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Risk of postpartum episodes in women with bipolar disorder after lamotrigine or lithium use during pregnancy: A population-based cohort study

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ABSTRACT

Background: Women with bipolar disorder are at high risk for relapse/recurrence postpartum. Among all mood stabilizers, lithium has the largest evidence base for efficacy in the peripartum period, but lamotrigine is increasingly prescribed for bipolar spectrum disorders during pregnancy. The aim of this study was to investigate whether lamotrigine use during pregnancy is as effective as lithium in the prevention of severe episodes postpartum.

Methods: Danish national registries were used to identify pregnancies of women with a diagnosis of bipolar spectrum disorders at the time of conception who used lamotrigine or lithium during pregnancy. We compared the risk of inpatient psychiatric admission within three months postpartum between women who used lamotrigine (N = 55) versus lithium (N = 59) during pregnancy. A logistic regression model was used to calculate crude and adjusted odds ratios.

Results: We did not find a significant difference in the risk of postpartum psychiatric admission between women who used lamotrigine versus lithium during pregnancy (7.3% versus 15.3% respectively, adjusted OR 0.83; 95% CI 0.22–3.14). We adjusted for year of delivery, parity, previous admissions and antidepressant/benzodiazepine use during pregnancy. Other variables did not differ substantially between groups.

Limitations: We used an observational design and therefore patients were not randomized to lamotrigine or lithium. The study has a small sample size.

Conclusions: Lamotrigine was not inferior to lithium in the prevention of severe postpartum episodes. Our findings suggest lamotrigine could be a reasonable alternative treatment option for bipolar disorder during pregnancy in patients with vulnerability for depression and may prevent severe episodes postpartum.

1. Introduction

Guiding women with bipolar disorder through pregnancy and the postpartum period is a challenge for psychiatrists and obstetricians, especially because these women are at very high risk for relapse and recurrence postpartum (37%, 95% confidence interval 29% −45%) (Wesseloo et al., 2016). Treatment with a mood stabilizer increases the likelihood of maintaining mood stability during pregnancy and preventing postpartum episodes (Newport et al., 2008; Viguera et al., 2007). However, the benefits of medication use during pregnancy need to be carefully weighed against the risks to the fetus. Lithium is the most effective known mood stabilizer and therefore remains the gold standard for the treatment of bipolar disorder (Geddes and Miklowitz, 2013). However, data on lithium teratogenicity have been inconclusive, thereby complicating decision-making for women with bipolar disorder during pregnancy. In a recent meta-analysis, the association between lithium use during pregnancy and fetal malformations was non-significant, but the results were mainly based on small case-control studies (total n = 264, range n = 13–89 cases) (McKnight et al., 2012). Over the past couple of decades, lamotrigine has increasingly been used during pregnancy as an alternative treatment option to lithium, due to its more favorable reproductive profile (Christensen et al., 2013; Hayes

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Table 1
Characteristics of women with either lamotrigine or lithium use during pregnancy[a,b].

	Lamotrigine (N = 55)	Lithium (N = 59)
Postpartum psychiatric admission (< 3 months)	4 (7.3)	9 (15.3)
Demographics		
Age at delivery (years), mean ± SD	31.8 ± 4.7	34.1 ± 4.5
Year of delivery[c]		
1996 – 2007	11 (20.0)	34 (57.6)
2008 – 2012	44 (80.0)	25 (42.4)
Married or cohabiting	39 (70.9)	46 (78.0)
Income above the lowest quartile	38 (69.1)	33 (55.9)
Preconception		
Age at bipolar disorder diagnosis (years), mean ± SD	26.8 ± 4.1	25.2 ± 4.6
First lithium/lamotrigine prescription < 1 year before conception	8 (14.5)	7 (11.9)
Other mood stabilizer prescriptions < 1 year before conception	< 4 (< 7.3)	0
Psychiatric admissions < 2 years before conception[c]	24 (43.6)	17 (28.8)
Psychiatric outpatient visit(s) < 2 years before conception	45 (81.8)	29 (49.2)
Depressive episodes < 2 years before conception	17 (30.9)	5 (8.5)
(Hypo)manic episodes < 2 years before conception	8 (14.5)	12 (20.3)
Pregnancy		
Antipsychotic co-medication	18 (32.7)	19 (32.2)
Antidepressant co-medication[c]	34 (61.8)	20 (33.9)
Benzodiazepine co-medication[c]	8 (14.5)	17 (28.8)
Psychiatric admissions(s)	< 4 (< 7.3)	4 (6.8)
Outpatient visit(s)	23 (41.8)	23 (39.0)
Primiparity[c]	30 (54.5)	27 (45.8)
Caesarean section	12 (21.8)	14 (23.7)
Preterm birth	8 (14.5)	10 (16.9)
Obstetric complications[d]	17 (30.9)	14 (23.7)
Postpartum[e]		
Continuation lamotrigine / lithium postpartum	45 (81.8)	53 (89.8)
Antipsychotic co-medication	19 (34.5)	35 (59.3)
Antidepressant co-medication	40 (72.7)	30 (50.8)
Benzodiazepine co-medication	17 (30.9)	32 (54.2)

[a] Medication use during pregnancy was defined as the dispensation of two prescriptions between conception and delivery, with at least one prescription after the first trimester.
[b] Figures are numbers (%) unless stated otherwise.
[c] Variables included in a multivariate logistic regression model: year of delivery, psychiatric admission < 2 years prior to conception, antidepressant and benzodiazepine co-medication during pregnancy and primiparity.
[d] Pre-eclampsia, fetal stress, gestational diabetes, gestational hypertension, nausea/vomiting or postpartum hemorrhage.
[e] These proportions are likely to be an underestimation, because we could not include prescriptions written during inpatient hospitalization.

et al., 2011). Large register-based studies including women with epilepsy (n = 1019 and n = 1280) reported finding no evidence for an increased risk of fetal malformations associated with in utero lamotrigine exposure (Mølgaard-Nielsen and Hviid, 2011; Tomson et al., 2011). However, the efficacy of lamotrigine during the peripartum period is largely unknown (Newport et al., 2008). Therefore, the aim of this study was to compare mood stabilization during pregnancy with lamotrigine versus lithium in the prevention of severe postpartum episodes.

2. Methods

We conducted a population-based cohort study using Danish national registers. This was possible as all live births and residents in Demark are assigned an unique personal identification number and registered in the Danish Civil Registration System, which allows linkage of data at the individual level within and between registers (Pedersen, 2011). Women with a history of bipolar spectrum disorder (including bipolar disorder I, II and not otherwise specified classifications) were identified in the Danish Psychiatric Central Research Register (DPCRR) (Mors et al., 2011) with International Classification of Diseases (ICD) codes 296.xx, 298.19 (ICD-8, 1969–1993) and F30-F31 (ICD-10, 1994 – present). Afterwards, pregnancies of women with at least one live born child in the period of 1996–2012, occurring after the diagnosis of bipolar disorder, were identified by linking the DPCRR to the Danish Medical Birth Registry (Knudsen and Olsen, 1998) Our exposure of interest was lamotrigine or lithium use during pregnancy. The information on the dispensation of prescriptions was extracted from the Danish National Prescription Registry (Kildemoes et al., 2011). We defined medication use during pregnancy as at least two prescriptions dispended between conception and delivery, with at least one prescription after the first trimester. Pregnancies in which women were prescribed more than one of the following mood stabilizers were not eligible for inclusion: lithium, lamotrigine, carbamazepine, oxcarbazepine, valproic acid, topiramate, or gabapentin.

The primary outcome of the study was severe psychiatric relapse or recurrence, defined as any psychiatric admission for mental disorders (ICD-10 codes F00–F99) within three months postpartum. Unfortunately, we were not able to examine less severe psychiatric relapse/recurrence (operationally defined as episodes not resulting in an inpatient psychiatric admission). The Danish Registers do not allow for access to individual patient records, and therefore symptom-based information at outpatient visits during pregnancy and in the postpartum period was not available. We analyzed the data using Stata 13.1 (StataCorp, College Station, TX, USA). To compare the postpartum relapse/recurrence risk between women with lamotrigine or lithium use during pregnancy, a logistic regression model was used to calculate crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Robust standard errors were used to account for multiple pregnancies in the same woman during the study period. We divided the total dose of all prescriptions during pregnancy by gestational age (in days), in order to calculate the average prescribed dose of lamotrigine and lithium during pregnancy.

Antipsychotic co-medication during pregnancy may prevent relapse/recurrence. Therefore, we performed a sensitivity analysis by repeating the analyses after exclusion of women with prescriptions of