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Review Article

Pregnancy and bipolar disorder: the risk of recurrence when discontinuing treatment with mood stabilisers: a systematic review

Larsen ER, Saric K. Pregnancy and bipolar disorder. The risk of recurrence when discontinuing treatment with mood stabilisers: a systematic review.

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Objective: Bipolar disorder in pregnancy may be difficult to treat. The dilemma is whether the women should continue medication throughout pregnancy, and maybe accept a minor risk to harm their unborn child, or discontinue medication and increase the risk of recurrence, which can lead to maternal morbidity, thereby endangering themselves and their foetus.
Design and methods: In September 2016, three electronic search databases; PubMed, Scopus and PsycInfo, were used searching for clinical trials concerning this question. Eight clinical trials concerning risk of recurrence after discontinuation of medication in pregnancy were included.
Results: There is no consensus concerning the risk of discontinuation of medication during pregnancy among bipolar women. The evidence from the trials included underscore that there seem to be a group of pregnant women who are stable despite they are not receiving mood stabilisers during pregnancy. Besides, there is a group of more severe and more unstable bipolar disorders that seem to benefit of a more close monitoring, support and prophylactic medication during pregnancy and *postpartum* period to prevent recurrence.
Conclusion: For the more stable bipolar women we recommend a well planned and more slowly discontinuation of medication before pregnancy. For the unplanned pregnancies it is important to consider the possibility of a more slowly discontinuation. For the more severe conditions of bipolar disorder, it is important to secure a close monitoring of medication. As the risk of *postpartum* relapse is high, medication may be started soon after delivery.

Keywords: bipolar disorder; medication; mood disorder; pregnancy; discontinuation

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Summations

- For the more stable bipolar women we recommend a well planned and more slowly discontinuation of medication before pregnancy.
- For the unplanned pregnancies it is important to consider the possibility of a more slowly discontinuation. For the more severe conditions of bipolar disorder, it is important to secure a close monitoring of medication.
- An increased risk of recurrence is seen among women rapidly discontinuing medication when they become aware of an unplanned pregnancy. This underscores the importance of discussing pregnancy with fertile bipolar women at an earlier stage.

Considerations

- In order to reduce the risk of teratogenicity it seem important to investigate if there are subgroups of women that under close follow-up may not need medication, perhaps primarily in first trimester.
- As the risk of *postpartum* relapse is high medication may be started soon after delivery.

Introduction

Bipolar disorder can be a severe psychiatric disorder. It is an illness known with two polarities; depression and mania. The aggregated lifetime prevalences has been estimated to 0.6% for bipolar I disorder, 0.4% for bipolar II, 1.4% for subthreshold bipolar disorder and 2.4% for bipolar spectrum disorder (1), men and women equally. Mean age at first affective episode has been estimated to 20.2 years among out-patients in the United States (2). Furthermore, there is a high risk of morbidity, comorbidity and suicidality (3,4) not least *postpartum* relapses (5–10). There has been controversy regarding the risk of teratogenicity using mood stabilisers (11,12). This can be a dilemma for young women with bipolar disorder, who want to have children. The question is whether they should continue medication throughout pregnancy, and maybe accept a minor risk to harm their unborn child, or discontinue medication and increase the risk of relapse, which can lead to maternal morbidity, thereby endangering themselves and their foetus. The illness course during pregnancy is discussed in a review by Sharma et al. from 2012 (13) who conclude that there might be a possible protective effect of pregnancy that could have been offset by the destabilising effect of abrupt withdrawal of mood stabilisers during pregnancy. As many pregnancies are unplanned it is important to discuss the risk with women of childbearing age (14). The Danish guidelines (12) for treatment of bipolar disorder during pregnancy recommend lithium as a first choice, and lamotrigine can be used in some cases. Valproate and carbamazepine are contraindicated because of their teratogenicity, especially neural tube defects.

The American diagnoses system DSM-IV distinguish between bipolar I and II, whereas the ICD-10 system does not differentiate between the two types. Bipolar I is given when the patient has had two episodes with at least one incidence of mania throughout their life. Most of the patients have longer periods with depression compared with mania. Bipolar II is classified in patients who have depressions and hypomania, but never mania.

To identify risk factors for illness episodes Viguera et al. (10) compared rates of specific types of affective disorders between pregnancy and *postpartum* periods among women with bipolar disorder ($N = 1162$) and unipolar depression [recurrent major depression (RMD)] ($N = 541$). Data were from the perinatal psychiatry programmes collected during the years 1980–2010 from Massachusetts General Hospital in Boston and the Lucio Bini Mood Disorders Centers in Cagliari and Rome.

In 2252 pregnancies, affective episodes occurred among bipolar I in 24.7% during pregnancy (major depression 8.9%, mixed states 8.1%), and in 38% during *postpartum* period (major depression 19.2%, mixed states 6.5%, mania 7.9%). Among bipolar II, it occurred in 20.8% during pregnancy (major depression 10.4%, mixed states 3.6%), and in 34.5% during *postpartum* period (major depression 28.7%, mixed states 2.5%). Among unipolar depressed, it occurred in 4.7% during pregnancy and in 17.2% during *postpartum* period. Risk factors during pregnancy were evaluated in a multivariate Poisson regression model. Important risk factors were younger onset age of affective disorder, previous *postpartum* episodes, fewer years of illness, bipolar disorder versus unipolar depression, fewer children and not being married.

Di Florio et al. (9) published in 2013 results from the incidence and timing of mood episodes in pregnancy and perinatal in women with bipolar disorder I ($N = 980$) and II ($N = 232$) and RMD ($N = 573$). Participants were recruited in two clinical and genetic studies of mood disorders. Women in this study continued medication throughout pregnancy or were receiving no medication before the pregnancy. Participants were interviewed about the lifetime occurrence of mood episodes in all their 3017 pregnancies and *postpartum* periods. Among bipolar I, 4.3% (60/1404) reported an episode during pregnancy versus 7.8% (33/424) among bipolar II and 4.7% (56/1189) among RDM. During the *postpartum* period, an episode was reported among 45.7% (640/1404) of bipolar I versus 34.4% (46/424) among bipolar II and 38% (452/1189) among RDM.

This review will focus on clinical trials concerning pregnant women with bipolar disorder and recurrence during pregnancy. It aims to evaluate if pregnant women with bipolar disorder, who discontinue treatment with mood stabilisers, are at higher risk of relapse during pregnancy.

Method

In September 2016, three electronic search databases; PubMed, Scopus and PsycInfo, were used searching

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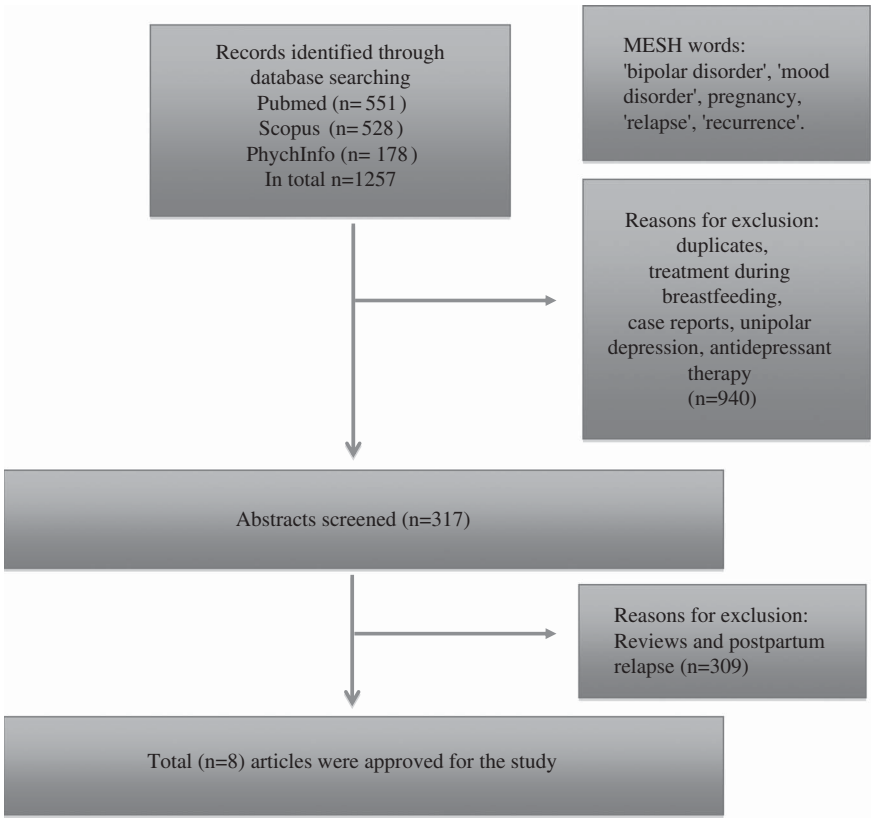

Fig. 1. Summary of literature search and study selection.

for clinical trials or cohort studies concerning risk of relapse in pregnant women with bipolar disorder, who did not receive mood stabilising treatment for their illness. Combinations of following key words were used: ('bipolar disorder' OR 'mood disorder') AND ('pregnancy') AND ('relapse' OR 'recurrence'). Only articles in English dealing with clinical trials were included. The PRISMA flow diagram and checklist were used for the review (Fig. 1). Searching the databases, eight articles regarding the subject were included in this review. Articles concerning other subjects as *postpartum* recurrences, unipolar depression or other events in pregnancy were sorted out. Abstracts from articles that could cover the subject were read, as well as reviews. The reference lists of the found articles were also carefully looked through, to see if there were more articles regarding the subject.

Results

Lamotrigine

1. Newport et al. (15) compared in an prospective observational study the recurrence risks among 26 initially stable pregnant women with bipolar disorder who discontinued mood stabilisers (lamotrigine $N = 5$), (lithium $N = 6$) and (divalproex $N = 5$) versus women who continued lamotrigine treatment throughout their pregnancies ($N = 10$). Among the 16 women who discontinued treatment, 14 did so rapidly (1–13 days). The only significant difference between the two groups was, that women who discontinued medication had an unplanned pregnancy in 81.3% of the cases versus 20% in the second group ($p = 0.005$). In total, 31.3% were primigravida in the first group versus 70.0% in the second group. In total, 75% were bipolar I in the first group versus 70% in the second group. Among women discontinuing mood stabilisers, the recurrence rate was 100%, versus 30% among women who continued treatment with lamotrigine [$p < 0.0001$, odds ratio (OR) = 23.2 (95% confidence interval (CI) = 1.5–366)]. Both groups had depressive (68.8 % vs. 66.7%) or mixed episodes (12.5% vs. 33.3%), but manic (12.5%) and hypomanic (6.3%) episodes were exclusively seen in women discontinuing treatment. Illness latency was 4.2 times shorter without treatment, and the time-to-25%-recurrence risk was 14 times earlier (28.0 vs. 2.0 weeks), when continuing treatment with lamotrigine versus stopping rapidly [$p < 0.0001$ (95% CI = 1.6–91)]. The mean dose of lamotrigine was 252 ± 143 mg for women continuing, 300 ± 173 mg

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for women with recurrence and 232 ± 138 mg for those who remained euthymic, possible reflecting differences in illness severity as perceived by prescribing clinicians.

Lithium

2. In a retrospective study published in year 2000, Viguera et al. (7) compared the relapse risk in pregnant women and 24 weeks *postpartum* ($N = 42$) with non-pregnant age-matched women ($N = 59$) during equivalent periods, all with bipolar disorder (bipolar I and II), who discontinued treatment with lithium. The recurrence rate among the 101 non-pregnant woman during the year before discontinuing was 20.8% ($N = 21/101$). The pregnant women discontinued treatment within 6 weeks of the date of conception. The non-pregnant decisions regarding lithium discontinuation arose clinically, usually at the patient's insistence after periods of relative euthymia (75% of the cases) or in response to treatment-emergent adverse effects (25%). With respect to illness episodes (four or more prior episodes), there was no significant difference between the groups (64.3% vs. 59.3%). The two groups only differed at one point; pregnant women discontinued lithium more rapidly compared with the cohort [73.8% ($N = 31$) versus 54.2% ($N = 32$), $p = 0.05$]. Rapid discontinuation happened over 1–14 days and gradually over 15–30 days. The results showed no significant difference in relapse between pregnant and non-pregnant women [52.4% ($N = 22$) vs. 57.6% ($N = 34$)] during the first 40 weeks. Among women who remained euthymic for 40 weeks after discontinuation of lithium, significantly more pregnant subjects experienced a recurrence *postpartum* [70% ($N = 14$)] than did the non-pregnant subjects during the corresponding time [24% ($N = 6$), $p = 0.0002$]. None of the nine women with bipolar disorder who continued lithium treatment during pregnancy relapsed during week 1–40, but three experienced a recurrence soon after delivery. Women with a high number of prior episodes had a significantly higher risk of recurrence than those with 1–3 episodes [66.1% ($N = 41$) versus 38.5% ($N = 15$), $p = 0.006$]. The time to recurrence during pregnancy was 2.5 times shorter when abruptly discontinuing versus gradually (8 weeks vs. 20 weeks, $p = 0.006$). Pregnant women more often had depressive/mixed-dysphoric episodes than non-pregnant (63% vs. 38%, $p = 0.02$).

3. A retrospective study by Grof et al. (8) from year 2000 investigated the protective effect of pregnancy in women with bipolar disorder type I, who had their pregnancies after the onset of affective disorder, and who had been pregnant before treatment with lithium prophylaxis ($N = 28$) by comparing them to childless women with bipolar disease ($N = 33$). Although some of the subjects had received lithium for the treatment of their acute episodes, all of the subjects had discontinued medications long before their pregnancies. The data derived from the International Group for the Study of Lithium-treated Patients database of excellent lithium responders. Grof et al. argues that unless investigation focusses on a well-defined subgroup, the heterogeneity may obscure research findings. Data were compared both intra-individually, using data from three 9-month periods – immediately before pregnancy, during pregnancy and *postpartum* – and inter-individually, using the 33 never pregnant women as controls. Four women took lithium when they re-experienced depression towards the end of their pregnancy. One woman appeared anxious about a possible relapse, thus resuming lithium treatment again. The conclusion in this study was that women suffering from typical, lithium-responsive bipolar I disorder experience fewer abnormal moods during pregnancy, in terms of both frequency and duration of recurrence.

4. Rosso et al. (16) evaluated the efficacy of lithium prophylaxis and supporting psychotherapy in a non-randomised prospective follow-up study during pregnancy and the *postpartum* period in 17 women with lithium-responsive bipolar type I disorder. The women were treated in the Psychiatric Unit of Department of Neurosciences in Turin from 2008 to 2013. Before lithium treatment, 83.3% had psychotic symptoms and 88.9% mixed episodes.

All women had been hospitalised at least once and nearly 50% had a history of compulsory treatment. Four women with previous pregnancies had experienced severe *postpartum* mood episodes. None of the included women had shown severe bipolar recurrences and/or had been hospitalised for psychiatric disorders in the 24 months before the study. The women were followed with monthly appointments, and plasma levels of lithium were adjusted in a flexible manner. Lithium was stopped 24–48 h before caesarean deliveries or at the onset of labour until the day after the childbirth. Psychiatric recurrences during pregnancy were found in two pregnancies (11.2%); one with a mild depressive episode and one with a hypomanic episode. Both were treated by increasing the lithium dose. *Postpartum* disorders occurred after five childbirths (27.8%); two with mild depressive episodes, one hypomanic episode with mixed features and two with anxiety disorders Not Otherwise Specified (DSM IV-TR). The depressive disorder was treated by increasing the lithium dose and the hypomanic with a low adjunctive olanzapine dose (5 mg/day). Anxiety was treated with benzodiazepines.

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5. Abdel-Hay et al. (17) enrolled 83 women in a prospective observational study during year 2006–2010 at the Neuropsychiatry Outpatient Clinic at Tanta University Hospital in Egypt. The women had to be euthymic for at least 8 weeks before their last menstrual episode at inclusion. The women all had a history of bipolar I disorder and were planning to become pregnant or had unplanned pregnancy. The women were followed throughout the pregnancy and 4 weeks *postpartum* with visits at each trimester or when needed. All participants were married. Only 24 (29%) were employed outside home. No information concerning when and how medications were discontinued is reported. In total, 54 (65%) had recurrence of bipolar disorder, 28 (33.7%) during pregnancy and 26 (31.3%) during *postpartum*. During pregnancy, recurrence occurred in one woman in the first trimester, 11 during second trimester and 16 during third trimester. During pregnancy and *postpartum*, 31 (37%) women continued medication. Among those who stopped medication recurrence of bipolar disorder during pregnancy and *postpartum* occurred in 40/52 (76.9%) ($p < 0.05$). Among those who continued medication, recurrence was seen in 14/31 (45.2%).

6. In a prospective open label follow-up trial, Bergink et al. (18) compared lithium use during pregnancy to its initiation *postpartum* in women at high risk for *postpartum* psychosis. Between 2003 and 2010, 70 pregnant women at high risk for *postpartum* psychosis were referred to the authors' psychiatric outpatient clinic. In total, 29 women had a history of *postpartum* psychosis but without any manic or psychotic symptoms outside the *postpartum* period. Furthermore, 41 women with a diagnosis of bipolar disorder based on a history of non-puerperal episodes with or without puerperal episodes. All women with a history of psychosis limited to the *postpartum* period ($N = 29$) remained stable throughout pregnancy despite being medication free. Bipolar women who were initially medication free were advised to start lithium prophylaxis immediately *postpartum*. Women already taking maintenance lithium during pregnancy were advised to continue treatment. The relapse rate during the pregnancies of the women with bipolar disorder who used prophylaxis was 19.4%, compared with 40.0% in bipolar women without prophylaxis. Of the 29 patients with a history of *postpartum* psychosis only, 20 began prophylactic treatment within 24 h of delivery. In total, 17 used lithium and three used antipsychotics. Notably, there were no cases of relapse among the 20 women with *postpartum* psychosis who initiated *postpartum* prophylaxis upon delivery. Nine of the 29 patients decided against prophylactic medication, and among those nine women, 44.4% relapsed *postpartum*. The *postpartum* relapse rate was highest in women with bipolar disorder who experienced mood episodes during pregnancy (60.0%).

Mood stabilisers

7. Viguera et al. (19) investigated in a prospective observational clinical cohort study published in 2007 the risk and time to recurrence among women with bipolar disorder who continued ($N = 27$) or discontinued ($N = 62$) mood stabiliser treatment at conception. If they discontinued all mood stabilisers more than 6 months before conception they were excluded from the study. The included women were euthymic at conception and continued or discontinued treatment proximate to conception. In total, 61 were bipolar I and 28 bipolar II. As primary mood stabiliser, lithium was used among 61.8% ($N = 55$), anticonvulsant among 36% ($N = 32$) and atypical antipsychotics among 2.2% ($N = 2$). Over half of the study group was exposed to antidepressants 51.7% ($N = 46$) in addition to a mood stabiliser. In total, 66.1% of subjects who discontinued with mood stabilisers used antidepressants versus 18.5% who continued taking a mood stabiliser. In total, 21.0 % of subjects who discontinued with mood stabilisers used antipsychotics versus 40.7% who continued taking a mood stabiliser.

The overall risk of recurrence in pregnancy was 71%. The primary outcome variable of recurrence was determined by a researcher blind to treatment status. For the women discontinuing mood stabilisers the risk was 2.3 (CI = 1.4–3.8) times greater compared with women continuing medication (85.5% vs. 37%, $p < 0.001$). The duration of illness was longer; 43.3 % of the pregnancy versus 8.8% ($p < 0.001$). Median time to first relapse was 9.0 weeks after discontinuing medication versus >40 weeks for women who continued treatment. 47.2% of recurrence appeared in the first trimester, 31.9% in the second and 18.8% in the third trimester.

Comparing abrupt/rapid (1–14 days) with gradual (≥15 days) discontinuation, the risk of 50% recurrence was 2 weeks versus 22 weeks ($p < 0.0001$). Unplanned pregnancies co-varied with greater likelihood of rapid discontinuation 95.8% versus 20.3% ($p < 0.0001$). The majority of first recurrences were depressive or mixed episodes, 88.7% of episodes after discontinuing mood stabilisers versus 18.5% when treated. A Cox multivariate regression analysis showed, that use of antidepressants and treatment discontinuation of mood stabilisers were both independent risk factors. Illness severity and bipolar type were not associated with increased risk.

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8. In a prospective, observational study of 37 women with bipolar II, disorder Sharma et al. (20) evaluated pharmacotherapy during pregnancy and the *postpartum* period. During pregnancy, the majority of participants (54%) were not on any psychotropic medication; approximately one-third (35%) received monotherapy, and the rest received combination therapy. During the *postpartum* period, 35% received monotherapy and 50% received combination therapy. During pregnancy, 51% had a recurrence compared with 70% in the *postpartum* period.

Discussion

There is no consensus concerning the risk of discontinuation of medication during pregnancy among bipolar women. The risk goes from 18% to 100 % without medication and from 11.2% to 45.2% with medication. Although we do not have double-blind randomised controlled trials dealing with the risk of recurrence of mood disorders the present trials do not, however, leave us in total darkness. The evidence from the trials included underscore that there seem to be a group of pregnant women who are stable despite they are not receiving mood stabilisers during pregnancy. Further, there is a group of more severe and more unstable bipolar disorders that seem to benefit of a more close monitoring, support and prophylactic medication during pregnancy and *post-partum* period to prevent recurrence. An important risk factor for recurrence seem to be women with unplanned pregnancy who rapidly stop their medication in order not to harm the foetus. Different risk of recurrence may to some extent be explained by the fact that specialised centre often treat more severe cases giving rise to a higher risk estimate.

Newport et al. (15) argue that continued lamotrigine treatment reduces the risk of mania and hypomania as well as depressive recurrences. The sample size is too small to detect a difference concerning depression. The first group of women discontinuing mood stabilisers had more unplanned pregnancies and a higher dose of lamotrigine before discontinuing treatment. The second group of women continuing lamotrigine were exclusively treated with lamotrigine indicating a less severity compared with the first group treated with lithium or divalproex as well. As the pregnancy was unplanned or the dose of lamotrigine higher the first group may be more unstable.

In the trial by Viguera et al. from year 2000, the recurrence rate among all women after discontinuation of lithium was rather high (52.4%–57.6%) but no difference was found among pregnant and non-pregnant women until after delivery (7). The resulting computed time to 50% recurrence risk was 30.0 weeks in the pregnant women versus 24.0 weeks in non-pregnant women after discontinuing lithium. These differences were not significant. The results are nevertheless interesting as it may indicate that pregnancy to some extent protect against the risk of recurrence. Among the 101 women in the study 21 relapsed before pregnancy when they were on lithium prophylaxis. None of nine women taking lithium during pregnancy relapsed. This may indicate a protective influence of pregnancy among some lithium responders. The pregnant women discontinued lithium more rapidly, thus further increasing the risk of recurrence.

The study by Grof et al. (8) focussed on a group of bipolar I women who were excellent lithium responders and who were able to discontinue lithium during pregnancy. The trial is commented by Viguera et al. in 2002 (21) who argue that available research provides little empirical support for a protective effect of pregnancy. For those with milder illnesses, pregnancy may not be destabilising and might even have a beneficial effect for some women. However, for patients with severe bipolar illness who then proceed with treatment discontinuation, recurrence risk may be much greater. At our mood disorder clinic in Risskov we experience that some of the more stable bipolar women go through their pregnancy without recurrence after well-planned discontinuation and close follow-up. Grofs et al.'s work may be a step closer to identify those subjects.

Unfortunately, information concerning medication is lacking in the quite interesting follow up study by Abdel-Hay et al. (17) Another matter that differs from other studies is the low risk of relapse in the first trimester. The question arises what could have prevented this; perhaps a protective effect of being married and working at home.

Bergink et al. (18) showed that a subgroup with *postpartum* psychosis may not need prophylactic medication during pregnancy but after delivery.

Viguera et al. (19) demonstrate in their study that the risk of destabilisation among those who discontinued with a mood stabiliser seem to have been increased further due to less use of antipsychotics and more use of antidepressants. Unplanned pregnancy indicated a more rapid and higher degree of discontinuation of mood stabilisers. This underscores the importance of discussing pregnancy with fertile bipolar women at an earlier stage. In our psycho educational programme in Risskov, this is not a mandatory subject, though studies support that it probably should be. In most trials, it has been shown that the highest risk of affective episodes occur in the first trimester of pregnancy. Unfortunately, this is the

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period where medication may give rise to the highest risk of teratogenicity. Treatment discontinuation just before or at the start of pregnancy is common and may contribute to the risk of recurrence early in pregnancy. As women were excluded from the study by Viguera et al. (19) if they discontinued treatment with all mood stabilisers more than 6 months before conception we do not get the opportunity to see if pregnancy may be a stabilising factor for this group.

Many other aspects of treating pregnant bipolar women could be mentioned. In the following, I will draw attention to a few. Burt et al. (22) go through a case with a women with bipolar disorder that are discouraged by her doctors from becoming pregnant. The case is intended to provoke discussion about what ethical and moral role a physician should play when a patient wants treatment that poses significant risk to her well-being and possibly the life of a child.

Collaboration with obstetrician-gynaecologists may be important in order to take care of bipolar pregnant women. At our department we have monthly conferences where we discuss patients with mood disorders referred to the local obstetric clinic. Yonkers et al. (23) refer to that it is not uncommon for a women with bipolar disorder to present for treatment when she is past 28 days and thus beyond the period when neural tube closure occurs. Termination of treatment at this point puts the mother at risk while providing minimal benefit to the foetus. Women who discontinued medication secondary to concerns about teratogenicity but who have a history of relapse after medication discontinuation should consider medication reinstatement. The risk of neural tube defect using carbamazepine over 1000 mg is 2%. When using valproate below 700 mg, the risk of neural tube defects is 1% and over 700 mg 2%. When using over 1500 mg valproate, the risk of multiple malformations is 7%, of heart malformations is 7% and of hypospadias is 5%. Valproate may possibly affect the foetal brain, and a high association between valproate exposure in utero and later risk of autism is found (24). The use of valproate and carbamazepine is contraindicated during pregnancy. In a review article by Khan et al. (25) they draw attention to the risk of unrecognised bipolar disorders in pregnant women presenting with depressive symptoms treated with antidepressant monotherapy.

In a review by Wald et al. (26) a key point is that clinicians serve the bipolar pregnant women best by being as transparent as possible about the risk/benefit analysis of each patient's situation with the realisation that ultimately the decisions are made by the patient and family. To monitor treatment with lamotrigine in pregnancy the group recommend blood concentration levels before conception to provide a patient-specific target to aide dose adjustments throughout pregnancy and perhaps a monthly monitoring as in treatment of epilepsy. This is just to mention another field that needs more research.

The evidence from the trials included in this review underscore that there seem to be a group of pregnant women who are stable despite they are not receiving mood stabilisers during pregnancy. Moreover, different guidelines draw attention to the group of more severe and more unstable bipolar disorders that seem to benefit of a more close monitoring, support and prophylactic medication during pregnancy and *postpartum* period to prevent recurrence. The trials included in this review demonstrate that discontinuing medication more rapidly as well as letting the women stay on antidepressants alone may inflate this risk. Trials with a well-planned and more slowly discontinuation are needed. Besides, it is important to investigate if there are subgroups of women who under close follow-up may not need medication during pregnancy in order to reduce the risk of teratogenicity.

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Conflicts of Interest

The authors have no conflicts of interest.

Supplementary material

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