Medicines Adverse Reactions Committee

Meeting date	**6 December 2018**	Agenda item 3.2.4	
Title	**Fetal exposure to lithium during pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Lithium	**Medicines** Lithicarb FC film coated tablet 250 mg (400mg)* Lithium Carbonate capsule 250 mg Priadel modified release tablet 400 mg	**Sponsors** Mylan NZ Ltd Douglas Pharmaceuticals Ltd W M Bamford & Co Ltd	
Funding	Yes		
Previous MARC meetings	Lithium and pregnancy has not been discussed previously.		
Prescriber Update	No articles on lithium in relation to pregnancy have been published previously.		
Schedule	Prescription medicine		
Usage data	Number of lithium carbonate prescriptions dispensed at a community pharmacy 2017: Lithium carbonate cap 250 mg 9160 Lithium carbonate tab 250 mg 8659 Lithium carbonate tab 400 mg 3127 Lithium carbonate long-acting tab 400 mg 12082 Source: MoH Pharmaceutical Collection, extracted 30 May 2018.		
Advice sought	**The Committee is asked to advise whether:** – The pregnancy section of the data sheets for lithium products need to be updated. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.		

Note that the supplier has discontinued Lithicarb FC, 400 mg lithium carbonate tablets. Patients can switch to the 400 mg long-acting tablet (Priadel). The 250 mg tablets remain available for now and the 250 mg capsules will remain available (PHARMAC).

Table of Contents

1.0 PURPOSE

Lithium is a common treatment for bipolar disorder. This illness is diagnosed in many women of childbearing age. There have been concerns about teratogenicity and both maternal and offspring complications if lithium is used in pregnant women, especially during the first trimester of pregnancy. Results of animal and human studies have not been consistent in this respect. However, many of the clinical studies included small numbers of patients, which adds uncertainty to the results.

In August 2018, an international collaborative meta-analysis of six cohorts of pregnant women and their children was published aiming to investigate the association between *in-utero* lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity and congenital malformations (1).

The purpose of this paper is to review this article, other published data and reported cases to assess if any updates to the data sheets of products containing lithium are required, and if further communication of this issue is needed.

2.0 BACKGROUND

2.1 Lithium

2.1.1 History, properties and indications

Lithium is a monovalent cation which is used in in salt forms to treat psychiatric disease. In the 19th century large doses of lithium were used to dissolve uric acid crystals in urine obtained from patients with gout, which proved to be toxic. Later lithium was used to treat mania because at that time it was believed that high uric acid levels caused many psychiatric disorders like depression and mania. When sodium was found to be an important cause of hypertension and cardiovascular disease, physicians prescribed lithium salts to replace sodium chloride as table salt. This led to serious side effects and deaths and lithium salts were banned. Later lithium has returned as an important medicine with appropriate dosing (2).

The products available in NZ all contain lithium carbonate and are given as oral tablets. The dosing is individualised, but for patients of average weight (70 kg) the initial dose is 400-1,200 mg per day. Lithium concentrations in serum are then measured and the dose is adjusted accordingly. Lithium is rapidly and completely absorbed after oral administration. Being a cation, it is not metabolised but excreted unchanged via the kidneys with a half-life of 12 hours. It is totally distributed in the body fluid and ultimately slowly enters the cells. Lithium has a narrow therapeutic/toxic ratio and the therapeutic range is 0.5-1.0 mmol/l (higher levels are needed to treat acute mania)(2). Note that a blood sample for testing lithium levels should be collected 10–14 hours after the last dose (3). There are several interactions described involving lithium.

The indications for lithium carbonate in NZ are:

- Treatment of mania and hypomania.
- Lithium may also be tried in the treatment of some patients with recurrent bipolar depression, for which treatment with other antidepressants has been unsuccessful.
- Prophylactic treatment of recurrent affective disorders.

Lithium is believed to be a mood stabiliser in bipolar mood disorders, preventing the relapses of manic attacks rather than hampering the depressive episodes. It has also been shown to reduce the risk of self-harm (2).

2.1.2 Side effects

Most side effects of lithium are dose-dependent. Reported adverse effects include fine hand tremor, nystagmus, hypothyroidism, weight gain, cardiovascular effects and memory impairment. Other unwanted metabolic effects are hyperparathyroidism and hypercalcemia. Renal damage is a rare complication of lithium therapy.

As lithium is an electrolyte, it can affect the balance of electrolytes in the body. Some minor side effects such as nausea and headache can be generally overcome by increased fluid intake (2) .

2.2 Bipolar disorder

2.2.1 Characterisation, epidemiology and symptoms

Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania (changes in mood, energy, activity, behaviour, sleep, and cognition that are similar to those of mania, but less severe) and major depression. The cause is unknown, although there is a family tie (genetic inheritance). The subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes, and nearly always experience hypomanic and major depressive episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes (4).

It is thought that between 1–5 in 100 people might have some form of bipolar disorder(5). In New Zealand, bipolar disorder may be more prevalent among Māori (4.6%), compared to Pacific peoples (3.7%) and people of European and other ethnicities (1.8%). The first noticeable mood disturbance in people with bipolar disorder often occurs during adolescence; one study found the mean age of onset was 17 years (+/- 4 years) (6).

Below are clinical features of the different states of bipolar disorder.

<u>Depression</u>

- Loss of interest and pleasure in activities enjoyed before.
- Overwhelming sadness.
- Withdrawing from friends and avoiding social activities.
- Ceasing self-care tasks like shopping and showering.
- Changes to appetite and sleep patterns.
- Lack of concentration, extreme tiredness, and feelings of guilt or worthlessness.
- Development of false beliefs (delusions) of persecution or guilt for some people.

<u>Mania</u>

- Elevated mood - the person feels extremely high, elated, and full of energy.
- Increased energy and over-activity.
- Reduced need for sleep.
- Irritability.
- Rapid thinking and speech.
- Recklessness, such as spending large amounts of money buying items that are not really needed.
- Grandiose plans and beliefs.
- Lack of insight.

Mania is diagnosed when symptoms have been present for a week or more. Hypomania is less severe and may have shorter duration (7).

The presenting mood episode is usually major depression but it can also be mania, hypomania or mixed features (mood episodes that are accompanied by symptoms of the opposite polarity).

Patients with bipolar disorder may experience recurrent mood episodes that can be life-threatening. For each patient, manic and depressive episodes may recur in roughly equal proportions, or there may be a predominant polarity. Some patients return to their usual level of functioning after periods of illness. Some will have some ongoing difficulties.

Recurrence of bipolar mood episodes is associated with a greater number of suicide attempts, as well as poorer social and occupational functioning and cognitive impairment. In addition, treatment resistance for each episode appears to increase with each additional recurrence (4).

2.2.2 Bipolar disorder and pregnancy – what are the risks?

As onset of bipolar disorder typically occurs during early reproductive years (late teens to early 20s), women are at high risk for episodes during fertile years. Women with bipolar disorder have a significant risk of relapse both during pregnancy and especially following childbirth (1).

Episodes of postpartum psychosis occur after approximately 25% (25 in 100) of births to women with bipolar disorder. This is several hundred times higher than for women who have not had previous psychiatric illness. Postnatal depression follows a further 25% (25 in 100) of births. Therefore, about half of women with bipolar disorder (50 in 100) stay well after having a baby and about half may have an episode of illness.

Both high (manic) and low (depressive) episodes occur around childbirth in women with bipolar disorder, and can be severe. Mood symptoms like elation, irritability and depression are common. Psychotic symptoms such as delusions and hallucinations can also occur (8).

Comments: Many women with bipolar disorder have a high risk of episodes during reproductive years. During pregnancy there are risks of morbidity, complications or poor pregnancy outcome from the disorder itself that need to be balanced against risks from treatment of the disorder.

2.3 General aspects on use of lithium in pregnancy and historical data

Treatment with lithium can reduce the risk of relapse, both during pregnancy and post partum. However, there are concerns about teratogenicity and maternal and offspring complications. Still, lithium remains one of the mainstays for treatment of bipolar disorders, even during pregnancy.

Lithium crosses the placenta and the fetus receives 100% of the medicine during pregnancy. Generally, medication effects upon the fetus vary according to gestational age. The fetus is most vulnerable to major morphologic teratogenesis during organogenesis in the embryonic period of the first trimester (organogenesis occurs 5 to 10 weeks from the first day of the last menstrual period) while neonatal toxicity and withdrawal are the result of third trimester exposure.

The base rate for congenital defects in the general population is at least two to five percent. The incidence of defects is two to three percent at birth but increases to five percent or higher after one year when hidden defects are discovered (9).

Lithium use in early pregnancy has been linked to abnormalities of the central nervous system, heart and blood vessels in the exposed fetus in animal studies. Similar risks of malformation, preterm birth and other pregnancy and neonatal complications have been found in human studies, however, the

findings are not consistent across studies. Many older studies did not have enough statistical power or were subject to recall bias or other confounding factors (1).

In the 1970s, a register was established in Denmark called the Danish Register of Lithium Babies. Evaluation of infants born to mothers treated with lithium during the first trimester suggested an increased risk of a cardiac effect called Ebstein's anomaly by a factor of 400 and risk of overall cardiac defects that was increased with a factor of 5 (10). However, the reports from the Register of Lithium Babies were subject to recall bias resulting in an overestimation of adverse outcome data. The final report from 1979 included 225 children born to lithium exposed women. Of these 18 had congenital cardiac defects including 6 with Ebstein's anomaly (10).

Comments: The increased risk of Ebstein's anomaly after exposure of lithium during the first trimester of pregnancy has later been quantified at 20-fold an absolute rate of approximately 1 in 1000.

2.4 Data sheets

Information on use in pregnancy from data sheets and international product information is provided below. Note that lithium carbonate is contraindicated during breastfeeding in all NZ data sheets.

2.4.1 Lithicarb FC NZ data sheet

The data sheet for Lithicarb (Mylan New Zealand Limited) currently includes the following information on use in pregnancy (11):

<u>In section 4.6, Pregnancy</u>
Category D: Medicines which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These medicines may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The risk of birth defects may be increased by when lithium is used during the first trimester. Second trimester detailed ultrasound examination and foetal echocardiography should be considered for women who have been treated with lithium during the first trimester of pregnancy. The newborn may show signs of lithium toxicity.

There is epidemiological evidence that lithium may be harmful to the foetus in human pregnancy.

Total no. "lithium babies" reported	Malformed infants	Ebstein's anomaly and other major cardiovascular malformations
225	25 (11%)	18 (8%)

It is strongly recommended that lithium be discontinued before a planned pregnancy. If it is considered essential to maintain LITHICARB FC treatment during pregnancy, serum lithium levels should be monitored closely since renal function changes gradually during pregnancy and suddenly at parturition, requiring dosage adjustments. It is recommended that lithium be discontinued shortly before delivery and recommenced a few days post-partum.

Babies may show signs of lithium toxicity necessitating fluid therapy in the neonatal period. Babies born with low serum lithium concentrations may have a flaccid appearance which returns to normal without any treatment.

The data sheet was updated 30 August 2017. One change in the update was in section 4.6: Risk category added. Additional safety information for use during first trimester of pregnancy.

2.4.2 Lithium Carbonate NZ data sheet

The data sheet for Lithium Carbonate (Douglas Pharmaceuticals Limited) states the information from section 3 in the Lithicarb FC data sheet above: "There is epidemiological evidence….recommenced a few days post-partum". This data sheet was updated 18 April 2017 (12).

2.4.3 Priadel NZ data sheet

The text is the same for Priadel (W M Bamford & Co Ltd) as for Lithicarb FC above (13). The data sheet was updated 30 August 2017.

2.4.4 Priadel UK product information

The UK product information for Priadel (Aventis Pharma Limited) currently includes the following information on use in pregnancy (14):

Lithium therapy should not be used during pregnancy, especially during the first trimester, unless considered essential. There is epidemiological evidence that it may be harmful to the foetus in human pregnancy. Lithium crosses the placental barrier.

In animal studies, lithium has been reported to interfere with fertility, gestation and foetal development. Cardiac effects, especially Ebstein anomaly, and other malformations have been reported. Therefore, a pre-natal diagnosis such as ultrasound and electrocardiogram examination is strongly recommended. In certain cases where a severe risk to the patient could exist if treatment were stopped, lithium has been continued during pregnancy.

If it is considered essential to maintain lithium treatment during pregnancy, serum lithium levels should be closely monitored and measured frequently since renal function changes gradually during pregnancy and suddenly at parturition. Dosage adjustments are required. It is recommended that lithium be discontinued shortly before delivery and reinitiated a few days post-partum.

Neonates may show signs of lithium toxicity including symptoms such as lethargy, flaccid muscle tone, or hypotonia. Careful clinical observation of the neonate exposed to lithium during pregnancy is recommended and lithium levels may need to be monitored as necessary.

<u>Women of child-bearing potential</u>
Women of child-bearing potential should use effective contraceptive methods during treatment with lithium.

<u>Fertility</u>
Published studies in rats exposed to lithium have reported spermatogenesis abnormalities that may lead to impairment of fertility. This risk may also potentially apply to humans.

This product information was updated 13 September 2018.

2.4.5 Lithium carbonate US product information

The US product information for Lithium carbonate (Mylan Pharmaceuticals Inc) currently includes the following information on use in pregnancy (15):

Adverse effects on implantation in rats, embryo viability in mice, and metabolism *in vitro* of rat testis and human spermatozoa have been attributed to lithium, as have teratogenicity in submammalian species and cleft palate in mice.

In humans, lithium may cause fetal harm when administered to a pregnant woman. Data from lithium birth registries suggest an increase in cardiac and other anomalies especially Ebstein's anomaly. If this drug is used in women of childbearing potential, or during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised by their physician of the potential hazard to the fetus.

2.4.6 Two examples of Australian product information

The product information for Lithicarb (16) and Quilonum SR (17) (both Aspen Pharmacare Australia Pty Limited) currently include the following information on use in pregnancy:

Lithicarb 250 mg

Category D of Australian Categorisation Risk of Drug Use in Pregnancy.
Lithium enters the fetal circulation and cases of disturbance of the thyroid function of the newborn infant have been reported. Available data also indicate that lithium during pregnancy may cause malformations of the cardiovascular system.

Therefore, the potential benefits of continued administration during pregnancy must be weighed against the possible adverse effects. If administration of lithium is considered essential and continued during pregnancy, serum lithium levels must be monitored closely at routine intervals, particularly at parturition. Babies showing signs of lithium intoxication may require fluid therapy and they may have a flaccid appearance which returns to normal without treatment. It is strongly recommended that lithium be discontinued before a planned pregnancy.

Effects on fertility
In animal studies, lithium has been reported to interfere with fertility, gestation and fetal development.

This product information was last updated (reformatted) 22 August 2018.

Quilonum SR Lithiumcarbonate 450 mg

Use in Pregnancy (Category D)
Lithium crosses the placental barrier. In animal studies, lithium has been reported to interfere with fertility, gestation, and foetal development. In humans, lithium may cause foetal harm when administered to a pregnant woman. Data from the lithium birth register, which collects data on the known cases of first trimester exposure to lithium suggests an increase in cardiac and other abnormalities, especially Ebstein's anomaly. As of 1980, 225 infants were included in the register. Of these, 25 infants were born with congenital abnormalities, including 18 with serious cardiovascular malformations, 6 of which were cases of Ebstein's anomaly.

Lithium taken near term may produce symptoms of lithium toxicity in the newborn which include disturbance of thyroid function. Most effects are self-limiting with resolution within 1-2 weeks. Lithium should not be used in pregnancy, especially during the first trimester, unless in the judgement of the physician it is considered necessary. Patients should be informed of potential hazards to the foetus.

In certain cases where a severe risk to the patient could have existed if treatment were stopped, lithium has been continued during pregnancy. If given, serum levels should be measured frequently because of the changes in renal function associated with pregnancy and parturition.

This product information was updated 12 December 2017.

Comments: One product information updated recently was the UK Priadel. It was updated one month after the publication of the meta-analysis. This data sheet contains information on lithium use during the first trimester and in the following trimesters, the importance of performing a pre-natal diagnosis such as ultrasound and electrocardiogram examination and also to closely monitor lithium levels through the pregnancy. This is not included in all of the product information above, although, except for the Lithium carbonate data sheet, it is included in the NZ data sheets.

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

The information on the safety of lithium during pregnancy is to a large extent based on case reports and small studies. In the last years, two larger cohort studies have been published. These studies are described in the sections 3.1.1 and 3.1.2 below.

3.1.1 Munk-Olsen T,Liu X, Viktorin A et al 2018 (1)

The aim of this meta-analysis was to investigate the association between *in-utero* lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity, and congenital malformations. The study is attached to this paper as Annexe 1.

Data from pregnant women and their children from 3 population-level register-based cohorts from the community (Denmark, Sweden, and Ontario, Canada) and in 3 clinical cohorts (the Netherlands, UK, and the US) were analysed. Definitions of exposures, outcomes, potential confounders, and statistical analyses were harmonised across sites a priori by use of a shared study protocol to reduce heterogeneity and bias.

Pregnancies were eligible for analysis if the pregnancy resulted in a live-born singleton between 1997 and 2015, if health-related information was available for both mother and infant, and if the mother had a mood disorder (bipolar disorder or major depressive disorder) or if she had been given lithium during pregnancy (at least two dispensations of lithium during pregnancy that were dispensed any time from 1 month before conception until the delivery, or a single lithium dispensation during pregnancy when there was at least one other lithium dispensation within 6 months before or after this date). For the lithium-exposed group, a documented psychiatric diagnosis was not required, since non-psychiatric indications for lithium are rare. Pregnancies during which the mother had been prescribed known teratogenic drugs were excluded.

Pregnancies were grouped into a lithium-exposed group and a mood-disorder reference group. Lithium exposure during early pregnancy was further defined for register-based cohorts, as at least two dispensations of lithium in the first trimester (from 1 month before conception to 90 days of gestation), or one dispensation in the first trimester with at least one other dispensation within 6 months before or after this date; and for clinical cohorts, medical records were used to define lithium use in the first trimester.

The mood-disorder reference group comprised pregnant women with a known history of mood disorder (bipolar disorder or major depressive disorder), without exposure to lithium from 90 days before pregnancy until delivery.

Outcomes were divided into four subcategories:

1. Pregnancy complications, identified during pregnancy or within 42 days after delivery by use of hospital-based diagnoses for pre-eclampsia, diabetes during pregnancy, fetal distress, and post-partum haemorrhage.
2. Labour and delivery outcomes, identified in hospital, including caesarean section, preterm birth (<37 weeks of gestation), low birthweight (<2500 g), and small for gestational age.
3. Neonatal hospital readmission within 28 days of birth.
4. Congenital malformations in the infant. Excluding chromosomal abnormalities, major malformations considered were those diagnosed by age 1 year, such as cardiovascular defects, neural tube defects, hypospadias, and epispadias. Major cardiac malformations were defined as atrial and atrioventricular septal defects and Ebstein's anomaly, but excluding atrial septal defect and patent ductus arteriosus in infants born before 37 weeks of gestation.

Study sites did analyses independently according to the a-priori protocol, and data was then combined. Outcomes were modelled as binary variables (ie yes or no), and a binary logistic-regression model was used to estimate odds ratios (ORs) and 95% CIs comparing the lithium-exposed group to the reference group. ORs of major malformations and major cardiac malformations were also compared between the patients in the lithium-exposed group who had been exposed during the first trimester and the reference group. ORs were adjusted for maternal age at delivery (in years), primiparity, calendar year of birth, and treatment with any other psychotropic medication during pregnancy.

To account for possible heterogeneity and estimate the influence of a single cohort on overall estimates, the pooled adjusted ORs (aORs) were recalculated by leaving one cohort out of the analyses each time. To assess whether the results were influenced by the type of data source, each meta-analysis was repeated by stratifying on the basis of whether the source of data was a register based or clinical cohort. In additional sensitivity analyses (post hoc) only Danish and Swedish data was used to explore the potential for residual confounding.

Results

A total of 22 124 eligible pregnancies were identified, of which 727 were included in the lithium exposed group. Of the 727 pregnancies, 77% were from register-based cohorts. At baseline, women in the lithium-exposed group tended to be older, nulliparous, and more likely to have filled a prescription for a psychotropic drug other than lithium during pregnancy, compared with the reference group. In the lithium exposed group and the reference group, 49% and 67% respectively of the pregnancies came from Sweden or Denmark.

Results from the study are listed in table 1.

Table 1.Pooled prevalence and aOR of health outcomes in the lithium-exposed group versus the reference group.

	Lithium exposed group			Reference group			Pooled aOR (95% CI)	I^2 (%)
	N	Number with outcome	Pooled prevalence (%, 95% CI)	N	Number with outcome	Pooled prevalence (%, 95% CI)		
Pre-eclampsia*	612	13	1·8% (0·1–3·5)	21309	187	2·1% (0·9–3·2)	0·97 (0·52–1·80)	0·0%
Diabetes†	489	35	6·4% (4·1–8·8)	7990	512	5·4% (2·5–8·2)	1·20 (0·81–1·78)	0·0%
Fetal distress‡	727	90	14·1% (3·9–24·2)	21397	1561	13·2% (4·0–22·4)	1·00 (0·76–1·32)	0·0%
Post-partum haemorrhage†	489	38	7·4% (3·3–11·6)	7990	391	7·1% (3·7–10·5)	1·28 (0·64–2·57)	53·5%
Labour and delivery outcomes								
Caeserian section‡	727	201	26·5%(20·3-32·6)	21392	4844	25·8%(20·9–30·7)	0·94 (0·66–1·33)	62.0%
Preterm birth‡	717	96	13·1%(10·6-15·6)	21397	1949	10·0% (7·3–12·7)	1·24 (0·83–1·84)	49.7%
Low birthweight‡	719	50	6·4% (4·5–8·2)	21338	1339	7·2% (4·6–9·7)	0·98 (0·72–1·35)	0·0%
Small for gestational age§	692	58	7·5% (2·3–12·8)	21302	1614	9·3% (1·5–17·1)	0·90 (0·67–1·21)	0·0%
Neonatal readmission to hospital within 28 days of birth‡	718	172	27·5%(15·8-39·1)	21158	2625	14·3%(10·4-18·2)	1·62 (1·12–2·33)	56·6%
Congenital malformations								
Major malformations¶	693	51	7·2% (4·0–10·4)	20957	856	4·3% (3·7–4·8)	1·58 (0·90–2·79)	57·3%
Major cardiac malformations¶	693	17	2·0% (0·5–3·6)	20957	316	1·6% (1·0–2·1)	1·31 (0·50–3·47)	54·9%
Congenital malformations (for lithium exposure in first trimester)								
Major malformations¶	621	47	7·4% (4·0–10·7)	20957	856	4·3% (3·7–4·8)	1·71 (1·07–2·72)	34·8%
Major cardiac malformations¶	621	16	2·1% (0·5–3·7)	20957	316	1·6% (1·0–2·1)	1·54 (0·64–3·70)	43·0%

The number of participants is different for each outcome since not all sites contributed to the calculation of all outcomes and not all participants at each site had information on all outcomes. aOR=adjusted odds ratio. *Data from five cohorts (Denmark, Sweden, Canada, the UK, and the USA) were available for this pooled estimate. †Data from five cohorts (Denmark, Canada, the Netherlands, the UK, and the USA) were available for this pooled estimate. ‡Data from all six cohorts were available for this pooled estimate. §Data from four cohorts (Denmark, Sweden, Canada, and the Netherlands) were available for this pooled estimate. ¶Data from five cohorts (Denmark, Sweden, Canada, the Netherlands, and the USA) were available for this pooled estimate.

In-utero lithium exposure was associated with an increased risk of neonatal readmission to hospital within 28 days of birth. By age 1 year, lithium exposure during pregnancy was not significantly

associated with an increased risk of major malformation, nor with major cardiac malformations (except in Denmark), but statistical heterogeneity was high and there were differences between different countries. Lithium exposure during the first trimester was associated with an increased risk of major malformations but for major cardiac malformations the difference was not significant (except in Denmark). No cases of Ebstein's anomaly were observed.

The "leave-one-out" analyses showed stability of the main findings, except for the association between lithium exposure in the first trimester and major malformations, which became non-significant when each of Denmark, Sweden, and the USA were left out. Results from sensitivity analyses in a subgroup only including only Danish and Swedish data were generally consistent with the main analysis.

The authors discuss that the meta-analysis method improved statistical power and a shared protocol for analyses minimised heterogenicity. Limitations were that only pregnancies that resulted in live-born babies were included, power to study very rare events is lacking (only 16 cases of major cardiac malformations were seen in the exposed group), some confounding may still be present, no lithium levels were analysed and no active comparator was used.

The reason for the increase of readmissions to hospital within 28 days is suggested to be lithium withdrawal after birth or lithium exposure via lactation.

The authors conclude that there is an increased risk of congenital malformations when lithium is used in the first trimester of pregnancy, but the absolute risk of malformation is much smaller than previously reported. Implications of all the available evidence:

- Encourage healthcare professionals and women to make lithium treatment decisions before conception.
- Especially during first-trimester, lithium use should be used with caution
- Consider restarting lithium either after the first trimester or immediately post partum for some patient groups.

Comments: The result of the study is to a large extent captured in some of the current data sheets in NZ.

A strength is that the study compares pregnancies among women with mental illness rather than among all women, as mental illness in itself may lead to pregnancy outcome problems.

As there were no information on doses and no levels of serum lithium were measured, this study does not reveal if a lowering of the lithium dose would be an option.

3.1.2 Patorno MD, Huybrechts KF, Bateman BT et al 2017 (10)

This was an observational cohort study including 1,325,563 pregnancies in women who were enrolled in the Medicaid system in the US, and who delivered a live-born infant between 2000 and 2010.

The aim of the study was to compare the risk of cardiac malformations among infants exposed to lithium during the first trimester with unexposed infants and, in secondary analyses, with infants exposed to lamotrigine.

Exposure for lithium was defined as at least one filled prescription during the first trimester (first 90 days after the date of the last menstrual period). The primary reference group included women with no lithium or lamotrigine dispensings during the 3 months before the start of pregnancy or during

the first trimester. A second reference group included women who had at least one filled prescription for lamotrigine during the first trimester. Propensity scores adjustment was done.

The primary outcome was presence of cardiac malformations in the infant. Secondary outcomes were major congenital malformations overall, major malformation in the absence of a cardiac defect and also overall right ventricular outflow tract obstruction defects (as this general effect includes Ebstein's anomaly).

Results

Of the included pregnancies, 663 women were exposed to lithium and 1945 to lamotrigine in the first trimester. Cardiac malformations were present in 16 of the 663 infants exposed to lithium (2.41%), 15,251 of the 1,322,955 non exposed infants (1.15%), and 27 of the 1945 infants exposed to lamotrigine (1.39%).

The adjusted risk ratio for cardiac malformations among infants exposed to lithium as compared with unexposed infants was 1.65 (95% confidence interval [CI], 1.02 to 2.68). The risk ratio was 1.11 (95% CI, 0.46 to 2.64) for a daily dose of 600 mg or less, 1.60 (95% CI, 0.67 to 3.80) for 601 to 900 mg, and 3.22 (95% CI, 1.47 to 7.02) for more than 900 mg.

The prevalence of right ventricular outflow tract obstruction defects was 0.60% among lithium-exposed infants versus 0.18% among unexposed infants (adjusted risk ratio, 2.66; 95% CI, 1.00 to 7.06). Results were similar when lamotrigine-exposed infants were used as the reference group. The results showed a modest increase in the risk of cardiac malformations in infants associated with lithium use in early pregnancy. The relative risk appeared to be higher for right ventricular outflow tract obstruction defects than for other cardiac defects. Lithium was not significantly associated with non-cardiac malformations in this study although these results are uncertain.

The authors conclude that there is a modest increased risk of cardiac defects in infants whose mother has used lithium during the first trimester of pregnancy, although the risk is considerably lower than previously suggested. The study also suggests that the association is dose-dependent with an increase by a factor of approximately 3 beyond doses of 900 mg a day.

Comments: The absolute risk for infant cardiac malformations after exposure to lithium during the first trimester in the study by Patorno et al (2·4%) was similar to the absolute risk in the Munk-Olsen study (2·1%).

3.1.3 McCrea RL, Nazareth I, Evans SJW et al 2015 (18)

This was a primary care database study from the UK with the aims to determine the prevalence of lithium prescribing during pregnancy and to assess how many of the women who are taking lithium before pregnancy actually stop their medication when they become pregnant.

Women receiving any lithium prescriptions before and during pregnancy between January 1995 and December 2012 were identified using The Health Improvement Network (THIN) primary care database. A comparison group included twice as many non-pregnant women who were prescribed lithium. THIN is a UK primary care database containing the electronic health records of approximately 12 million patients who have received care from a general practitioner GP or family doctor.

Out of 458,761 pregnancies, there were only 67 pregnancies (0.015%) in which the woman received one or more prescriptions of lithium at any time during pregnancy and in only 47 (0.01%) of these

pregnancies lithium was prescribed after the 6th week of pregnancy (when the pregnancy was likely to be known).

Pregnant women were more likely to stop lithium than those who were not pregnant. Of the 52 women who were being continuously prescribed lithium three months before pregnancy, only 17 (33%) continued receiving prescriptions beyond the 6th week of pregnancy. Most of these 17 women continued treatment throughout pregnancy and 6 months after delivery 57% of the 52 were prescribed lithium.

Comments: Even in this large group of pregnancies, there was only a very small group of pregnancies where the mother had been prescribed lithium. No data has been found describing the situation in NZ.

3.1.4 Diav-Citrin O, Shechtman S, Finkel-Pekarsky V et al 2014 (19)

In this prospective observational study, a total of 183 lithium-exposed pregnancies of women who contacted the Israeli Teratology Information Service were followed up (90.2% had at least been exposed in the first trimester) by interviews and medical documents verifying any malformation diagnosis and compared with 72 disease-matched (no lithium treatment but other drug treatment) and 748 nonteratogenic-exposed pregnancies. In all groups the women had contacted the information service between 1994 and 2010.

The primary outcome of interest was the rate of major anomalies. The classification of anomalies was done by a certified paediatrician blinded to the exposure group.

The mean daily intake of lithium in the lithium-exposed group was 906 mg. The medication was taken throughout pregnancy in 58.5% of these pregnancies. Concurrent psychiatric medications were taken by 66.1% of women in this cohort. The median age of women in the lithium-exposed group was 2 years older than that of women in the nonteratogenic exposure group.

There were significantly more miscarriages (adjusted odds ratio=1.94, 95% CI=1.08–3.48) and elective terminations of pregnancy in the lithium-exposed group compared with the nonteratogenic exposure group. The rate of major congenital anomalies after exclusion of genetic or cytogenetic anomalies was not significantly different between the three groups. Cardiovascular anomalies were significantly more frequent in the lithium group where exposure had occurred during the first trimester when compared to the nonteratogenic exposure group (5/123 (4.1%) compared to 4/711 (0.6%)) but not after excluding anomalies that spontaneously resolved. Ebstein's anomaly was diagnosed in one lithium-exposed fetus. The rate of non-cardiovascular anomalies was not significantly different between the groups. The rate of preterm deliveries was higher in the lithium group compared to the nonteratogenic exposure group.

The authors concluded that lithium treatment in pregnancy is associated with a higher rate of cardiovascular anomalies and women who are treated with lithium during organogenesis should undergo fetal echocardiography and level-2 ultrasound.

Comments: This study also measured miscarriages and elective terminations. A mean daily dose is stated but it is not known if any dose reductions have taken place. The study only includes women who actively made contact with the center and not the general population. The follow up was made by interviews and no physical examinations were performed. The study captured a relatively large number of lithium-exposed cases which makes it interesting despite the limitations.

3.2 NICE recommendations on use of lithium in pregnancy

The National Institute for Health and Care Excellence in the UK, NICE, regularly develops clinical guidelines. The process includes both review of available evidence and discussions with clinical experts and other stakeholders, for example a GDG (Guideline Development Group including healthcare and other professionals and people familiar with patient and carer issues). Guidelines for antenatal and postnatal mental health: clinical management and service guidance were published in December 2014(20). These guidelines had been reviewed and updated since the first version was published in 2007. The latest update were in April 2018 (addition of valproate warnings).

The recommendations for use of lithium during pregnancy are presented below. In the background material it is stated: “After considering these factors and the significant limitations of the evidence, the GDG decided that prescribing lithium should be guided by a set of principles, which are set out in the sections”.

Sections that were reviewed and updated in 2014 are marked “new2014”. If the text was reviewed in 2014 but no changes were made, it is marked “2014”.

Lithium

Do not offer lithium to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective. (new2014)

If antipsychotic medication has not been effective and lithium is offered to a woman who is planning a pregnancy or pregnant, ensure:

- the woman knows that there is a risk of fetal heart malformations when lithium is taken in the first trimester, but the size of the risk is uncertain
- the woman knows that lithium levels may be high in breast milk with a risk of toxicity for the baby
- lithium levels are monitored more frequently throughout pregnancy and the postnatal period. (new2014)

If a woman taking lithium becomes pregnant, consider stopping the drug gradually over 4 weeks if she is well. Explain to her that:

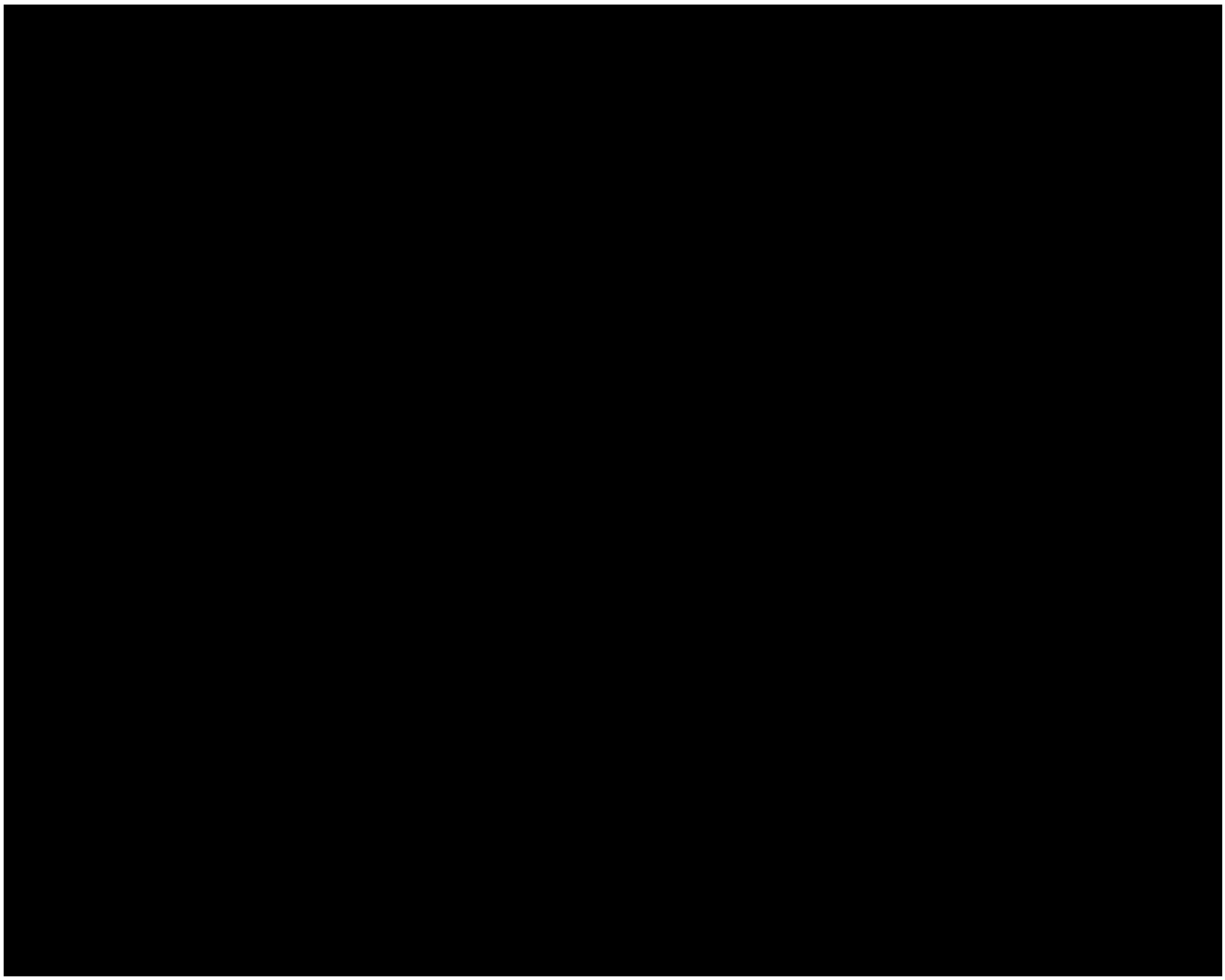
- stopping medication may not remove the risk of fetal heart malformations
- there is a risk of relapse, particularly in the postnatal period, if she has bipolar disorder. (2014)

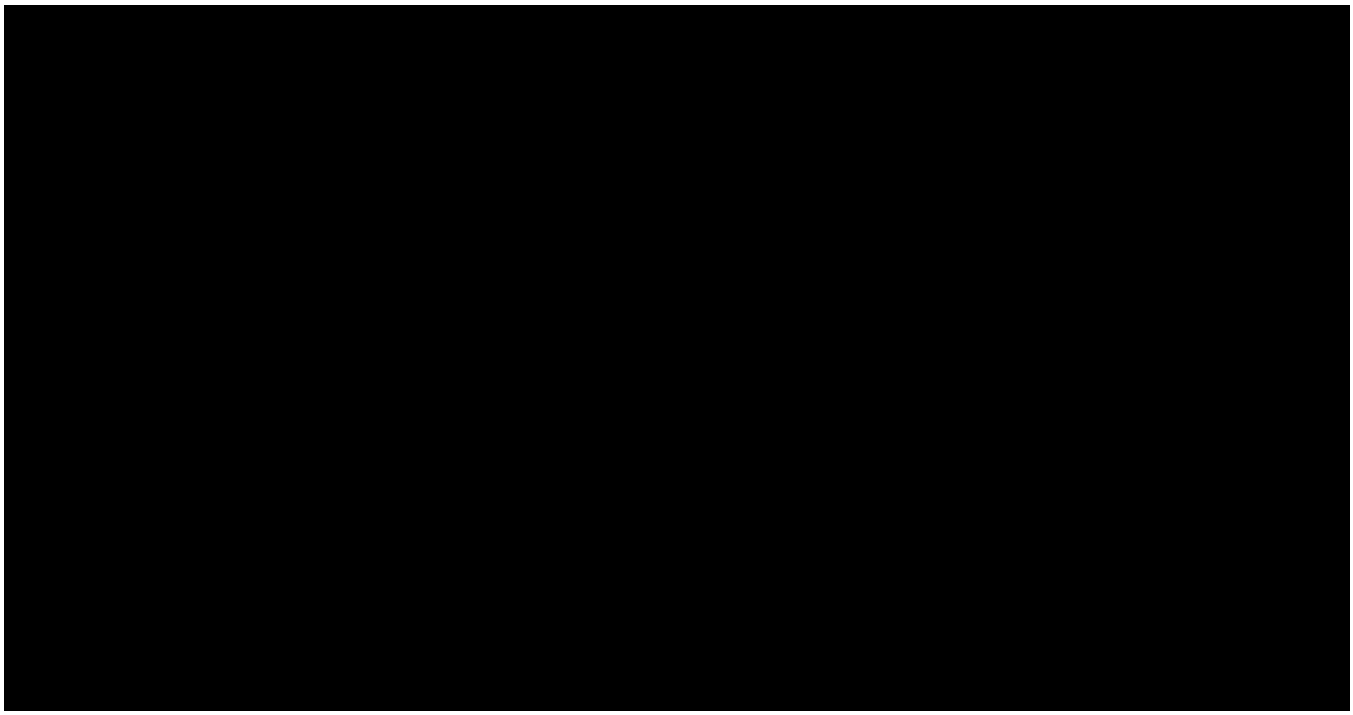
If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider:

- switching gradually to an antipsychotic or
- stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms have responded better to lithium than to other drugs in the past) or
- continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective. (new2014)

If a woman continues taking lithium during pregnancy:

- check plasma lithium levels every 4 weeks, then weekly from the 36th week
- adjust the dose to keep plasma lithium levels in the woman's therapeutic range
- ensure the woman maintains an adequate fluid balance
- ensure the woman gives birth in hospital
- ensure monitoring by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity
- stop lithium during labour and check plasma lithium levels 12 hours after her last dose. (2014)





4.0 DISCUSSION AND CONCLUSIONS

Women with bipolar disorder are often affected during their reproductive years. If a woman with bipolar disorder becomes pregnant there are risks of morbidity, complications or poor pregnancy outcome from the disorder itself that need to be balanced against risks from treatment of the disorder.

Lithium remains one of the mainstays for treatment of bipolar disorder, and is sometimes used during pregnancy. However, there are concerns about teratogenicity and maternal and offspring complications also from the treatment.

Many of the older studies on lithium were either small and therefore did not have enough power to show reliable results, or were subject to confounding factors and bias.

One concern has been an increased risk of the cardiac effect Ebstein's anomaly after exposure of lithium during the first trimester of pregnancy, which in newer studies has been shown to be substantially lower than initially suggested.

Two larger studies have recently been published, one of them a meta-analysis. They are described above. The authors conclude that there is an increased risk of congenital malformations and a modest increased risk of cardiac defects respectively, in infants whose mother used lithium during the first trimester of pregnancy, although the risks are considerably lower than previously suggested.

Implications of the available evidence that has been recommended are:

1. Encourage healthcare professionals and women to make lithium treatment decisions before conception.
2. Especially during first-trimester, lithium use should be used with caution.
3. Consider restarting lithium either after the first trimester or immediately post partum for some patient groups.
4. Monitor plasma levels of lithium.
5. If lithium is used during organogenesis, fetal echocardiography and level-2 ultrasound should be performed.

All these points, except number 3, are already reflected in the data sheet for Lithicarb, while the other NZ data sheets contain less information.

Point 1, however, could be emphasized to more clearly explain the need for effective contraception throughout treatment and support informed, joint decision making between the woman and her doctor.

Point number 3 is not reflected in any of the product information texts described in this paper, but mentioned in the meta-analysis and in the NICE recommendations.

[redacted]

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The pregnancy section of the data sheets for lithium products need to be updated.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Study by Munk-Olsen T, Liu X, Viktorin A et al (1).
2. CARM report.

7.0 REFERENCES

1. Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. The lancet Psychiatry. 2018 Aug;5(8):644-52. PubMed PMID: 29929874. Pubmed Central PMCID: PMC6077091. Epub 2018/06/23. eng.

2. Oruch R, Elderbi MA, Khattab HA, Pryme IF, Lund A. Lithium: a review of pharmacology, clinical uses, and toxicity. European journal of pharmacology. 2014 Oct 5;740:464-73. PubMed PMID: 24991789. Epub 2014/07/06. eng.

3. bpac. Key Points Introduction Indications for Lithium - bpac NZ 2014 [cited 2018 14 November]. Available from: https://bpac.org.nz/magazine/2007/february/pdfs/bpj3_lithium_pages16-27.pdf.

4. UpToDate. Bipolar disorder in adults and lithium: Pharmacology, administration, and management of side effects UpToDate2018 [updated 13 July 2018; cited 2018 14 November 2018]. Available from: https://www.uptodate.com/contents/bipolar-disorder-in-adults-and-lithium-pharmacology-administration-and-management-of-side-effects?search=lithium&source=search_result&selectedTitle=2~148&usage_type=default&display_rank=1.

5. Navigator H. Bipolar disorder 2015 [updated 27 September 2018; cited 2018 14 November]. Available from: https://www.healthnavigator.org.nz/health-a-z/b/bipolar-disorder/.

6. bpac. Bipolar disorder: Identifying and supporting patients in primary care 2014 [cited 2018 14 November]. Available from: https://bpac.org.nz/BPJ/2014/July/bipolar.aspx.

7. Department of Health A. What are the symptoms of bipolar mood disorder? 2007 [updated 7 May 2007; cited 2018 14 November]. Available from: http://www.health.gov.au/internet/publications/publishing.nsf/Content/mental-pubs-w-whatbip-toc~mental-pubs-w-whatbip-dis.

8. Health NCfM. Bipolar disorder, pregnancy and childbirth 2014 [cited 2018 14 November]. Available from: https://www.app-network.org/wp-content/uploads/2014/09/Bipolar-Pregnancy-Childbirth-Booklet.pdf.

9. UptoDate. Teratogenicity, pregnancy complications, and postnatal risks of antipsychotics, benzodiazepines, lithium, and electroconvulsive therapy 2017 [cited 2018 14 November 2018]. Available from: https://www.uptodate.com/contents/teratogenicity-pregnancy-complications-and-postnatal-risks-of-antipsychotics-benzodiazepines-lithium-and-electroconvulsive-therapy?search=teratogenic%20drugs%20in%20pregnancy&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.

10. Patorno E, Huybrechts KF, Hernandez-Diaz S. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. The New England journal of medicine. 2017 Aug 31;377(9):893-4. PubMed PMID: 28854098. Epub 2017/08/31. eng.

11. Ltd MNZ. Lithicarb FC NZ data sheet 1988 [updated 30 August 2017; cited 2018 14 November]. Available from: http://www.medsafe.govt.nz/profs/Datasheet/l/LithicarbFCtab.pdf.

12. Ltd DP. Lithium Carbonate Capsule NZ data sheet 1985 [updated 18 April 2017; cited 2018 14 November]. Available from: http://www.medsafe.govt.nz/profs/Datasheet/l/Lithiumcarbonatecap.pdf.

13. Ltd WMBC. Priadel Modified release tablet 1969 [updated 10 July 2017; cited 2018 14 November]. Available from: http://www.medsafe.govt.nz/profs/Datasheet/p/priadeltab.pdf.

14. Limited AP. Priadel product information UK 1985 [updated 13 September 2018; cited 2018 14 November]. Available from: http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1536898072308.pdf.

15. Inc MP. Lithium carbonate product information US [updated 17 October 2018; cited 2018 14 November]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=52205c7d-1483-446b-aeae-47709656a4cf&audience=consumer.

16. Ltd APAP. LITHICARB product information Australia 1994 [updated 22 August 2018; cited 2018 14 November]. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2012-PI-01382-3.

17. Ltd APAP. Quilonum SR product information Australia 1995 [updated 12 December 2017; cited 2018 14 November]. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01350-1&d=201811141016933.

18. McCrea RL, Nazareth I, Evans SJ, Osborn DP, Pinfold V, Cowen PJ, et al. Lithium prescribing during pregnancy: a UK primary care database study. PloS one. 2015;10(3):e0121024. PubMed PMID: 25793580. Pubmed Central PMCID: PMC4368741. Epub 2015/03/21. eng.

19. Diav-Citrin O, Shechtman S, Tahover E, Finkel-Pekarsky V, Arnon J, Kennedy D, et al. Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. The American journal of psychiatry. 2014 Jul;171(7):785-94. PubMed PMID: 24781368. Epub 2014/05/02. eng.

20. giudeline N. Antenatal and postnatal mental health: clinical management and service guidance 2014 [updated April 2018; cited 2018 14 November]. Available from: https://www.nice.org.uk/guidance/cg192/chapter/1-recommendations.