Lithium prophylaxis during pregnancy and the postpartum period in women with lithium-responsive bipolar I disorder

Lithium Prophylaxis During Pregnancy And The Postpartum Period In Women With Lithium-responsive Bipolar I Disorder.

Abstract

The aim of this study was to evaluate the efficacy of lithium prophylaxis during the peripartum period in women with lithium-responsive bipolar I disorder. Seventeen lithium-treated patients were selected and underwent preconception counselling that included both a psychiatric and an obstetric evaluation. Treatment was continued with flexible-doses of lithium combined with supportive psychotherapy throughout the pregnancy and the postpartum period. The results support the prophylaxis efficacy of lithium in lithium-responder bipolar women who have a high risk of severe peripartum recurrences.

Keywords

Bipolar disorder, postpartum, pregnancy, lithium, psychotherapy

Introduction

The onset of bipolar disorder (BD) typically occurs during youth and early adulthood, placing women at risk throughout their childbearing years.
Recent psychiatric literature, while containing no clear evidence that pregnancy per se increases risk of bipolar recurrences, indicates that the postpartum is a high-risk period for recurrences in bipolar patients (Sharma 2012, Di Florio 2013). Moreover, our previous study on a large sample of medication-free bipolar women showed a higher incidence of postpartum recurrences in type I disorder (Maina 2014).
It is known, women who discontinue mood stabilizers before or during pregnancy are particularly at high risk of mood episodes. Viguera and colleagues found that postpartum recurrences after lithium discontinuation in pregnant women with BD were 2.9 times more frequent than recurrences in non-pregnant women (Viguera 2000).
To date, lithium has substantial evidence that supports the efficacy in the peripartum period (Bergink 2014) and the efficacy/safety ratio still seems to be in favor of lithium in respect to other mood stabilizers (Gentile 2012). Nevertheless, the current available data on the efficacy of lithium in bipolar pregnant women is still limited. Furthermore, data on specific subgroups of women with BD is needed.
The aim of the present study was to evaluate the efficacy of lithium prophylaxis during pregnancy and the postpartum period in a sample of women with lithium-responsive bipolar I disorder (BDI).

Materials and Methods

Subjects
The subjects selected for this study were women with BD being treated in the Psychiatric Unit of the Department of Neurosciences (University of Turin) and who wished to become pregnant. The recruitment period was from 2008 to 2013.
The inclusion criteria was: minimum 18 years of age, main diagnosis of BDI according to DSM-IV-TR, pregnancy planning and verbal consent to participate in the study.
The general exclusion criteria: presence of any medical illness, current alcohol and/or substance abuse, being heavy cigarette smoker (≥10 cigarettes/day), drug treatment with any agent (except lithium) which may interfere with fetal growth.

Procedures
Socio-demographic data and clinical characteristics were obtained through a clinical interview and a review of individual patients' medical records.
All women fulfilling the inclusion criteria underwent preconception counselling that included both a psychiatric and an obstetric evaluation on the risk-benefit ratio of lithium treatment during pregnancy and the postpartum period. They were also informed that breastfeeding was not recommended. All the participants made the decision to continue prophylaxis with lithium following a thorough discussion with their clinicians.
The women started a daily supplementation of 4 mg folic acid beginning 1 month before trying to get pregnant and continuing through the first 3 months of pregnancy (Huhta 2015).
From the preconception period until the third month after delivery, all subjects were followed up by psychiatrists (monthly appointments). Where necessary, the plasma levels of lithium were adjusted before pregnancy in order to be within the range of 0.5 and 0.8 Mmol/l. During pregnancy and the postpartum period dosage adjustments were permitted in a flexible manner based on the clinical

efficacy for individual patients and the level of lithium in their plasma. As suggested by recent guidelines, lithium was stopped 24 to 48 hours before the scheduled cesarean deliveries or at the onset of labor in the event of a spontaneous delivery (Ng 2009). Discontinuation of lithium lasted until the day after the childbirth.
Furthermore, all patients received supportive psychotherapy from the first trimester of pregnancy until the third month after childbirth with the primary objective of improving the patient's adaptation to her new life situation. All women underwent preconception counselling, prenatal care and delivery at a specialized center for high risk pregnancies with a neonatal intensive care unit.

Results

Of the seventeen lithium-responsive female patients selected, one of them had two pregnancies, which were both included and followed in the study. The statistical analysis carried out took into account both the number of enrolled patients (n=17) and the total number of pregnancies (n=18). None of the included patients had shown severe BD recurrences and/or had been hospitalized for psychiatric disorders in the 24 months before the study.
The socio-demographic and clinical characteristics of the sample women are shown in Table 1. The sample was characterized by a high number of past episodes (before prophylaxis with lithium) with severe symptomatology. A history of psychotic symptoms emerged in 83.3% of the subjects, mixed features in 88.9%, and suicide attempts were reported in 17.6%. All 17 women had been hospitalized at least once, and nearly 50% had a history of compulsory treatment. Finally, the four women with previous pregnancies (before prophylaxis with lithium) had experienced severe postpartum mood episodes. The mean daily lithium dose and the lithium plasma levels during pregnancy are shown in Table 2. Lithium was generally well tolerated: three women became overweight, two women reported mild polyuria and polydipsia (which had already been reported in the lithium treatment before pregnancy). Table 2 also shows the pregnancy outcomes. No congenital abnormalities occurred. Three babies with mild hypotonia ('Floppy Infant Syndrome') spontaneously recovered.
Psychiatric recurrences during pregnancy were found in 2 pregnancies (11.2%) in 2 different women (11.8%): one mild depressive episode and one hypomanic episode, both were treated by increasing the lithium dosage slightly. Postpartum disorders occurred after 5 childbirths (27.8%) in 5 patients (29.4%): two mild depressive episodes, one hypomanic episode with mixed features and two anxiety disorders NOS. Both postpartum depressive episodes were successfully treated with an increase in the lithium dosage and by intensifying psychotherapy sessions.
The postpartum hypomanic episode was treated with low doses of adjunctive olanzapine (5 mg per day). Such an episode occurred after the first childbirth of the patient with two pregnancies during the study period, while there was no bipolar recurrences after the second childbirth.
Finally, both postpartum anxiety disorders NOS were successfully managed by intensifying psychotherapy sessions and by prescribing benzodiazepines as needed.

Discussion and Conclusions

The aim of this prospective observational study was to assess the efficacy of lithium prophylaxis during pregnancy and after childbirth in a specific subpopulation of patients suffering from lithium-responsive BDI.
Our hypothesis was that the continuation of lithium prophylaxis would help such high-risk patients avoid experiencing peripartum bipolar recurrences.
We found that bipolar recurrences of any polarity during pregnancy occurred in 11.1% of the women. This result is consistent with the findings of Bergink and colleagues (2012) who found a relapse rate of 19.4% in lithium-treated pregnant women. It should also be emphasized that in our

sample the severity of recurrences during the pregnancies was mild and that hospitalization was avoided.

Furthermore, the rate of psychiatric disorders after delivery was 29.4%. In other studies of unmedicated bipolar women the postpartum recurrence rate was generally much higher: in a recent study carried out on a group of non-medicated bipolar women during pregnancies, the postpartum recurrence rate was 75% (Maina 2014). The finding, nonetheless, is not consistent with several investigations on lithium-treated women during pregnancy that reported lower recurrence rates: in a study of high-risk women with BD who remained stable throughout pregnancy and who used prophylactic treatment with lithium, only 7.7% relapsed postpartum (Bergink 2012). There are two reasons which may explain the higher prevalence (29.4%) that we found. First, it should be considered that only three patients (17.7%) showed postpartum mood episodes, while two patients (11.7%) presented transient anxiety disorders. Moreover, the recurrences observed were mild without any need for hospital admission. Second, our data was derived from a sample with severe BDI, with high rate of previous psychotic symptoms, suicide attempts, and compulsory treatments.

The positive results of this study could be also explained by the effect of the supportive psychotherapy. As stated by Frank and Swartz (2001), psychosocial therapies are important adjunctive treatments to medication for BD and they help the woman and her family to understand the disorder, adhere to medication, manage stress, and prevent relapse. Lithium was generally well tolerated, and no serious side effects occurred both to the pregnant women and to the babies. The association between lithium treatment during pregnancy and a higher risk of cardiovascular defects was recently confirmed (Diav-Citrin 2014). On the other hand, Bodén and colleagues stated that BD in women during pregnancy, whether treated or not, was associated with increased risks of adverse pregnancy outcomes (Bodén 2012). Our findings can firstly be explained by the small sample size. Secondly, all patients underwent a daily supplementation of folic acid from the preconception period. Thirdly, all women were treated with lithium monotherapy (no other drugs were allowed) and the lithium serum levels were kept close to the lower limit of efficacy range.

In conclusion, our results support the prophylaxis efficacy of lithium throughout pregnancy in lithium-responder BDI women. They also indicate that preconception counselling, as well as dedicated prenatal care by a multidisciplinary group comprising of psychiatrists and maternal-fetal medical specialists, could have contributed to the good outcome of the pregnancy for both mother and baby. These results should be interpreted in the light of the several limitations of the study: the very small sample size, the absence of a control group of unmedicated bipolar women, the presence of potential confounding factors such as the adjunctive supportive psychotherapy.

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Table 1: Socio-demographic and clinical characteristics of the sample (n=17 patients)

Age, years *(mean±S.D.)*	37.11 ± 3.42
Age at onset of bipolar disorder, years *(mean±S.D.)*	22.29 ± 3.19
Length of bipolar disorder, years *(mean±S.D.)*	15.06 ± 3.17
Previous hospitalizations, *(mean±S.D.)*:	1.59 ± .79
- Manic episodes	1.12 ± 78
- Depressive episodes	0.41 ± 50
History of compulsory treatment, *n (%)*	8 (47.1)
History of psychotic symptoms, *n (%)*:	14 (82.4)
- During manic episodes	12 (70.6)
- During depressive episodes	2 (11.8)
History of mixed symptoms, *n (%)*:	15 (88.2)
- During manic episodes	9 (52.9)
- During depressive episodes	6 (35.3)
History of suicide attempts, *n (%)*	3 (17.6)
Type of Bipolar Cycle, *n (%)*:	
- Mania-Depression-Free Interval	6 (35.3)
- Depression-Mania-Free Interval	2 (11.8)
- Irregular	9 (52.9)
Previous pregnancies, *n (%)*:	
- Yes	4 (23.5)
- No	13 (76.5)
History of past perinatal altered mood episodes, *n (%)*:	3 (17.6)
- Major depressive Episode	1 (5.88)
- Hypomanic Episode with Mixed Features	0 (0.0)
- Manic Episode with Mixed Features	1 (5.88)
- Puerperal Psychosis	1 (5.88)
History of past pregnancy loss, *n (%)*	1 (5.9)

Table 2: Characteristics of lithium treatment and pregnancy outcomes (n=18 pregnancies)

Lithium plasma levels, *(mean±S.D.)*:	
- Preconception	0.6 ± 0.05
- Pregnancy *(range)*	0.5 ± 0.1 – 0.66 ± 0.05
Lithium dose, *(mean±S.D.)*:	
- Preconception	708.3 ± 112.8
- Pregnancy (maximal dose)	716.6 ± 109.8
- End of pregnancy (ninth month)	675.0 ± 92.7
Lithium side effects, *n (%)*:	5 (27.8)
- Weight gain	3 (16.7)
- Polidypsia/polyuria	2 (11.1)
Obstetric outcomes, *n (%)*:	
- Pregnancy loss	0 (0)
- Preterm delivery	2 (11.1)
- Natural childbirth	13 (72.2)
- Caesarean section	5 (27.8)
- Congenital Malformation	0 (0)
- Floppy Infant Syndrome	3 (16.7)
- APGAR score (mean±S.D.)	9.0 ± 1.03
Psychiatric disorders during pregnancy, *n (%)*:	2 (11.2)
- Depressive episodes	1 (5.6)
- Hypomanic episodes	1 (5.6)
Psychiatric disorders during the postpartum period, *n (%)*:	5 (27.8)
- Depressive episodes	2 (11.1)
- Hypomanic episodes	1 (5.6)
- Anxiety Disorders NOS	2 (11.1)