on neurodevelopmental outcome after intrauterine exposure to lithium were published in the literature. These clinical studies generally reported typical development at the time of follow-up (between 1 and 15 years). However, methodological concerns limit the interpretation of the results of these studies. Preclinical studies on the neurodevelopmental effect of prenatal exposure to antipsychotics consistently reported adverse neurodevelopmental and behavioural effects. Several clinical studies reported a delay in neurodevelopment among infants with intrauterine exposure to antipsychotics. The most consistent clinical finding was a transient delay in motor development. This was confirmed in our meta-analysis with a relative risk of 1.36 for neuromotor deficits after intrauterine exposure to antipsychotics at the 6 month follow-up visit.

5. *Is prenatal lithium exposure associated with neuropsychological functioning in children aged 6 to 14 years old?*

A clinical cohort study was performed to investigate the neurodevelopmental effects of lithium exposure *in utero* on the neuropsychological functioning of children aged 6 to 14 years. The results of this study were described in **chapter 7**. Participants were 99 children of women with a diagnosis of bipolar spectrum disorder, 56 were exposed to lithium *in utero* and 43 were not exposed to lithium. Lithium use during pregnancy was associated with the total number of mistakes made on the Auditory Attention task (NEPSY-II-NL subtest), but this result was not statistically significant after full adjustment for potential confounding factors. No association between prenatal lithium exposure and IQ was found. Also, no relationship between lithium blood level during pregnancy and neuropsychological functioning was found after adjustment for potential confounders. Based on these findings we conclude that there is no evidence for significantly altered neuropsychological functioning of lithium-exposed children at the age of 6 to 14 years, when compared to non-lithium-exposed controls.

Part I: Consequences for the fetus and neonate

Several studies have shown that lithium use during pregnancy increases the risk of congenital cardiac and non-cardiac malformations (9-11). We additionally found that the risk of miscarriage was increased in lithium-exposed pregnancies. Based on our data in a group of pregnancies from women with bipolar type I disorder, 20.8% of lithium-exposed pregnancies ended in a miscarriage versus 10.9% of unexposed pregnancies. The most important limitations of our study were the retrospective collection of exposure and outcome data by questionnaire, which may be prone to recall bias, and the fact that information about the use of other medications during pregnancy was not available in as

much detail as it was for lithium. Interestingly, our results are consistent with data from an earlier study by Diav-Citrin et al. (9), who evaluated 183 lithium-exposed pregnancies compared to 72 disease-matched unexposed pregnancies. They found a 16.% rate of miscarriage in lithium-exposed pregnancies compared to 8.3% in unexposed pregnancies (9). Both of these studies showed the risk of miscarriage to be twice as high when lithium was used during pregnancy. In contrast, another prospective cohort study by Jacobson et al. did not find an association between lithium use during pregnancy and the risk of miscarriage (12). Remarkably, the miscarriage rates reported in this study (lithium-exposed 9%, unexposed 8%) are rather low when compared to the other two studies and to the expected rate of miscarriage in the general population, which is 10–15% of pregnancies (13). Since two out of three studies show an increased risk of miscarriage this warrants attention from clinicians treating women with bipolar I disorder of childbearing age. Notably, there is no imminent need to change clinical guidelines for lithium use during pregnancy, as current guidelines already warn against prescribing lithium during the first trimester of pregnancy. The methodological limitations of these three studies are reason for caution when interpreting the risk of miscarriage associated with lithium use during pregnancy. When discussing the risk of miscarriage with women preconceptionally, it is important to mention that miscarriage is common (10-15% of all pregnancies regardless of medication use). The occurrence of a single miscarriage in women who use lithium should not directly be linked to the lithium use.

Lithium appears to influence fetal growth. We found increased fetal parameters at 20 weeks of gestational age and increased birth weight in lithium-exposed pregnancies. Lithium-exposed neonates also had a higher risk for being large for gestational age (LGA). This association was previously studied in an environmental study by Harari et al. (14). Lithium exposure was through drinking water in the Argentinean Andes in very low concentrations (median 25 µg/L, which corresponds to 0.0036 mmol/L). This low exposure dose may explain the fact that this study did not find a significant association with fetal size or birth weight. It is possible that the association with fetal growth and birth weight is dose-dependent. Unfortunately, we did not have sufficient data to perform dose-response analyses. Our findings are consistent with the findings by Jacobson et al., as this study also found birth weight to be increased in lithium-exposed pregnancies (12). Three other studies reported no association with birth weight (9, 10, 15). Importantly, the largest study on this subject investigated only the association of lithium with low birth weight and being small for gestational age (<10th percentile) and was therefore not able to detect other differences in birth weight (10). Several methodological limitations of our study require attention, with the most important one being the possible influence of confounding by indication. By directly comparing the lithium-exposed group to a control group from the general population we were not able to determine the effect of maternal bipolar disorder on fetal growth

independent of lithium exposure. Although we did not find an association between maternal bipolar spectrum disorder and fetal growth in a sensitivity analysis within the control group, the severity of maternal bipolar disorder was likely lower in this subgroup when compared to the lithium-exposed group. Additionally, residual confounding may have been present since information on maternal education and socioeconomic status was not available in this study.

While several guidelines recommend to discontinue lithium or lower the lithium dose prior to delivery, we do not find evidence to support this recommendation in our study. We found no change in lithium levels around delivery and no association between neonatal lithium blood levels and neonatal outcome. The latter is in contrast with a study by Newport et al, in which lithium concentrations and obstetrical outcomes were available for 24 neonates, of which 14 neonates were identified from published case reports (1). They found that high prenatal lithium exposure was associated with a higher rate of neonatal complications. A potential explanation for these contrasting findings is that neonatal blood level range differed substantially between our sample and the sample of Newport et al. The high lithium exposure group in Newport's study included several lithium blood levels higher than 0.7 mmol/L and with some neonates classified as being within the toxic range (>1.2 mmol/L) while in the low lithium exposure group blood levels were mostly subtherapeutic (<0.5 mmol/L) (1). In our sample, most women were within the therapeutic window and no toxic levels were observed. It is plausible that neonatal lithium levels are associated with neonatal complications if high (toxic) lithium dosages are used. Moreover, the use of case reports in this study might have caused a higher rate of neonatal complications. In our study we had neonatal lithium blood levels available in 29 neonates which meant that statistical power was limited to study the association between neonatal lithium levels and neonatal outcomes. An additional limitation is that neonatal lithium levels were not routinely assessed, and might have been measured due to suspected neonatal lithium toxicity or neonatal complications. This is a possible explanation for the rather high rate of neonatal complications we find in our study (48.3%). This study was not designed to compare the rate of neonatal complications in lithium-exposed and non-exposed neonates. In a large meta-analysis of six study sites lithium use during pregnancy was associated with an increased risk of neonatal readmissions (10). For this reason it is always important to critically assess the indication for lithium use during pregnancy. Our study shows that if lithium is used during pregnancy there is little evidence to support the recommendation of lithium discontinuation or dose reduction prior to delivery.

Part II: Neurodevelopmental consequences for the child

In our systematic review article and meta-analysis of the available literature regarding long-term neurodevelopmental effects of prenatal exposure to lithium and antipsychotics we included both preclinical and clinical studies. Preclinical findings may not always be directly translatable into clinical practice but they do have the potential to investigate the effect of medication exposure using more optimal study designs. Overall, findings from preclinical studies suggest a deleterious effect of lithium on neurodevelopment. The risk of bias in these studies was mostly unclear due to a lack of methodological description. Only three clinical studies of offspring neurodevelopment after intrauterine exposure to lithium were published in the literature and they generally reported typical development. The quality of these studies, as assessed by the Newcastle-Ottawa Scale, was poor. Preclinical studies on prenatal exposure to antipsychotics consistently reported adverse neurodevelopmental and behavioural effects. Most studies of antipsychotics involved haloperidol and chlorpromazine, while a much smaller number focused on varied atypical antipsychotics, limiting our conclusion on neurodevelopmental impact related to a specific type or class of antipsychotic. Also for these preclinical studies the risk of bias was often unclear. Findings from clinical studies of antipsychotic exposure were inconsistent and difficult to interpret due to the considerable differences in methodology and follow-up period. The quality of these clinical studies varied. Several studies reported a transient delay in neurodevelopment among infants with intrauterine exposure to antipsychotics. The most consistent finding was a transient delay in motor development. The relative risk estimate of 1.36 for neuromotor deficits after *in utero* exposure to antipsychotics at 6 months of follow-up was based on only two studies and should therefore be interpreted with caution. Publication bias may have influenced our results since scientific papers with statistically significant associations are more likely to be published (16).

In our own clinical study on the influence of prenatal exposure to lithium on the neuropsychological functioning of offspring, lithium-exposed offspring did not significantly differ from non-exposed offspring in IQ and neurodevelopmental NEPSY tasks, after correction for potential confounding variables. Also, no relationship between lithium blood level during pregnancy and neuropsychological test outcomes was found. This is in line with previously published clinical studies on the neurodevelopmental effects of prenatal lithium exposure (12, 17-19). Even though our study is the largest to date with detailed information on neuropsychological functioning, it is important to consider the possibility of a small effect in some of the children that could not be detected in our study due to lack of power. Notably, when visually inspecting the violin plots we saw that lithium-exposed children make more mistakes on several NEPSY subtests, but no statistically significant difference was found in our analyses. In addition, for both the Auditory Attention and Visuomotor Precision total mistakes outcomes associations with prenatal lithium exposure were found in the simple

or less conservative models but not in the fully adjusted models. Another limitation is the fact that dose-response analyses were likely underpowered. Nevertheless, these results can be used to reassure women with bipolar disorder about the probably limited long term neurodevelopmental consequences of lithium use during pregnancy. It is important to mention that the possibility of a small effect is not ruled out and that information on emotional development is lacking, but that clinical studies do not show large deviations from typical cognitive functioning.

PATHOPHYSIOLOGICAL MECHANISMS

Lithium is the most effective and best established pharmacotherapy for bipolar disorder. For about one-third of patients with bipolar I disorder, monotherapy with lithium will result in clinical stability for many years and often decades (20). The specific mechanism through which lithium establishes its therapeutic effect remains largely unclear. Even though lithium is a simple element, it has many diverse effects on multiple signalling pathways, and other cellular processes (21). Inhibition of glycogen synthase kinase 3β (GSK3β) by lithium appears to be a key mechanism through which lithium mediates several cellular and higher-order biological mechanisms and dampens excessive neuronal activity (20). Also through GSK3β inhibition and the influence of lithium on brain-derived neurotrophic factor (BDNF), lithium is suggested to have a neuroprotective effect in adults. Neuroimaging studies in adults suggest that the use of lithium can influence brain structure. Structural magnetic resonance imaging (MRI) studies have shown that lithium is associated with increases or normalization of gray matter volume in fronto-limbic brain structures (22). GSK3β has been reported to regulate gene expression, embryonic development, and neuronal survival, among other processes, through various downstream pathways (20). BDNF plays an important role in fetal metabolic programming (23). Importantly, lithium crosses the placenta completely (1). Hence, it can be assumed that lithium use during pregnancy has the potential to influence fetal development. In our studies we found several clinical effects of lithium use during pregnancy but we did not study the pathophysiological mechanism of these effects. Below we discuss several hypotheses based on our findings and previous (pre)clinical studies.

The pathophysiological mechanism of the association between lithium use during pregnancy and miscarriage has not yet been investigated. We proposed the mediating role of maternal thyroid function as a hypothetical mechanism of this association. Lithium use has been associated with overt and subclinical hypothyroidism in several studies (24) and (sub)clinical hypothyroidism has been associated with pregnancy loss (25). Since maternal thyroid levels during pregnancy were not available in our study we were not able to investigate this mechanism. Interestingly, a recent preclinical study in rats investigated the effect of lithium exposure through breast milk on the health of the pups (26). They found that lithium-

exposed pups had higher TSH and reduced blood thyroxine (T4) levels. This hypothyroidism remained present after weaning. As a mechanism the authors propose that lithium ions may interfere with the sodium-iodide symporter, limiting iodine uptake in the thyroid which initiates a mechanism where iodine cannot bind with tyrosine molecules on thyroglobulin, resulting in reduced thyroid hormone production (26). Additionally, they observed increased body weight in the lithium-exposed pups. In our study, we also observed increased fetal growth and birth weight in our clinical lithium-exposed sample. Whether there is a relationship between lithium exposure and maternal or fetal/neonatal thyroid function remains unclear, thyroid function was not measured in this study. As another interesting hypothesis for increased fetal growth we propose the role of brain-derived neurotrophic factor (BDNF). Lithium use has been associated with increased BDNF levels (27, 28) and BDNF plays a crucial role in fetal metabolic programming through regulation of energy homeostasis and by regulating glucose metabolism in peripheral tissues (23). Further, it has been shown that placental BDNF gene expression is upregulated in maternal type 1 diabetes and gestational diabetes mellitus, and downregulated in neonates with non-diabetic macrosomia, compared with normal birth weight neonates (23). Hence, one of the possible mechanisms underpinning the association between lithium use and increased fetal growth might be that lithium results in increased maternal serum BDNF, which might subsequently result in altered regulation of placental BDNF. This in turn could alter the regulation of fetal growth by interfering with the energy homeostasis and regulating glucose metabolism.

CLINICAL RECOMMENDATIONS

1. *Weighing the risks and benefits*

In order to decide on lithium continuation during pregnancy, the risks and benefits of lithium treatment during pregnancy and the postpartum period need to be weighed. But what does this mean in clinical practice? As described in this thesis, lithium use during pregnancy is associated with an increased risk of congenital malformations, an increased risk of miscarriage, increased fetal growth and birth weight, and potentially with premature birth and neonatal complications. These are the risks. On the other hand, there are benefits to lithium use during pregnancy since it reduces the risk of perinatal mood episodes (29-31). In this context it is important to note that also relapse of bipolar disorder carries a fetal risk. High maternal stress but also high-risk behaviour, such as self-medication against stress with e.g. alcohol or drugs or lack of compliance to antenatal care are associated with adverse fetal outcomes (32). If a woman with bipolar disorder has a history of frequent and severe mood episodes and a good response to lithium treatment, lithium continuation may be recommended because the risk of a severe perinatal episode is high while the risk of a

congenital malformation due to lithium use in the child is low. However, if a woman with bipolar disorder has a history of few mild episodes it may be better to consider tapering off lithium preconceptionally or during the first trimester, or even during the entire pregnancy. In this case a restart immediately postpartum is still very important to prevent a postpartum mood episode. These are only theoretical examples, whereas clinical situations are often more complex. It is paramount to always ask what is important to the individual woman and to assess her support network. Pregnancy is a period with high vulnerability for women with bipolar disorder and it is important to make decisions that the individual woman supports. In this shared decision making process it is essential that the clinician provides complete and comprehensible information during consultation, making use of e.g. patient information folders.

2. *A thorough evaluation of indication and diagnosis*

The indication for which maintenance treatment during pregnancy is considered should - if possible - always be evaluated preconceptionally. The course of illness should be examined and the diagnosis may need to be reconsidered. Clinically, it is common that, after a single postpartum mania/affective psychosis, women have a diagnosis of bipolar disorder, since a distinctive DSM-5 diagnosis for this condition is not available. Some of these women are given recommendations to continue their lithium treatment for several years, while based on a treatment algorithm we would recommend to taper off lithium after nine months (33). Women with recurrent episodes of bipolar disorder may need prophylactic treatment during pregnancy while research has shown that for women with mania/affective psychosis limited to the postpartum period prophylaxis only during the postpartum period is sufficient (34). Careful evaluation of diagnosis and indication for pharmacological treatment preconceptionally will reduce unnecessary exposure of the fetus.

3. *Consider other options for prophylactic mood stabilising medication*

While lithium use during pregnancy is shown to be effective in the prevention of peripartum bipolar episodes (31), it also has consequences for the unborn child as mentioned before. Other options for mood stabilising medication should be considered. In Table 1 the adverse effects of lithium during pregnancy are compared with those of carbamazepine, lamotrigine, valproic acid and atypical antipsychotics.

Table 1. A comparison of the reported adverse effects of mood stabilising medication during pregnancy

Medication	Teratogenicity	Obstetric and neonatal effects	Long-term effects	Breastfeeding
Lithium	Pooled prevalence of congenital malformations: 4.1%, cardiac malformations in specific: 1.2%	- Increased risk of miscarriage - Increased fetal growth and birth weight - Neonatal complications	No evidence for significantly altered neuropsychological development	Infant serum lithium level is 17-58% of maternal serum level
Carbamazepine	Pooled prevalence of major congenital malformations: 4.93%	- Risk of vitamine K deficiency - Potential risk of intrauterine growth restriction	Decreased verbal skills, no association with IQ	Variable concentration in breastmilk, no reported negative effects for the neonate
Lamotrigine	Risk not increased	No obstetric complications	Not reported	Variable concentration in breastmilk, a few cases reported negative effects for the neonate
Valproic acid	7x increased risk of congenital malformations: neural tube defects, atrial septal defect, cleft palate, hypospadias, polydactyly en craniosynostosis Estimated prevalence of 6-12%	Intrauterine growth restriction, fetal distress en neonatal hepatotoxicity	- Associated with increased risk of autism spectrum disorders - Lower IQ score - Problems with non-verbal communication	Low concentration in breastmilk, no reported negative effects for the neonate
Atypical antipsychotics	Risk not increased, with the possible exception of risperidone	Associated with: - Gestational diabetes - Maternal obesity	Transient delay in neuropsychological development	Depends on the type of antipsychotic medication, no adverse effects are reported for olanzapine en quetiapine

Valproic acid is mentioned in this table since it is recommended in clinical guidelines as a maintenance treatment option for individuals with bipolar disorder. But as shown in table 1, valproic acid is highly teratogenic and associated with obstetric complications and adverse neurodevelopmental effects (35). For this reason, valproic acid should not be prescribed during pregnancy to women with bipolar disorder. One could even argue that it should be avoided in the treatment of all women of child-bearing ages since the risks associated with a possible unplanned pregnancy are extremely high and alternative options are generally available. Carbamazepine is also associated with congenital malformations, the risk is lower compared to valproic acid but higher compared to lithium (4). Atypical antipsychotics are, with the possible exception of risperidone, not teratogenic (36). Notably, the use of atypical antipsychotics use during pregnancy is associated with gestational diabetes and our meta-analysis showed potential neurodevelopmental effects (37). Lamotrigine has the best profile when considering the adverse effects for the exposed child (4). Both atypical antipsychotics and lamotrigine should be considered as possible alternatives to lithium treatment during pregnancy. Unfortunately, not much is known about the efficacy of these medications in the prevention of perinatal bipolar episodes. One register based study showed that lamotrigine is not inferior to lithium in the prevention of postpartum relapse (38). However, the efficacy of lamotrigine in the prevention of postpartum episodes was established in a group of women with a high vulnerability to depressive episodes and its efficacy in the prevention of mania remains unknown.

4. *Individualised treatment plan*

We advise all women with bipolar disorder to plan their pregnancy and to make an individualised treatment plan with their healthcare providers in a specialised centre. Antenatal care should take place in a multidisciplinary setting, with close collaboration between psychiatric and obstetric services. Decisions about the continuation of mood stabilising medication should be made preconceptionally because the risk of congenital malformations is highest in the first trimester of pregnancy (11). When lithium therapy is continued during pregnancy, regular antenatal visits are warranted for checking lithium blood levels, evaluation of fetal growth, and for monitoring signs of preterm labour. Lithium blood levels need to remain within the therapeutic window throughout pregnancy to reduce the negative effects of lithium toxicity for the developing fetus and neonate. At 20 weeks of gestational age, detailed fetal anomaly scanning, including detailed fetal cardiac scanning should be offered. Furthermore, evaluation of maternal thyroid (TSH and free T4) levels and kidney function is recommended. We do not recommend to discontinue lithium treatment or to lower the lithium dose prior to delivery. Maintaining a stable and therapeutic lithium blood level is important in the postpartum period, when recurrence risks are high for women with bipolar disorder. Delivery should take place in a specialised hospital where psychiatric

and obstetric care for the mother is provided and neonatal evaluation and monitoring of the child can take place immediately after birth. Finally, monotherapy of psychotropic medication is always preferred over a combination of medications.

5. *Postpartum recommendations*

If lithium was discontinued during pregnancy it should be restarted immediately after delivery for women with bipolar disorder. The target therapeutic lithium level immediately after delivery and during the first month postpartum is relatively high (e.g., 0.8–1.0 mmol/L) to optimize relapse prevention. Lithium blood levels should be obtained twice weekly in the first 2 weeks postpartum. Due to the lack of information on the effects of lithium exposure through breastmilk in infants, in combination with the vulnerability of the developing neonatal kidneys, we do not recommend breastfeeding while using lithium. Additionally, we want to emphasize the importance of adequate sleep in the first four weeks postpartum for women with bipolar disorder or women with a history of postpartum mania/affective psychosis. Lack of sleep is a known trigger for a manic episode (39). Nighttime feedings by the partner can help to improve sleep quality for the mother.

FUTURE RESEARCH

Brain development

In our clinical cohort study we do not find evidence for significantly altered neuropsychological functioning of lithium-exposed children at the age of 6 to 14 years, when compared to non-lithium-exposed controls. This is consistent with other clinical studies, while preclinical studies have suggested detrimental effects of gestational lithium exposure in rodents and zebrafish on locomotor activity, developmental milestones and reflexes, spatial memory and brain weight. Interestingly, evidence from clinical neuroimaging studies in adults suggests that the use of lithium can influence brain structure. Structural magnetic resonance imaging (MRI) studies have shown that lithium is associated with increases or normalisation of gray matter volume in fronto-limbic brain structures (22). It would be relevant to determine if prenatal lithium exposure has an effect on the development of brain structure in the offspring. MRI brain studies may provide further insight to this question. Within the Image_AL study MRI brain data of lithium-exposed and non-lithium exposed children has been collected and we are currently analysing the data.

Long-term growth and the risk of obesity

The theory of Developmental Origins of Health and Disease refers to the concept that early life events could explain an individual's risk for non-communicable disease in later life (40). According to this theory, the intrauterine environment can change fetal programming, which

bears an impact on much more than just birth weight, including changes in physiology and metabolism. This means that small prenatal changes, such as the increased fetal growth, we found in our study, can have impact in later life (41). For example, large for gestational age fetuses have an increased risk of developing components of the metabolic syndrome during childhood (42). We currently do not have information on the growth of lithium-exposed children in later life. Future studies could collect growth information from birth until adolescence in lithium-exposed and non-exposed children with the aim to investigate growth trajectories and the risk of obesity later in life.

The efficacy of lamotrigine and atypical antipsychotics in the prevention of postpartum episodes

As is discussed in this thesis, lithium use during pregnancy is associated with several adverse effects for the unborn child. Nevertheless, lithium is often continued during pregnancy because many women with bipolar disorder need pharmacological treatment to achieve or maintain mood stability during pregnancy. As discussed, lamotrigine has a more favourable profile when it comes to adverse effects of its use during pregnancy. Also, atypical antipsychotics are not associated with congenital malformations. Therefore, both lamotrigine and atypical antipsychotics could be considered as alternatives to lithium, but clinicians should be cautious. Medication changes are best done before conception, when women are in a stable mood, but many women have an unplanned pregnancy and switching is therefore not feasible. Moreover, some women only respond well to lithium, but not to other treatments and they need lithium to maintain mood stability. The efficacy of lamotrigine in the prevention of postpartum bipolar episodes is unknown for women with a strong manic component to their bipolar disorder. There are no studies that have investigated the efficacy of atypical antipsychotics in the prevention of postpartum bipolar episodes. Future research should therefore investigate the efficacy for both lamotrigine and atypical antipsychotics in order to properly compare risks and benefits of these medications to lithium. Since a randomized trial is not feasible nor ethical to answer this question, large prospective naturalistic cohort studies can provide answers. Detailed clinical information is important, as well as information on the decision-making processes. To create enough statistical power, considering the base-rate of bipolar disorder in the population, collaboration between multiple centers is warranted.

The influence of thyroid functioning

It would be interesting to investigate the role of maternal and fetal/neonatal thyroid functioning in the pathophysiological mechanism underlying the increased risk of miscarriage and increased fetal growth and birth weight associated with lithium use during pregnancy. For this aim, thyroid (regulating) hormone levels (T4 and TSH) in pregnant women who use lithium during pregnancy and in pregnant control women could be collected and the

association between lithium use during pregnancy and maternal thyroid functioning could be tested. In addition, it would be interesting to study neonatal thyroid functioning after lithium exposure by assessing thyroid hormone levels in blood immediately after birth.

FINAL CONCLUSION

The risk of a depressive or manic episode is high during the postpartum period for women with bipolar disorder. Maintaining mood stability during the peripartum period can be challenging but treatment with lithium is shown to be effective. Notably though, lithium use during pregnancy is associated with adverse effects for the unborn child. As shown in this thesis, lithium use during pregnancy is not only associated with a small but increased risk of congenital malformations, but also with an increased risk of miscarriage and increased fetal growth and birth weight. The data on the long-term development of lithium-exposed children are reassuring. We did not find evidence for significantly altered long-term neuropsychological functioning. Since lithium blood levels around delivery remain stable and neonatal lithium blood levels are not associated with neonatal complications when lithium is dosed within the therapeutic range, we do not advise to reduce the dose prior to delivery. Women of childbearing age requiring mood stabilisation, should be given the opportunity to weigh the risks and benefits of lithium treatment during pregnancy and the postpartum period. For this reason, knowledge of all potential consequences of lithium use during pregnancy is important. This thesis adds to the knowledge on this topic and provides information which can be used by clinicians to inform their patients.

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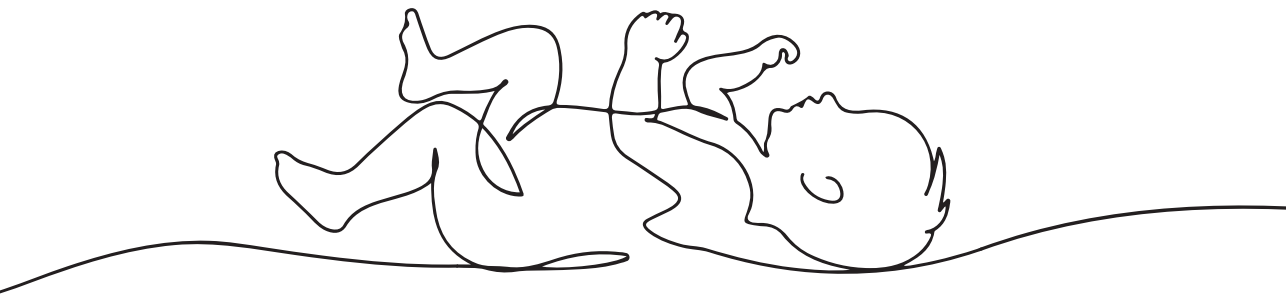

ADDENDUM

SUMMARY

Bipolar disorder is a psychiatric disorder, characterised by recurrent episodes of depression and (hypo)mania. The onset of bipolar disorder is often in late adolescence or early adulthood and it is therefore a disorder that affects women of childbearing age. Pregnancy is a major life event for any woman and women with bipolar disorder are faced with extra challenges. Following childbirth women with bipolar disorder are at high risk (37%) of a bipolar episode. Additionally, mood stabilising medication may be required during pregnancy to prevent bipolar episodes during pregnancy and in the postpartum period. Lithium is the most effective pharmacological treatment for the prevention of both manic and depressive episodes and several studies have shown its efficacy in the prevention of postpartum episodes. Since lithium may be continued during pregnancy it is important to know about the potential consequences for the unborn child. **Chapter 2** presents a review of the literature on the risks and benefits of lithium use during pregnancy, with clinical recommendations. Previous studies have mostly focused on the risk of congenital malformations and showed an increased risk of congenital malformations associated with lithium use during the first trimester of pregnancy. The aim of this thesis was to expand the knowledge of potential consequences by investigating the risk of miscarriage, the influence on fetal growth and birth weight and the long-term consequences for neuropsychological functioning. In addition we investigated whether lithium should be discontinued prior to delivery to prevent neonatal complications.

Consequences for the fetus and neonate

The risk of miscarriage after lithium use during pregnancy was examined in **chapter 3**. We present the results of a retrospective cohort study. This study was part of the DBC study, a study designed to investigate the genetic and phenotypic information of individuals with bipolar disorder. A subcohort was selected of women who had experienced one or more pregnancies, with a diagnosis of bipolar I disorder before pregnancy, and for which detailed data on lithium use and pregnancy outcomes were available. In a self-report questionnaire women were asked about the dates of the abortions, miscarriages, and births of their children. In other questionnaires they were asked for detailed information on their current and lifetime medication use and specific questions were asked on both their current and past use of lithium. The odds of miscarriage were determined for pregnancies with and without lithium use and a logistic regression model was used to calculate the unadjusted odds ratio. Miscarriages occurred in 20.8% of the lithium-exposed pregnancies (16/77), compared with 10.9% of the unexposed pregnancies (40/366) (Odds ratio = 2.14, 95% CI: 1.13–4.06). After adjustment for the age at conception, the clustering of pregnancies per woman, and their lifetime use of valproate and carbamazepine the odds ratio of miscarriage after lithium use during pregnancy was 2.94 (95% CI: 1.39–6.22). Since information on

both lithium exposure and the occurrence of miscarriage were assessed retrospectively by questionnaire, recall bias may have influenced our results. Importantly, this is the second studies that reported an increased risk of miscarriage. This information warrants attention from clinicians treating women with bipolar I disorder of childbearing age.

In **chapter 4** we investigated the effect of prenatal lithium exposure on fetal growth parameters at 20 weeks of gestation and birth weight. This study compared lithium-exposed pregnancies (N = 199) from women referred for advanced fetal ultrasound scanning to the University Medical Centers in Leiden and Rotterdam, with unexposed pregnancies (N = 8148) from the Generation R study, a population-based cohort. Fetal head circumference, abdominal circumference, femur length, and transcerebellar diameter were measured by ultrasound at 18-22 weeks of gestation. Multiple linear regression models were used to examine the association between prenatal lithium exposure and fetal growth parameters and birth weight, after adjustment for maternal BMI, gestational age at the time of measurement, sex of the child, parity, smoking, and psychotropic medication use other than lithium. Lithium use during pregnancy was associated with an average increase in head circumference of 1.77 mm (95% confidence interval: 0.53, 3.01), in abdominal circumference of 5.54 mm (95% confidence interval: 3.95, 7.12) and in femur length of 0.59 mm (95% confidence interval: 0.22, 0.96) at 18-22 weeks gestation. Furthermore, lithium use during pregnancy was associated with an average increase in birth weight of 142.43 grams (95% confidence interval: 58.01, 226.89), whereas it was associated with an average decrease of 1.41 weeks in gestational duration (95% confidence interval: -1.78, -1.05). We performed sensitivity analyses within the Generation R cohort using a using a selection of pregnancies in women with a broadly defined bipolar spectrum disorder but no lithium exposure and compared these with control pregnancies in women with no bipolar spectrum disorder. The purpose was to address the issue of confounding by indication (i.e., the indication for which lithium is most often described, bipolar disorder, can potentially also affect fetal growth independent of lithium exposure). We found no association between maternal bipolar spectrum disorder and fetal growth or birth weight, which may suggest a more specific effect of lithium. Notably, this subcohort of women with bipolar spectrum disorder within the Generation R study likely had a less severe form of bipolar spectrum disorder. Small prenatal changes, such as the increased fetal growth we found in our study, can have impact in later life. As an example, large for gestational age fetuses have an increased risk of developing components of the metabolic syndrome during childhood. Additional research is needed to study growth trajectories in lithium-exposed children.

Several reviews and guidelines recommend to discontinue lithium or reduce its dose at the start of delivery to prevent an increase in lithium blood level with potential negative consequences for the neonate. The aim of **chapter 5** was to explore the evidence behind

these recommendations by investigating lithium blood level changes around delivery and by examining the association between neonatal lithium blood level and neonatal outcome and complications. For this aim we used data of the NP3 study, a prospective multicenter study designed to investigate the clinical outcome of pregnancies in women with bipolar disorder or a history of postpartum psychosis. Lithium blood levels during the final week of pregnancy and the first postpartum week were available for 100 lithium-exposed pregnancies. We found no association between time and lithium blood level/dose ratio. Information on neonatal blood lithium level within 24 hours after birth was available in 29 neonates. We found no association between neonatal lithium blood level and neonatal outcome or complications. Based on these findings, we do not recommend to lower the lithium dose prior to delivery.

Neurodevelopmental consequences for the child

In **chapter 6** the results of a meta-analysis and systematic review of the literature was presented. The objective was to review and synthesize findings from studies examining long-term neurodevelopmental outcomes following intrauterine exposure to lithium or antipsychotics. For this aim preclinical and clinical studies were included. Findings from preclinical studies suggest a deleterious effect of lithium on locomotor activity and delayed development of eye opening and righting reflexes. Additionally, brain weight was found to be lower in lithium-exposed offspring. The risk of bias in these studies was generally unclear due to poor methodological reporting. Only three clinical studies on intrauterine exposure to lithium were found and two out of three studies based their findings solely on maternal reports. These clinical studies reported normal development after intrauterine exposure to lithium. In preclinical studies, antipsychotics seem to increase locomotor activity and anxiety, as well as impair cognition, in exposed offspring. Also, for offspring with intrauterine exposure to haloperidol and risperidone, brain weight was found to be lower. Findings from clinical studies of antipsychotic exposure were inconsistent and difficult to interpret due to the considerable differences in methodology and follow-up period. Several studies reported a transient delay in neurodevelopment among infants with intrauterine exposure to antipsychotics. In our meta-analysis we found a relative risk of 1.36 for neuromotor deficits after in utero exposure to antipsychotics at 6 months of follow-up. However, this estimate was based on only two studies. More studies are needed to provide a more robust estimate and to study the course of motor development over time.

In **chapter 7** the first results of the Image_AL study are reported. This clinical cohort study was performed with the aim to investigate the effects of lithium exposure *in utero* on the neuropsychological functioning of children aged 6 to 14 years. Participants were 99 children of women with a diagnosis of bipolar spectrum disorder (bipolar I, bipolar II and mania/affective psychosis limited to the postpartum period), 56 were exposed to

lithium *in utero* and 43 were not exposed to lithium. Lithium exposure was determined based on the mother's medical file. The Snijders-Oomen Nonverbal Intelligence test and NEPSY-II NL assessments were used to investigate multiple neuropsychological domains. Multiple linear and Negative Binomial regression models were used to study the association between prenatal lithium exposure and neuropsychological functioning after adjusting for several potential confounders (age, sex, parental IQ or education level, maternal disease severity, gestational age at birth, household income, maternal folate use, smoking or alcohol use during pregnancy and other psychotropic medication used during pregnancy). Lithium-exposed offspring did not significantly differ from non-exposed offspring in IQ and neurodevelopmental NEPSY tasks, after correction for potential confounding variables. Also, no relationships between lithium blood level during pregnancy and neuropsychological test outcomes were found. Even though we did not find evidence for significantly altered neuropsychological functioning, it is important to consider the possibility of a small effect in some of the children that could not be detected in our study due to lack of statistical power. For both the Auditory Attention and Visuomotor Precision subtests associations were found between prenatal lithium exposure and the total mistakes made on these tests in simple or less conservative models but not in fully adjusted models. These smaller differences in neuropsychological functioning require further investigation.

In **chapter 8** we present a discussion of all main findings and the final conclusion of this thesis. We emphasise the clinical relevance of our findings and compare lithium to other mood stabilising medication. In addition, hypotheses about the pathophysiological mechanism underlying these findings are proposed. Several clinical recommendations and ideas for future research are discussed. We conclude that lithium use during pregnancy is not only associated with a small but increased risk of congenital malformations, but also with an increased risk of miscarriage and increased fetal growth and birth weight. The data on the long-term development of lithium-exposed children are reassuring. Women of childbearing age requiring mood stabilisation, should be given the opportunity to weigh the risks and benefits of lithium treatment during pregnancy and the postpartum period.

NEDERLANDSE SAMENVATTING

De bipolaire stoornis is een psychiatrische stoornis die gekenmerkt wordt door depressieve en (hypo)manische episoden. De eerste episode ontstaat vaak in de adolescentie of jongvolwassenheid en de stoornis is dus bij veel patiënten reeds aanwezig in de vruchtbare levensfase. Zwangerschap en het krijgen van een kind zijn voor iedere vrouw ingrijpende gebeurtenissen, maar voor vrouwen met een bipolaire stoornis is de peripartum periode extra uitdagend. Na de geboorte van een kind hebben vrouwen met een bipolaire stoornis een hoog risico (37%) op een recidief manie of depressie. Daarnaast kan het nodig zijn om stemmingsstabiliserende medicatie te gebruiken tijdens de zwangerschap, en dit heeft potentiële gevolgen voor het ongeboren kind. Lithium is de meest effectieve stemmingsstabilisator en vermindert het risico op depressieve en manische episoden. Een aantal onderzoeken hebben aangetoond dat lithium tevens effectief is in het voorkomen van een postpartum episode. Daarom is het belangrijk om te weten welke potentiële negatieve effecten lithium gebruik tijdens de zwangerschap kan hebben voor het ongeboren kind. **Hoofdstuk 2** is een review van de literatuur en in dit hoofdstuk worden alle voor- en nadelen van lithiumgebruik tijdens de zwangerschap besproken. De meeste studies rapporteren over onderzoek naar het risico op aangeboren afwijkingen en zij tonen aan dat lithium gebruik tijdens het eerste trimester van de zwangerschap geassocieerd is met een verhoogd risico op aangeboren afwijkingen. Minder is bekend over het risico op miskramen, de foetale groei en het geboortegewicht, neonatale complicaties en de lange termijn ontwikkeling van blootgestelde kinderen. Dit proefschrift had als doel om de kennis hierover te vergroten.

De gevolgen voor de foetus en pasgeborene

Het risico op een miskraam na lithium gebruik tijdens de zwangerschap is onderzocht is **hoofdstuk 3**. We presenteren de resultaten van een retrospectieve cohort studie. Dit onderzoek was onderdeel van de Bipolar Genetics studie (BIG), een cohort studie naar de genetische en fenotypische eigenschappen van de bipolaire stoornis. Er werd een subgroep geselecteerd van vrouwen die één of meer zwangerschappen hadden doorgemaakt, de diagnose bipolaire stoornis al voor de zwangerschap hadden gekregen en van wie informatie beschikbaar was over zwangerschapsuitkomst en lithium gebruik tijdens de zwangerschap. Deze vrouwen werden middels een vragenlijst gevraagd op welke datum zij een miskraam, abortus of levende geboorte van een kind hadden doorgemaakt. In een andere vragenlijst werd gevraagd naar het gebruik van medicatie gedurende het hele leven en meer specifiek werden vragen over lithium gebruik gesteld. De kans (*odds*) op een miskraam werd berekend voor zwangerschappen met of zonder lithium gebruik. Een logistisch regressiemodel werd gebruikt om de ongecorrigeerde *odds* ratio te berekenen. 20,8% (16/77) van de aan lithium blootgestelde zwangerschappen eindigden in een miskraam versus 10,9% (40/366) van de niet blootgestelde zwangerschappen (*Odds* ratio = 2,14, 95% CI: 1,13–4,06). Na correctie

voor leeftijd gedurende conceptie, meerdere zwangerschappen per vrouw, en het gebruik van valproïnezuur of carbamazepine op enig moment in het leven, was de *odds* ratio voor het krijgen van een miskraam na lithium gebruik tijdens de zwangerschap 2,94 (95% CI: 1,39–6,22). Aangezien zowel het krijgen van een miskraam als het gebruik van lithium retrospectief was vastgesteld, moet rekening gehouden worden met de mogelijke invloed van herinneringsbias op onze resultaten. Dit is het tweede onderzoek dat een verhoogd risico op een miskraam vindt. Deze informatie verdient aandacht van behandelaren van vrouwen met een bipolaire I stoornis in de vruchtbare leeftijd.

In **hoofdstuk 4** onderzoeken we het effect van lithium gebruik tijdens de zwangerschap op de foetale groei en het geboortegewicht. In deze studie werden twee groepen vergeleken: 1) een groep lithium-blootgestelde zwangerschappen van vrouwen die voor een geavanceerde echo werden verwezen naar het Erasmus Medisch Centrum of het Leids Universitair Medisch Centrum (N = 199), 2) een groep controle zwangerschappen uit de normale populatie van de *Generation R Study* (N = 8148). Hoofdomtrek, buikomtrek, femur lengte en trans-cerebellaire diameter van de foetus werden gemeten door middel van echo bij 18-22 weken zwangerschap. Multipele lineaire regressiemodellen werden gebruikt om de associatie tussen lithium gebruik tijdens de zwangerschap en foetale groei en geboortegewicht te onderzoeken. Hierbij werd gecorrigeerd voor BMI van de moeder, zwangerschapsduur bij meting, geslacht van het kind, pariteit, roken tijdens de zwangerschap en ander psychofarmaca gebruik tijdens de zwangerschap. Lithium gebruik tijdens de zwangerschap was geassocieerd met een gemiddelde toename in hoofdomtrek van 1,77 mm (95% betrouwbaarheidsinterval: 0,53-3,01), buikomtrek van 5,54 mm (95% betrouwbaarheidsinterval: 3,95-7,12) en femur lengte van 0,59 mm (95% betrouwbaarheidsinterval: 0,22-0,96) bij 18-22 weken zwangerschapsduur. Daarnaast was er een associatie met een verhoogd geboortegewicht van 142,43 gram (95% betrouwbaarheidsinterval: 58,01-226,89) en een kortere zwangerschapsduur van 1,41 weken (95% betrouwbaarheidsinterval: -1,78 - -1,05). Binnen de *Generation R* groep werd een sensitiviteitsanalyse gedaan waarbij zwangerschappen van vrouwen met een bipolaire spectrum stoornis werden vergeleken met zwangerschappen van vrouwen uit de normale populatie. Er werd geen associatie gevonden tussen maternale bipolaire stoornis en foetale groei of geboortegewicht, wat suggereert dat we te maken hebben met een specifiek effect van lithium. Het is echter belangrijk om op te merken dat deze groep vrouwen waarschijnlijk een minder ernstige vorm van de bipolaire stoornis had. Kleine veranderingen in foetale groei kunnen de latere ontwikkeling van het kind beïnvloeden. Zo hebben bijvoorbeeld te grote foetussen op de kinderleeftijd een hoger risico op afwijkingen die passen binnen het metabool syndroom. Aanvullend onderzoek is nodig om de groei van lithium-blootgestelde kinderen op latere leeftijd in kaart te brengen.

Verschillende richtlijnen en overzichtsartikelen raden aan om lithium te stoppen of te verlagen wanneer de bevalling start. De rationale hierachter is om te voorkomen dat de lithiumspiegel stijgt na de bevalling met negatieve consequenties voor de pasgeborene. In **hoofdstuk 5** onderzoeken we de evidentie achter deze aanbeveling door te testen of: 1) er sprake is van een verandering in lithium bloedspiegels rondom de bevalling, en 2) er een associatie is tussen neonatale lithiumspiegel en neonatale complicaties. Hiervoor is gebruik gemaakt van data van de *NP3 study*, een prospectief multicenter onderzoek naar zwangerschapsuitkomsten van vrouwen met een bipolaire stoornis of postpartum psychose in de voorgeschiedenis. Lithiumspiegels in de week voor en na de bevalling waren beschikbaar voor 100 zwangerschappen. We zagen geen verandering in de lithium bloedspiegel/dosering ratio over de tijd. Neonatale lithiumspiegels werden gemeten in de eerste 24 uur na geboorte bij 29 pasgeborenen. Er werd geen associatie gevonden tussen neonatale lithium bloedspiegel en neonatale complicaties. Op basis van deze bevindingen raden wij het af om lithium te stoppen of te verlagen voor de bevalling.

Gevolgen voor de neuropsychologische ontwikkeling van het kind

In **hoofdstuk 6** presenteren we de resultaten van een meta-analyse en systematisch literatuur onderzoek. Het doel was een overzicht te geven van alle tot dan toe gepubliceerde onderzoeken naar de lange termijn gevolgen van intra-uteriene blootstelling aan lithium en antipsychotica. Zowel klinische als preklinische onderzoeken werden geïncludeerd. Bevindingen uit preklinische onderzoeken laten een nadelig effect zien van blootstelling aan lithium op locomotorische activiteit en vertraagde ontwikkeling van het ogen openen en de oprichtreflex. Ook werd er een lager gewicht van het brein gevonden van lithium blootgestelde nakomelingen. Het risico op bias in deze studies was vaak onduidelijk door beperkte methodologische verslaglegging. Er werden slechts drie klinische onderzoeken naar de effecten van lithium gevonden en twee hiervan baseerden hun resultaten volledig op rapportage door de moeder. Deze studies rapporteerden een normale ontwikkeling van lithium-blootgestelde kinderen. Preklinische studies toonden ook nadelige effecten van intra-uteriene blootstelling aan antipsychotica. Er was sprake van een toegenomen locomotorische activiteit en angst, en de cognitieve ontwikkeling was gestoord. Daarnaast werd er een lager gewicht van het brein gevonden. De klinische studies naar antipsychotica blootstelling toonden grote variatie in methode en de uitkomsten waren inconsistent, waardoor het moeilijk was om deze resultaten de interpreteren. Meerdere studies toonden een vertraging in de neuropsychologische ontwikkeling, die van voorbijgaande aard leek te zijn. In onze meta-analyse vonden we een relatief risico van 1,36 voor motorische afwijkingen na blootstelling aan antipsychotica op de leeftijd van zes maanden. Deze schatting was gebaseerd op slechts twee studies en meer onderzoek is nodig om de motorische ontwikkeling goed in kaart te brengen.

De eerste resultaten van de *Image_AL study* worden beschreven in **hoofdstuk 7**. Deze studie was ontworpen met het doel om de neuropsychologische effecten van intra-uteriene blootstelling aan lithium te bestuderen bij kinderen van 6 tot 14 jaar. Er deden 99 kinderen mee aan deze studie, 56 waren blootgesteld aan lithium en 43 waren niet blootgesteld. Alle kinderen hadden een moeder met een diagnose van een bipolaire spectrum stoornis (bipolaire I stoornis, bipolaire II stoornis of een manie of affectieve psychose in de postpartum periode). Uit het medisch dossier van de moeder werd informatie gehaald over lithium gebruik tijdens de zwangerschap. Verschillende neuropsychologische domeinen werden onderzocht door middel van een intelligentieonderzoek (SON-R 6-40) en de NEPSY-II NL test. Multipele lineaire en negatief-binomiale regressiemodellen werden gebruikt om de associatie tussen prenatale lithium blootstelling en neuropsychologisch functioneren van het kind te onderzoeken. Hierbij werd gecorrigeerd voor potentiële *confounders* (leeftijd, geslacht, IQ of opleidingsniveau van de ouder, aantal bipolaire episoden in de voorgeschiedenis van moeder, zwangerschapsduur bij geboorte, inkomsten per huishouden en foliumzuurgebruik, roken, alcoholgebruik en ander psychofarmaca gebruik tijdens de zwangerschap). De aan lithium blootgestelde kinderen toonden geen significante verschillen ten opzichte van niet blootgestelde kinderen, na correctie voor potentiële *confounders*. Er werd ook geen relatie gevonden tussen de lithiumspiegel tijdens de zwangerschap en het neuropsychologisch functioneren. Toch moeten we rekening houden met de mogelijkheid van kleine effecten van lithium die wij niet konden aantonen in onze studie vanwege een gebrek aan statistische power. Voor zowel de Auditieve Aandacht en de Visuomotorische Coördinatie subtaken werden associaties gevonden tussen lithium blootstelling en het totaal aantal fouten in deze subtaken in de simpele of minder conservatieve regressiemodellen. Deze kleine verschillen verdienen aandacht in vervolgonderzoek.

In **hoofdstuk 8** presenteren we de discussie over alle bevindingen en de conclusie van dit proefschrift. We benadrukken de klinische relevantie van onze onderzoeksresultaten en vergelijken lithium met andere stemmingsstabiliserende medicatie. Daarnaast presenteren we ook enkele hypotheses voor de onderliggende pathofysiologische mechanismen van onze bevindingen. Klinische aanbevelingen worden gedaan en ideeën voor vervolg onderzoek worden besproken. We concluderen dat lithium gebruik tijdens de zwangerschap niet alleen geassocieerd is met een licht verhoogd risico op aangeboren afwijkingen, maar ook met een verhoogd risico op een miskraam en toegenomen foetale groei en geboortegewicht. De resultaten van het onderzoek naar de neuropsychologische ontwikkeling van aan lithium blootgestelde kinderen op latere leeftijd zijn geruststellend. Vrouwen in de vruchtbare leeftijd, die een indicatie hebben voor stemmingsstabiliserende medicatie, moeten de kans krijgen om de voor- en nadelen van lithium gebruik tijdens de zwangerschap en de postpartum periode af te wegen.

PHD PORTFOLIO

Name PhD student: Eline Poels
Erasmus MC, Department of Psychiatry
PhD period: April 2015- June 2021
Promotors: W.J.G. Hoogendijk, V. Bergink
Supervisor: T.J.H. White

PhD training and activities	Year	Hours	ECTS
Master of science in Clinical Epidemiology	2016-2018		70
Core:			
- Study design			
- Biostatistical Methods I: Basic Principles			
- Biostatistical Methods II: Classical Regression Models			
- Principles in Causal Inference			
- Principles of Research in Medicine and Epidemiology			
- Methods of Clinical Research			
- Clinical Trials			
- Health Economics			
- The Practice of Epidemiologic Analysis			
- Fundamentals of Medical Decision Making			
- Clinical Translation to Epidemiology			
- Clinical Epidemiology			
Electives:			
- Repeated Measurements in Clinical Studies			
- Psychiatric Epidemiology			
- Women's Health			
- Topics in Meta-analysis			
- Cohort Studies			
- Principles of Genetic Epidemiology			
- History of Epidemiologic Ideas			
- Maternal and Child Health			
- Missing Values in Clinical Research			
- Causal Mediation Analysis			

Other courses	Year	Hours	ECTS
Systematic literature retrieval in PubMed	2015		0.3
Workshop Endnote	2015		0.3
CPO course	2015		0.3
BKO-workshop 'Teach the teacher II'	2016	16	
BKO-workshop 'omgaan met groepen'	2016	4	
Good Clinical Practice (BROK) course	2016		4.0
Research Integrity	2017		0.3
MRI operator and safety	2017	10	
Freesurfer course	2017	32	
Linux course	2017	3	
Additional clinical courses in Child and Adolesent Psychiatry	2018	60	
FSL course	2018	40	
Presentations	**Year**		
Research meeting Child and Adolescent psychiatry Erasmus MC	2017		
Poster presentation VJC NVVP	2017		
Scientific meeting Department of Psychiatry Erasmus MC	2017		
KenBIS (Kenniscentrum Bipolaire Stoornissen)	2017		
Scientific meeting Department of Obstetrics LUMC	2018		
Women's Mental Health Group Erasmus MC	2018		
Patient Association Plus Minus	2019		
Keynote Lecture Perinatal Psychiatry Conference Leuven	2019		
Symposium lecture VJC NVVP	2020		
Lecture at Reinier van Arkel Groep	2021		
Najaarssymposium Bipolaire Stoornissen	2021		
Supervision and Teaching	**Year**		
Medical students (VO Psychiatrisch onderzoek en Bijzondere Tuchtzaak)	2016		
PANSS training research students	2018		
Weekly Journal Club Medical Students	2018-2019		
Elective Psychiatry for Medical Students	2018		
Master thesis:			
R. Hussainali, Psychology	2016		
M. Scheffer, Medicine	2017		
S. van Dijk, Psychology	2017		
E. van Schouwenburg, Pharmacy	2017		
L. van Dijke, Medicine	2018		
B. Schreuders, Medicine	2020		

CURRICULUM VITAE

Eline Poels was born in 1990 in Veghel, The Netherlands. She grew up in Gorinchem, where she received her VWO diploma in 2008. That same year she started her medical education at the Erasmus University in Rotterdam. During her study, she was a member of Skadi rowing club and part of the Women's Freshmen Eight in 2009. Eline worked as a student assistant at the Mother and Baby Unit of the Department of Psychiatry, Erasmus MC. In 2012 she worked on her master's thesis at Columbia University in New York City at the division of Translational Imaging. During this internship Eline was involved in imaging research (PET and MRS) on schizophrenia. After graduating from medical school in 2015 Eline commenced her PhD trajectory at the department of Psychiatry, Erasmus MC, supervised by Witte Hoogendijk, Sabine Roza, Veerle Bergink and Tonya White. A few months later she started her psychiatry residency at Erasmus MC. From 2016 to 2018 she studied Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES) and obtained her master degree in 2018 (cum laude). During her residency Eline worked at inpatient and outpatient clinics at Erasmus MC in Rotterdam and Parnassia Group and Youz in The Hague. She finished her residency in November 2021. Eline will continue to combine clinical work and research as a psychiatrist and postdoctoral researcher at the Department of Psychiatry of Erasmus MC.

LIST OF PUBLICATIONS

1. Gilden J, Poels E, Lambrichts S, Vreeker A, Boks M, Ophoff R, Kahn R, Kamperman A, Bergink V. Bipolar episodes after all reproductive events in women with bipolar I disorder, a study of 919 pregnancies. *Journal of Affective Disorders.* 2021 Dec 1.
2. Poels EMP, Schrijver L, Kamperman A, van Kamp IL, Honig A, Bijma HH, White T, Hoogendijk WJG, Bergink V. The effect of prenatal exposure to lithium on the neuropsychological development of the child. *Bipolar Disorders.* 2021 Sep 29.
3. Poels EMP, Sterrenburg K, Wierdsma AI, Wesseloo R, Beerthuizen A, van Dijke L, Lau C, Hoogendijk WJ, Marroun HE, van Kamp IL, Bijma HH, Bergink V. Lithium exposure during pregnancy increases fetal growth. *Journal of Psychopharmacology.* 2020 Jul 20.
4. Molenaar NM, Poels EMP, Robakis T, Wesseloo R, Bergink V. Management of lithium dosing around delivery: An observational study. *Bipolar Disorders*. 2020 Jun 11.
5. Poels EMP, Kamperman AM, Vreeker A, Gilden J, Boks MP, Kahn RS, Ophoff RA, Bergink V. Lithium Use during Pregnancy and the Risk of Miscarriage. *Journal of Clinical Medicine*. 2020 Jun 11.
6. Poels EMP, Bijma HH, Galbally M, Bergink V. Lithium during pregnancy and after delivery: a review. *International Journal of Bipolar Disorders*. 2018 Dec; 6:26.
7. Poels EMP, Schrijver L, Kamperman AM, Hillegers MHJ, Hoogendijk WJG, Kushner SA, Roza SJ. Long-term neurodevelopmental consequences of intrauterine exposure to lithium and antipsychotics: a systematic review and meta-analysis. *European Child & Adolescent Psychiatry*. 2018 Jun 11.
8. Poels EMP, Girgis RR, Thompson JL, Slifstein M, Abi-Dargham A. In vivo binding of the dopamine-1 receptor PET tracers [^{11}C]NNC112 and [^{11}C]SCH23390: a comparison study in individuals with schizophrenia. *Psychopharmacology (Berl).* 2013 Jul;228(1):167-74.
9. Poels EMP, Kegeles LS, Kantrowitz JT, Slifstein M, Javitt DC, Lieberman JA, Abi-Dargham A, Girgis RR. Imaging glutamate in schizophrenia: review of findings and implications for drug discovery. *Molecular Psychiatry.* 2014 Jan;19(1):20-9.
10. Poels EMP, Kegeles LS, Kantrowitz JT, Javitt DC, Lieberman JA, Abi-Dargham A, Girgis RR. Glutamatergic abnormalities in schizophrenia: a review of proton MRS findings. *Schizophrenia Research.* 2014 Feb;152(2-3):325-32.
11. Klumpers U, Poels E, Stevens A. Book chapter: 'Bipolaire stoornissen bij vrouwen' as part of the 'Handboek bipolaire stemmingsstoornissen'. *Accepted.*