TYGERBERG HOSPITAL
Department of Obstetrics and Gynaecology

Guidance for the use of Lithium during pregnancy and the puerperium

The use of lithium during pregnancy and in women who choose to breast feed should always be an individualised decision based on careful risk-benefit assessment and with consideration of the preferences of the woman, her partner and family supporters.

Lithium completely equilibrates across the placenta (1) and lithium use in pregnancy has been associated with increased risk in congenital malformations including cardiac malformations, particularly when used in the first trimester (2–4).

Neonatal toxicity events associated with lithium are dose related and usually transient and reversible. These include (5–7):

- Floppy baby syndrome (cyanosis and hypotonicity)
- Neonatal hypothyroidism
- Nephrogenic diabetes insipidus
- Hypoglycemia
- Jaundice
- Cardiac arrhythmia
- Thyroid dysfunction
- Neonatal lithium toxicity
- Renal disorders

Bipolar disorder itself as well as the abrupt stopping of lithium at any time preconception, during pregnancy or during breast feeding is associated with a significant risk for relapse of bipolar (8). Relapse is associated with suicide, infanticide, infant neglect and medical and psychiatric deterioration in the mother. The risk of relapse to the mother, infant, and the woman's community must be considered when making treatment decisions.

There is lack of consistency across guidelines and variance in global practices in the prescription and monitoring of lithium in the perinatal period (2,9). This document serves as a guidance for clinicians working in the Tygerberg Hospital (TBH) context and should always be read in conjunction with the latest evidence and evidence-based guidelines.

Women planning pregnancy

Women using lithium for the treatment of bipolar disorder who are planning pregnancy should undergo an antenatal risk assessment at the TBH Women's Mental Health clinic. The assessment will consider the mental illness history, the woman's ability to cope with symptoms, obstetric and medical history, support structures and the impact of untreated mental illness.

All women should be counselled on alcohol use, smoking, drug use, diet, exercise and stress management and started on preconception folate 5mg daily (10).

Women who are well, with long periods of remission, low risk of relapse and good support structures can consider slow reducing, over at least 4 weeks, and then stopping of lithium

treatment for the first trimester and potentially throughout pregnancy with close monitoring. Women may also consider reducing their lithium dose to the lower end of the therapeutic range and continuing lithium at this lower dose throughout pregnancy. Women should be followed up 2- 4 weekly at the Women's Mental Health clinic during tapering and or discontinuation. If discontinuation is unsuccessful women should be restarted on lithium or considered for an atypical antipsychotic or lamotrigine. If women remain stable following tapering or discontinuation, they can continue follow up at their local community health centre while trying to fall pregnant and be advised to return once they have fallen pregnant. They should book the pregnancy at their local Midwife Obstetric Unit (MOU), as early as possible, prior to referral to TBH. If possible, women should follow up at the Women's Mental Health clinic and the O&G High Risk Clinic (HRC) throughout pregnancy. Women should deliver at TBH and have a mental state check with consultation liaison psychiatry prior to discharge.

Women with severe illness who are at high risk of relapse can consider switching to an atypical antipsychotic or lamotrigine with close monitoring. Switching increases the risk of relapse and women should be followed up regularly at the Women's Mental Health clinic during cross titration of medications. If women remain stable following switching medications, they can continue follow up at their local community health centre and be advised to return once they have fallen pregnant. They should book the pregnancy at their local MOU prior to referral to TBH. If possible, women should follow up at the Women's Mental Health clinic and the O&G High Risk Clinic (HRC) throughout pregnancy. Women should deliver at TBH and have a mental state check with consultation liaison psychiatry (CLP) prior to discharge.

Women with severe illness who are at high risk of relapse who have not responded adequately to prophylaxis or treatment with an atypical antipsychotic or other treatment in the past should be maintained on lithium with close monitoring. Lithium should be given at the lowest effective doses for that woman. Twice daily dosing is preferred unless there are concerns around adherence in which case a once daily dosing regimen may be best. Women can be advised to continue follow up at their local community health centre and to return once they have fallen pregnant. Women should book the pregnancy at their local MOU prior to referral to TBH. If possible, women should follow up at the Women's Mental Health clinic and the O&G High Risk Clinic (HRC) throughout pregnancy. Women should deliver at TBH and have a mental state check with consultation liaison psychiatry prior to discharge.

Women using lithium who discover they are pregnant

The abrupt discontinuation of lithium in women who discover they are pregnant is not advised (11). Women should be seen as soon as possible at the Women's Mental Health clinic for a risk assessment regarding the possibility of discontinuing lithium treatment or switching to an atypical antipsychotic or lamotrigine. As above, women with severe illness who are at high risk of relapse who have not responded adequately to prophylaxis or treatment with an atypical antipsychotics or other treatment in the past should be maintained on lithium throughout pregnancy with close monitoring of mental state and monitoring of lithium levels as per guidance below.

On discovery of pregnancy women should book at their MOU and be referred to TBH O&G High risk clinic and TBH Women's Mental Health Clinic. Li level (blood sample should be taken 12 hours after the previous dose)(12), U&E and TSH should be checked at the CHC or at the Women's Mental health clinic. If possible, women should follow up at the Women's Mental Health clinic and the O&G High Risk Clinic (HRC) throughout pregnancy. Women with bipolar

disorder are at increased risk of antepartum haemorrhage, placental abnormalities, preterm delivery, small for gestational age neonates and caesarean section (13,14). A level III detailed fetal anomaly ultrasound should be offered at 20-weeks' gestation which would include detailed fetal cardiac scanning.

Lithium monitoring in pregnancy

Lithium levels fluctuate during pregnancy. An increase in glomerular filtration rate, total body water and plasma volume leads to a reduction of lithium levels throughout pregnancy and levels may rise postpartum (6,15,16). Different women benefit from different lithium dosages and lithium dosing during pregnancy needs to be individualized and based on pre-pregnancy dosing, efficacy, tolerability and clinical response (2,15). Lithium should be given at the lowest clinically effective doses for that woman, twice daily dosing is preferred unless there are concerns around adherence in which case a once daily dosing regimen may be best.

Lithium levels should be checked monthly at follow up at the TBH Women's Mental Health Clinic and lithium levels adjusted to maintain the therapeutic dose that has been clinically effective for that woman. Closer monitoring should be considered in women with hyperemesis gravidarum, pre-eclampsia, impaired renal function, concomitant medication use, and acute blood loss (16). In women who cannot follow up at the TBH Women's Mental Health clinic close follow up at their CHC should be negotiated.

Delivery

All mothers using lithium in pregnancy should deliver at Tygerberg Hospital. The on-call paediatrician should be alerted at the time of delivery that the neonate has been lithium exposed. Women should be adequately hydrated during delivery which may require intravenous fluids. Nephrotoxic and nonsteroidal anti-inflammatory medications should be avoided. For women requiring caesarean section delivery, the anaesthetist should be informed of the lithium use and drug- drug interactions with anaesthetic agents including succinyl choline, rocuronium, and other depolarising and non-depolarizing muscle relaxants must be considered. Patients should be monitored for increased and/or prolonged therapeutic effects of neuromuscular-blocking agents, specifically respiratory depression.(17–19). The neonate should be assessed by the paediatrician at the time of delivery. Lithium blood level, thyroid-stimulating hormone (TSH) and free thyroxine (T4) should be tested on the umbilical cord blood sample. If the lithium level in cord blood is greater than 0.64mEq/L longer inpatient infant monitoring may be required (1). All infants born to mothers who received lithium during pregnancy need to have at least 24hrs of pre-feed blood glucose monitoring regardless of whether breast or formula feeding. Maternal U&E and lithium level should be taken 24 hours after delivery. All women should be referred to the CLP service for mental state review and post-delivery planning before discharge. Lithium dose should be adjusted to the pre-pregnancy dose and maternal lithium level should be checked one week later. Women should be given a date at the psychiatry outpatient department J Lower Ground (contact 021 938 5121/0) or their CHC one week after delivery to check lithium levels and a follow-up date at the TBH Women's Mental Health clinic for a mental state check in 2-4 weeks post discharge.

Lithium and breastfeeding

Many guidelines advise against breastfeeding in women using lithium due to the high variability in the transfer of lithium in breast milk. However, there are many benefits to breast feeding (6), and women may choose to breast feed after receiving adequate counselling on the risks and benefits of breastfeeding while using lithium. Rapidly discontinuing or switching lithium postpartum is not advised because of the high risk of relapse. Discussions regarding breastfeeding should take place early on in pregnancy.

Breastfeeding can be considered in women who have stable mood, who are well enough to monitor their infants for signs of lithium toxicity and who have good support structures and access to health care. Infants should be term and medically stable.

Women should be advised not to breast feed if their infants are premature, if there is any risk for immature infant renal and hepatic function, if the infant has medical comorbidities that could impact the ability to detoxify and excrete lithium or if there is reduced ability to monitor infants for adverse effects. Women with active mental illness symptoms that could impair their ability to safely breast feed or to monitor the infant should be encouraged to formula feed with family support.

In women using lithium who plan to breastfeed, lithium levels and thyroid function should be checked on cord blood at delivery and again in the neonate at the G1/2 baby clinic at ten days to 4 weeks post-partum or ten days to 4 weeks after initiating lithium in women who start lithium post-partum. Neonate renal function should be tested at 48 hours after delivery and at the 10 day to 4 week G1/2 baby clinic follow up.

If infant lithium levels are below 0.3 mEq/L at 10 days to 4 weeks postpartum or 10 days to 4 weeks after maternal lithium initiation, then no further lithium level monitoring in the infant is required. Infant lithium levels should be checked if the mother or infant develop signs of lithium toxicity or if there is any evidence of abnormal growth or neurodevelopmental delay.

Infants exposed to lithium through breastfeeding should have routine weight and neurodevelopmental monitoring. All women and their partners or community supporters should be educated on how to monitor their infants for signs and symptoms of feeding problems, dehydration, hypotonia, and lethargy. Women should be particularly vigilant when infant's develop fever, gastrointestinal illness, or other loss of fluid and electrolytes (20). If infants develop signs of lithium toxicity, women should be advised to stop breast feeding and to present to their nearest emergency service immediately. The infant needs an urgent lithium level and aggressive intravenous fluid resuscitation. The decision to continue breast feeding should be discussed with the multidisciplinary team including paediatrics and psychiatry.

Women who are breastfeeding on lithium should be followed up monthly at the TBH Women's Mental Health clinic with monthly lithium level monitoring. If women cannot afford the transport costs, regular follow up at their local clinic should be arranged. As disrupted sleep increases the risk of relapse women should be encouraged to consider expressing breast milk or supplementing with formula feeds so that a partner or family member can assist with night feeds.

Summary Recommendations

Time Point	Management Approach
Woman on lithium planning pregnancy	TBH Women's Mental Health Antenatal risk assessment. Counselling on alcohol use, smoking, drug use, diet, exercise and stress management. Initiate Folate 5mg/d.
Woman on lithium discovers she is pregnant	Book at MOU and refer to TBH O&G HRC and TBH Women's Mental Health Clinic. Lithium level, U&E, TFT.
Woman on lithium during pregnancy	Follow up at TBH O&G HRC with detailed fetal anomaly ultrasound at 20 weeks. Monthly lithium level and mental state review at TBH Women's Mental health clinic. Discuss breastfeeding plan.
Delivery	Deliver at TBH with adequate hydration and fluid monitoring. Inform paeds of lithium exposure. Avoid nephrotoxic drugs and NSAIDS and consider drug-drug interactions with lithium during anaesthesia.
Post delivery	Neonatal assessment by paeds. Neonate lithium level, TSH, T4 on umbilical blood sample. Neonatal renal function, +/- repeat lithium level at +/-48hours after birth. Monitor neonatal pre-feed blood glucose whilst establishing feeding. Maternal lithium level and U&E 24 hours post-delivery. CLP mental state review. Continue lithium at pre-pregnancy dose. Book a date 7 days later at JLG or CHC for maternal lithium level and mental state review. **If breast feeding** book a date 10 days to 4 weeks later G1/G2 baby clinic for infant lithium level, U&E and thyroid function. Book Woman's Mental Health date 2-4 weeks postpartum for mental state review. Counselling on how to monitor for signs of lithium toxicity in mother and infant.
10 days to 4 weeks postpartum	Mental state review at Women's Mental Health Clinic. Maternal lithium level. Observe infant for signs of lithium toxicity and ensure mother understands how to monitor the infant. Continue monthly lithium levels at follow up if breastfeeding. G1G2 baby clinic paeds assessment and lithium level, U&E and TFT. If lithium <0.3 mEq/L no further blood monitoring is needed if >0.3 mEq/L discuss with paeds consultant.

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