Key Words: lamotrigine, mood stabilisers, bipolar disorder, fetal and maternal outcomes

Maternal and Fetal Outcomes After Lamotrigine Use in Pregnancy: A Retrospective Analysis from an Urban Maternal Mental Health Centre in New Zealand

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ABSTRACT ~ Introduction: *Pregnancy is a vulnerable period for recurrence of bipolar disorder. Discontinuation of mood stabilisers during pregnancy and the postpartum period can significantly increase the risk of recurrence of bipolar disorder. Lamotrigine is an anti-epileptic drug that has been approved for the maintenance treatment of bipolar disorder. Epilepsy literature has indicated that lamotrigine has a reassuring safety profile in pregnancy but there is little information on its effectiveness and safety in pregnant women with mental disorders.* ***Method:*** *We conducted a retrospective review of all pregnant women who presented to an urban maternal mental health centre in Auckland, New Zealand between 2012 and 2014 and were treated with antipsychotics and/or mood stabilisers. Pregnancy outcome, obstetric and perinatal complications, congenital malformations and maternal mental health in the postnatal period were considered.* ***Results:*** *Here, we present the outcomes in the subset of six women who were treated with lamotrigine 100–400 mg/day for the entire pregnancy. Five were diagnosed with bipolar disorder and one with major depression. Three women received additional psychotropic medication during pregnancy. No women needed psychiatric hospitalisation. All babies were live birth after 36 weeks gestation. Two babies had low birth weight and required NICU admissions. Two women required lower segment caesarean section and the other 4 were induced. A trachea-esophageal fistula was noted in one baby. Four babies who were breastfed while their mothers received uninterrupted treatment with lamotrigine, experienced no complications.* ***Discussion:*** *This naturalistic study indicates that lamotrigine can be an effective treatment option for maintenance of bipolar illness in women of childbearing age.*
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Introduction

Management of bipolar disorder in pregnancy poses a challenge for clinicians. Studies suggest that pregnancy is a vulnerable period for recurrence of bipolar illness, and discontinuation of mood stabilisers has been estimated to increase risk of recurrence in the postpartum period.[1] Yet, pregnant women are often undertreated for fear of teratogenicity.

The pharmacological options for mood stabilisation include lithium, carbamazepine, valproate and atypical antipsychotics. In infants exposed to lithium in-utero, the incidence of major malformations ranges from 4%–12%, with the occurrence of Ebstein's anomaly being 20-fold more common than in unexposed cohorts. Other lithium- related fetal and neonatal complications include premature delivery, floppy infant syndrome, transient neurodevelopmental deficits, nephrogenic diabetes insipidus, thyroid dysfunction and polyhydramnios.[2]

Carbamazepine has been associated with an increased risk of fetal malformations which include microcephaly, other craniofacial skeletal defects, growth retardation and cardiac defects. An increased risk of coagulopathies and spina bifida has also been reported.[2]

Similarly, treatment with valproate in pregnancy confers a significantly increased risk of major malformations and serious complications such as spina bifida, developmental retardation, skeletal and cardiac abnormalities, coagulopathies and hepatotoxicity as well as impaired cognitive development in children exposed in utero.[3]

Atypical antipsychotics such as olanzapine and quetiapine have been considered for their mood stabilisation effect. Olanzapine has been associated with a higher incidence of metabolic complications in pregnant women, including weight gain and glucose intolerance. This can confer a higher risk of perinatal complications for the infant.[2]

Lamotrigine is an anti-epileptic drug (AED) that has been approved by the US FDA for the maintenance treatment of bipolar disorder. Its low teratogenic risks and favourable adverse effect profile compared to other AEDs means that it is the preferred treatment option for women of childbearing age. However, there is limited information regarding the outcomes for mothers and infants after lamotrigine use in pregnant women with bipolar disorder rather than epilepsy and the few cited cases have either focused on changes in lamotrigine's pharmacokinetic profile during pregnancy[4] or its safety during breastfeeding.[5]

The aim of this report is to provide information regarding the maternal and fetal outcomes with lamotrigine use in pregnant women with mental illness.

Methods

A retrospective analysis was conducted of all women who presented to the urban maternal mental health centre (MMH) in Auckland, New Zealand between 2012 and 2014, and were treated with antipsychotics and/or mood stabilisers. In this report we present the maternal and fetal outcomes in the subset of pregnant women treated with lamotrigine. Approval for the study was obtained from the Auckland District Health Board research office.

Each subject's history and demographic data were gathered from electronic medical records. This included information on social supports, hospitalisations, prescription changes and mental state changes. Medication compliance was assessed through filling of prescriptions. Laboratory tests, additional medications prescribed by general practitioners, and maternity and obstetric records were also accessed. Fetal outcome data included birth weight, length, head circumference, the Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores, neonatal intensive-care unit (NICU) admissions and any congenital malformations recorded.

Results

Six women were maintained on lamotrigine therapy during pregnancy.

The women ranged between 26–33 years (mean age 30) and all were partnered. Five had a DSM-IV-TR diagnosis of bipolar disorder and the other had major depression with anxiety. Three had hypothyroid conditions and were maintained on thyroxine supplements. One woman had chronic hypertension, treated with enalapril. Three subjects received additional psychotropic medication during pregnancy which included quetiapine 50–100 mg/day (2) and nortriptyline 150 mg/day (1).

The lamotrigine dosage schedule and changes over pregnancy are shown in Figure 1. Three subjects received initial twice daily dosing with dosage range between 250–400 mg/day and 3 subjects received single daily dosing with dosage range between 100–200 mg/day. The 3 subjects receiving single daily dosing required an increase in lamotrigine dosage in the 3rd trimester due to breakthrough symptoms. In the postpartum period, 5 subjects maintained stability of their mental state while one experienced early warning signs of poor sleep and racing thoughts on lamotrigine 200 mg/day which settled with addition of olanzapine (5–7.5 mg/day). None required psychiatric hospitalisation.

Maternal and Fetal outcomes are presented in Table 1.

Two women developed gestational diabetes and one of them also developed gestational hypertension. This subject had pre-existing obesity and

FIGURE 1

Lamotrigine (LTG) Dose Changes in 6 Subjects

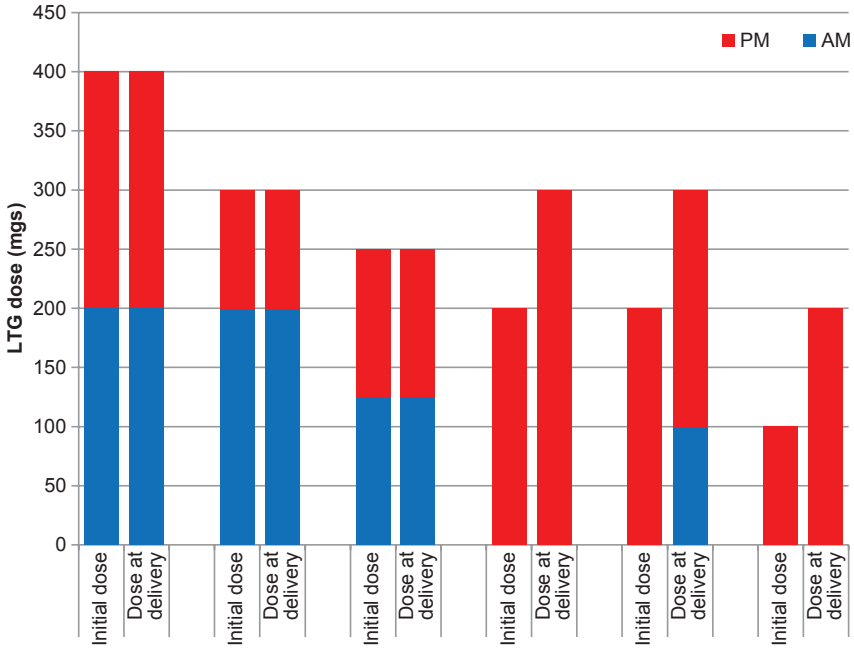

TABLE 1

MATERNAL OUTCOMES	N
Gestational diabetes	2[a]
Gestational hypertension	1[b]
Psychiatric hospitalisation	0
INFANT OUTCOMES	
Mode of delivery	
Induced	4
Caesarian section	2
Gestational age at delivery	
Preterm[c]	1
Term	5
Birth Weight	
LBW[d]	2
Other parameters	
Neonatal ICU admission	2
APGAR score 9–10 (5 minutes)	6
Major congenital malformation[e]	1

Notes: [a]One hypothyroid, receiving quetiapine and other with obesity (BMI: 31–35 kg/m^2). [b]One with obesity and gestational diabetes mellitus. [c]Less than 37 weeks. [d]Low birth weight defined as <2.5 kg. [e]Tracheoesophageal fistula.

required insulin and metformin during later pregnancy. All infants were live births. Two women had lower segment caesarean sections (LSCS): at 36 weeks (due to worsening pre-eclampsia, growth restriction and breech presentation) and at 39 weeks gestation (due to previous LSCS). Labor was induced in the other 4 subjects between 38–39 weeks gestation (due to small for gestational age [SGA], fetal distress or gestational hypertension). One infant was noted to have a tracheoesophageal fistula that required surgical repair in the immediate postpartum period. Of note, this infant was SGA and the mother was receiving thyroxine replacement with poor control in the first trimester. Two infants with low birth weights (2060 gms and 2365 gms) required NICU admission. Other growth parameters which included length at birth, head circumference and APGAR scores were within normal limits in all infants.

Four infants were breastfed with no complications while the mother received uninterrupted treatment with lamotrigine. One subject breastfed for 2 days before switching to formula, one subject was exclusively breastfeeding at the time of discharge from the service at 3 weeks postpartum and 2 subjects continued to mix feeds with breastmilk and formula till discharge at 8–13 weeks postpartum.

Discussion

Maintenance treatment with lamotrigine was effective in pregnant women with mental illness with acceptable fetal outcomes. In our study most of the pregnant women who were maintained on lamotrigine therapy had a diagnosis of bipolar disorder and were receiving lamotrigine for mood stabilisation. Lamotrigine has been reported to be effective as a mood stabiliser and there are some reports that it can also be used as an augmentation agent in individuals with treatment-resistant major depressive disorder.[6] The risk of relapse of bipolar disorder is quite high among women who discontinue prophylactic treatment during pregnancy and postpartum.[1] In our sample, 3 subjects experienced emergence of symptoms in the 3rd trimester and required increased lamotrigine dosing. This is consistent with findings reported by Clark et al.[4] that pregnant women with bipolar disorder receiving lamotrigine can experience emergence of symptoms with declining serum concentrations of lamotrigine and is analogous to findings reported in the epilepsy literature. These 3 subjects were maintained on a single day dosing of lamotrigine 100–200 mg. The other 3 subjects did not require any dosage change and were receiving twice daily dosing (total daily dose 250–400 mg). The pharmacokinetic profiles of once- and twice-daily dosing of lamotrigine have not been compared in pregnant women. One subject experienced early warning signs of relapse in the postpartum

period which was effectively managed with addition of olanzapine. No subject required psychiatric hospitalisation.

All infants were live births after 36 weeks gestation. In our sample, there were no spontaneous births. Two subjects had elective LSCS for established medical and obstetric indications that have not been known to be linked with lamotrigine use. In the other 4 subjects, labor was induced for established indications that have not been shown to have an association with lamotrigine use. Wakil et al.[7] reported a case series of 3 women with bipolar disorder receiving lamotrigine, in which all delivered vaginally and had birth weight and APGAR scores within normal limits. Our study is consistent with the findings of normal birth parameters for infants exposed to lamotrigine in-utero in women with bipolar disorder. The women in our study had co-morbid medical complications that can confound infant outcomes.

One infant had a tracheoesophageal fistula. Though there have been reports of duodenal/esophageal atresia associated with lamotrigine monotherapy exposure in the first trimester, samples have been too small to draw any conclusions and the literature to date suggests that lamotrigine does not cause any distinctive pattern of teratogenic effect.[8,9]

The small sample size, retrospective nature and lack of a control group in this study limit the strength of the conclusions that can be drawn from this study. However, there are scant data on maternal and fetal outcomes for pregnant women with mental illness treated with lamotrigine and, to our knowledge, this is the largest series so far.

Conclusion

This observational study adds to the limited psychiatric literature regarding lamotrigine use by pregnant women with mental illness. Lamotrigine appears promising as a relatively safe and effective option for maintenance treatment in women with bipolar disorder in the reproductive age group in a naturalistic setting. Our results suggest that consideration of frequency of dosing of lamotrigine may be important to maintain stability of mental state. ✤

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