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Research report

Protective effect of pregnancy in women with lithium-responsive bipolar disorder

Paul Grof^{a,*}, Wendy Robbins^b, Martin Alda^c, Anne Berghoef^d, Milos Vojtechovsky^e,
Agneta Nilsson^f, Carrie Robertson^g

^aDepartment of Psychiatry, University of Ottawa, Ottawa, Canada

^bJoint Chair in Women's Studies, University of Ottawa and Carleton University, Ottawa, Canada

^cDepartment of Psychiatry, Dalhousie University, Halifax, Canada

^dDepartment of Psychiatry, Benjamin Franklin University, Berlin, Germany

^eDepartment of Psychiatry, Charles University, Prague, Czech Republic

^fDepartment of Psychiatry, Karolinska University, Stockholm, Sweden

^gAffective Disorders Service, Royal Ottawa Hospital, Ottawa, Canada

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Abstract

Background: Recent psychiatric literature, while indicating a high incidence of postpartum depression, contains a few clinical reports which support our observations that women with episodic bipolar disorder often remain well without treatment during pregnancy. Our retrospective study statistically examines the clinical course of 28 women with RDC typical bipolar disorder, type I, who became pregnant prior to receiving successful lithium prophylaxis. **Methods:** We derived all data from the International Group for the Study of Lithium-treated Patients (IGSLI) database of excellent lithium responders. Data were compared both intraindividually, using data from three 9-month periods — immediately prior to pregnancy, pregnancy and postpartum — and interindividually, using never-pregnant women as controls. **Results:** Intraindividual data show that women with typical bipolar disorder, type I, experience significantly fewer and shorter recurrences during pregnancy than either before or after. Interindividual comparisons indicate that the recurrence risk during pregnancy is markedly lower than the clinical course would predict. Moreover, the few recurrences observed during pregnancy all took place in the last 5 weeks. **Limitations:** Limiting cases to lithium responsive patients could have reduced heterogeneity and perhaps generalizability. **Conclusions:** The findings, nonetheless, indicate a marked improvement of the clinical course of typical bipolar disorder, type I, lithium-responsive, during pregnancy. Exploring the underlying protective mechanisms may lead to new understanding of the pathophysiology of mood disorders and to new approaches to treatment and prevention. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Pregnancy; Bipolar disorder; Placenta; Lithium; Postpartum depression

*Corresponding author, Royal Ottawa Hospital, 1145 Carling Avenue, Ottawa, Ontario, K1Z 7K4, Canada. Tel.: +1-613-722-6521, ext. 7025; fax: +1-613-722-5048.

E-mail address: pgrof@rohcg.on.ca (P. Grof)

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1. Introduction

A major focus of the literature on pregnancy and bipolar disorder to date has been the safety of mood stabilizing medication during pregnancy and lactation (e.g. Schou et al., 1973; Weinstein, 1976; Linden and Rich, 1983; Stewart et al., 1991; Verdoux et al., 1994; Altshuler et al., 1996; Schou, 1998). In recent years, women with bipolar disorder have usually been advised to refrain from taking lithium during the first trimester of pregnancy and to resume it in the second trimester (Cohen et al., 1988; Schou, 1990). Yet, a few reports (Paffenbarger and McCabe, 1966; Targum et al., 1979; Kumar, 1982; Paffenbarger, 1982; Spielvogel and Wile, 1986; Kastrop et al., 1989; Lier et al., 1989; Sharma and Persad, 1995; Sharma et al., 1997) suggest that women with certain mood disorders remain well without treatment during their whole pregnancy. These findings are not generally accepted, mainly because psychiatric disorders during pregnancy have not been studied adequately (Brockington, 1982, 1998; Leibenluft, 1996). We have also observed in clinical practice that women with typical bipolar mood disorder who did not follow the usual recommendation and did not resume lithium, remained in most cases well during the 9 months of pregnancy, despite a history of frequent recurrences.

Aside from this handful of studies of beneficial aspects of pregnancy, psychiatric literature overwhelmingly concentrates on the high incidence (10%) of postpartum depression (e.g. Kendell et al., 1987; Parry, 1989), although one recent study finds the incidence possibly exaggerated (Terp and Mortensen, 1998). There are also a few reports of the worsening during pregnancy of some psychiatric disorders, for example, neurotic depressions and schizophrenias (Kumar, 1982; Spielvogel and Wile, 1986; Altshuler and Szuba, 1994; Kitamura et al., 1996). Until now, no study has tested the hypothesis of lower affective morbidity during pregnancy in a homogeneous subgroup of sufficient size. Yet, if pregnancy affords protection against typical bipolar disorder, and if pregnancy affects bipolar disorder differently from other mental illnesses, then the underlying mechanisms must have some specific features. Exploring these protective mechanisms may lead to new understanding of the pathophysiology of

mood disorders and to new approaches to treatment and prevention. Our study investigates systematically this putative 'protective effect' in women with typical bipolar disorder.

2. Methods

2.1. Subjects

The literature indicates that the effect of pregnancy may differ according to psychiatric diagnosis. Mood disorders is a fairly broad diagnostic category and affects a heterogeneous population. Unless investigation focuses on a well-defined subgroup, the heterogeneity may obscure research findings. To insure that we investigated a relatively homogeneous group of women with typical bipolar disorders, we included in this study only patients who suffered from a recurring RDC bipolar disorder, type I, and who later responded well to lithium prophylaxis.

The subjects for this study were selected from a cohort of 162 bipolar patients followed by the International Group for the Study of Lithium-treated Patients (IGSLI) in research clinics in Austria, Canada, the Czech Republic, Denmark, Germany, and Sweden. All subjects were interviewed using SADS-L semistructured interviews (Endicott and Spitzer, 1978) and diagnosed according to Research Diagnostic Criteria (RDC) (Spitzer et al., 1978). In addition to a diagnosis of bipolar illness, all subjects met criteria for definite prophylactic response to lithium as described previously (Grof et al., 1994; Turecki et al., 1998). During adequate lithium prophylaxis, there were no concomitant medications administered, with the exception of hypnotics.

The IGSLI database, developed during the last decade, contains observations on excellent lithium responders which we have systematically collected for biological studies. It contains, among other information, data on the onset, duration, and type of recurrences, and on the probands' children.

The research subjects drawn from the IGSLI database for the current study (excellent responders, female) were comprised of 85 women, half from North America (42 Canadians) and half from Europe (43 from Germany, the Czech Republic, and

Sweden). These women have been followed in specialized mood disorder clinics for a number of years, and details about their clinical course and their children have been thoroughly documented in long-term research studies. Their average age at the onset of illness was 28.4 ± 10.8 years. Their average age at the last follow-up was 55 ± 14.2 years. The average age of onset of BD was 27.6 ± 9.9 years. The probands had a high recurrence risk as evidenced by a high number of illness episodes prior to lithium treatment (8.2 ± 10.1), and they had been fully stabilized on lithium monotherapy for 14.4 ± 6.8 years. To further ensure reliability of the diagnoses and uniform determination of the lithium response, all case histories and records were reviewed by a single senior clinical investigator (PG). Almost all women (94%), excepting those in Sweden, in 1996–1997 were also reinterviewed by him. Full consensus on diagnoses was achieved, due to the fact that this international group has collaborated very closely for nearly a decade.

A large proportion (39%) of the 85 women ($n = 33$) remained childless, which reduced the size of the sample directly relevant for the hypothesis. The remaining 52 women had a total of 112 pregnancies, for a fertility rate of 2.2. Of these 52 women, 24 had their pregnancies before the onset of affective disorders and therefore contributed no information to this study, because presumably they were not at risk for affective illness during their pregnancies.

The remaining 28 women (17 from Canada, 11 from Europe) had their pregnancies (a total of 56) after the onset of affective disorder, and thus provided information relevant for testing our hypothesis. The age at onset of their illness was 21.8 ± 5.6 years. They experienced 9.5 ± 12.1 episodes of illness before being treated with lithium prophylaxis. Fifteen women had more than one pregnancy, but for statistical analysis only the first pregnancy was counted. All pregnancies included in this retrospective study took place before the women received systematic lithium prophylaxis. The women received medications for their acute episodes, which on five occasions included acute lithium administration, but no maintenance treatment. The medications were discontinued long before pregnancies. None of the women took lithium during pregnancy while well, but four women took lithium when they reex-

perienced depression towards the end of their pregnancy.

Mental health professionals did not provide advice about the timing of pregnancy. However, we have no information as to whether any of the women planned the timing of her pregnancy based on her own observations of the clinical course of her illness. Similarly, the database contains no reliable information about their breast-feeding. Women included in this study were also part of larger genetic studies of lithium-responsive bipolar illness (e.g. Turecki et al., 1996, 1998; Alda, 1999).

2.2. Comparisons

Investigating affective morbidity in pregnancy poses particular challenges. Because the investigator cannot randomize the research subjects, it is not possible to test experimentally the hypothesis about the safeguarding effect of pregnancy. The expected frequency and duration of episodes of affective disorder must be estimated, yet there is no generally accepted methodology for obtaining control values in the absence of randomization. Under the circumstances, we decided to employ intraindividual and interindividual comparisons in parallel. We hypothesized that these women would experience the highest affective morbidity during the postpartum period, and the lowest during pregnancy.

2.2.1. Intraindividual comparison

For each woman, the number and duration of episodes of affective illness were determined for the 9 months preceding pregnancy, during pregnancy, and for 9 months postpartum. The Wilcoxon test was employed to compare the durations of recurrence. To test the difference in episode frequency, we employed the McNemar test.

2.2.2. Interindividual comparison

From the total sample of 85, the 33 childless women served as a comparison group. Based on the frequency and duration of episodes of illness preceding lithium prophylaxis, the risk of recurrences and their duration was estimated for an average 9-month period between the onset of illness and the beginning of long-term treatment. We hypothesized that the observed frequency and duration of recurrences

during pregnancy would be lower than the expected morbidity.

3. Results

3.1. Affective morbidity during pregnancy

3.1.1. Intraindividual comparison

The duration of episodes postpartum was significantly longer than for episodes both before and during pregnancy. More importantly, the duration of episodes before pregnancy was significantly longer than those during pregnancy (Table 1).

The number of episodes postpartum was significantly higher than the number of episodes during both comparative periods, as one would expect. Again, more importantly, the number of episodes per 9-month period prior to pregnancy was significantly higher than during pregnancy (Table 2).

3.1.2. Interindividual comparison

During pregnancy, the group of 28 women experienced only one-fourth the expected number of

episodes and one-eighth the expected length of episodes. Their course of illness prior to pregnancy, in terms of the number and duration of recurrences, was not different from the course of non-pregnant women during the same length of illness, while the number of postpartum episodes was markedly higher than expected (Fig. 1).

3.2. Prepartum morbidity

Of the 28 women, four had a recurrence of depression during pregnancy, all during the last 5 weeks before delivery. In addition, one woman, interviewed during the 34th week of pregnancy, appeared anxious and preoccupied about a possible relapse, but not clinically depressed. She had experienced no mood problems during her previous pregnancy, but during postpartum had encountered an intense depression. Out of fear of recurrence, she resumed medication on her own initiative, during her 34th week. We have counted her as having experienced a recurrence as well, for the purpose of this study.

Table 1

Intraindividual comparison: duration of recurrences ($N = 28$; Mann–Whitney U -test)

During pregnancy (mean 0.9 weeks) vs. Before pregnancy (mean 6.1 weeks)
 $U=548$, p less than .01

During pregnancy (mean 0.9 weeks) vs. Postpartum (mean 12.2 weeks)
 $U=611$, p less than .001

Before pregnancy (mean 6.1 weeks) vs. Postpartum (mean 12.2 weeks)
 $U=468$, nonsignificant

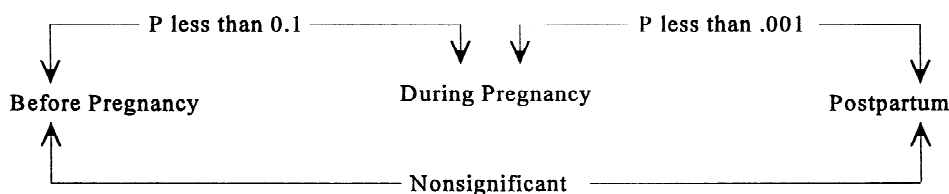


Table 2

Intraindividual comparison: change in the frequency of recurrences (N = 28; McNemar test for the significance of changes)

During pregnancy (mean 0.14/9m) vs. Before pregnancy (mean 0.43/9m)
Chi square = 5.14, p less than .05

During pregnancy (mean 0.14/9m) vs. Postpartum (mean 0.68/9m)
Chi square = 15.01, p less than .01

Before pregnancy (mean 0.43/9m) vs. Postpartum (mean 0.68/9m)
Chi square = 3.1, nonsignificant

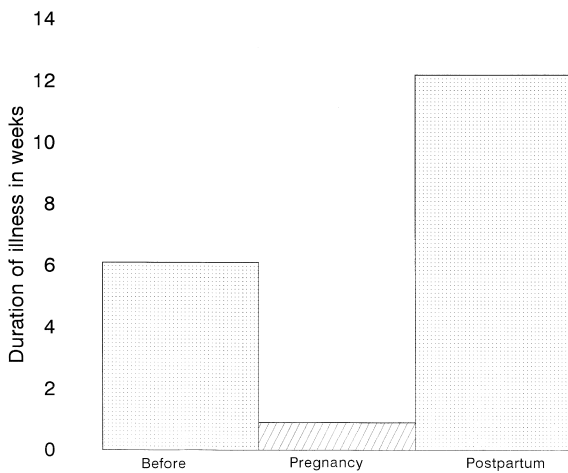
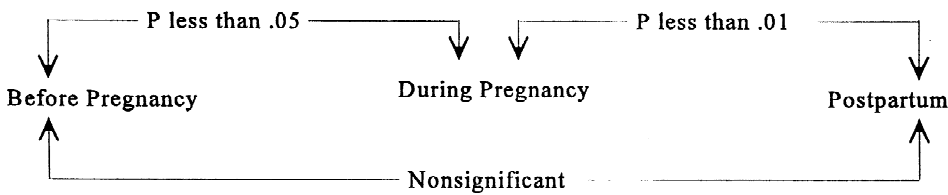


Fig. 1. Comparison of affective morbidity.

3.3. Postpartum morbidity

Twenty-five percent of women experienced postpartum episodes, most of them once, with a maximum of four times. We anticipated postpartum recurrences in 20–25% of patients (Miller, 1999).

The mean age at these episodes was 26.3 years, and they lasted 3.5 months on the average. Forty-two percent of these episodes were manic in character.

4. Discussion

4.1. Interpretation

The results of this study indicate that women suffering from typical, lithium-responsive bipolar disorder, type I, experience markedly fewer abnormal moods during pregnancy, in terms of both frequency and duration of recurrences. There is ample evidence that bipolar disorder, type I, differs from both bipolar II and rapid cycling bipolar disorder in major clinical characteristics, including gender differences (Goodwin and Jamison, 1990). Limiting the selection to lithium prophylaxis-responsive patients reduces heterogeneity of the sample (Grof et al., 1994). That we selected only these patients reduced the heterogeneity of the group but also limits generalizability. To achieve that, we have now initiated a more comprehensive, international, collaborative study.

To investigate the effect of pregnancy on the selected patients, we had to turn to observations on clinical course gathered in the past. The impact of pregnancy on the natural history of illness is nowadays difficult to evaluate because women with bipolar illness are placed on long-term, modifying treatments quite early on in the course of illness. Therefore, their particular recurrence risk and the impact of pregnancy are hard to estimate.

The ‘mirror method’ we employed for intraindividual comparison has been demonstrated as valid for investigations of the clinical course (Angst et al., 1969; Isaksson et al., 1969), although its application specifically to the effect of pregnancy raises some questions. Women suffering from a recurrent affective disorder may tend to plan a pregnancy when they have been stable for some time. It may be asked if the findings do not simply indicate that these women exhibited a low recurrence risk at this time period, independent of pregnancy. We feel that this is unlikely, as the group had a high affective morbidity both pre-pregnancy and postpartum. Out of 28 women, seven (25%) experienced postpartum episodes. In the total sample, the number of women with postpartum depression was 16 out of 85 (19%), or close to double the rate for women in the general population. In the absence of a matched control, the average morbidity rate of nonpregnant women served as an approximation for interindividual comparison. The figures do support, but cannot prove, the hypothesis.

The observation that all five women who became ill during pregnancy did so during the last 5 weeks of pregnancy supports earlier reports of ‘prepartum psychosis’ by Paffenbarger and McCabe (1966) and Brockington et al. (1990). The unknown process that initiates postpartum affective disorder may actually start, in some cases, during the last weeks of pregnancy. Viewed another way, it is possible that the mechanism safeguarding against recurrences of bipolar illness normally functions until delivery but may, at times, diminish or stop in the final weeks of pregnancy.

Although a number of explanations have been advanced for high postpartum morbidity, no plausible theory has been formulated as yet. Most current speculations revolve around the impact of a dramatic drop in the concentration of several hormones which

takes place perinatally. Recently, NIMH researchers (Chrousos, 1995; Magiakou et al., 1996) reported a large fall of CRH (corticotrophin releasing hormone) concentration in those women who experienced postpartum ‘blues’ or depression. Abnormal CRH function has also become one of the favored explanations of the genesis of depression (e.g. Modell et al., 1998).

4.2. Implications for management

The finding that pregnancy protects women from episodes of typical bipolar disorder, type I, has important implications for the care of women at risk for recurrences. Advice to women who have a history of affective illness and consider a pregnancy has been changing during recent decades. A number of women previously hospitalized for bipolar illness told us that, in the 1950s and 1960s, they were often advised by physicians to avoid pregnancy (because of the perceived likelihood of passing on a genetically-transmitted disease which had no effective treatment), and, in fact, many did remain childless. In the early 1970s, the prophylactic value of lithium salts was accepted, and the earlier recommendation to avoid pregnancy was replaced by the advice to avoid lithium during the first trimester. During the second trimester, lithium treatment was usually resumed, and the dosage increased in parallel with the accelerating glomerular filtration.

If our findings are replicated, it would be reasonable to recommend that pregnant women with previous recurrences of typical bipolar disorder, type I, suspend psychotropic medication until the last 6 weeks of pregnancy, and that they be monitored closely during those final weeks. Observations from other studies (e.g. Stewart et al., 1991; Cohen et al., 1995), as well as our own, would strongly support the recommendation to resume preventative medication in the final weeks of pregnancy or early postpartum, however.

4.3. Implications for research

This study suggests that powerful natural mechanisms preventing the recurrence of typical, lithium-responsive bipolar disorder, type I, may be at work during pregnancy. There is an emerging body of

observation which suggests that the placental production of hormones and peptides may be one of the important factors involved (e.g. Turnbull et al., 1974; Field, 1984). The placenta is an established, rich source of substances, such as corticotrophin releasing hormone (Tsigos and Chrousos, 1994), which have a potential effect on mood regulation in the central nervous system. The possible protective effect of CRH, which increases dramatically during pregnancy due to its production by the placenta as well as by the hypothalamus, and which is involved in the regulation of the onset of labor, is worth investigating carefully. Very low CRH values have been observed in women who experienced postpartum mood changes and a hypothesis formulated that, in such women, the hypothalamus adjusts poorly to the dramatic drop in CRH after delivery when placental CRH is no longer available (Chrousos, 1995; Dorn and Chrousos, 1997). The production of placental hormones (Smith et al., 1990) normally increases steadily during pregnancy, but if it occasionally lessens during the last weeks before delivery, this might explain the puzzling prepartum mood disorders that have been observed.

Changes in various neurohormones and neuropeptides might also play a protective role during pregnancy. These include CRH, ACTH, cortisol, progesterone and progesterone metabolites, estrogens, TSH, and prolactin. As previous work in typical bipolar disorders has identified neuroendocrine changes compatible with abnormalities of serotonin and endorphin function, we intend to focus particularly on these areas.

This search for biological explanations should be carried out in conjunction with research into the important psychological, psychosocial, and dietary changes which often occur during pregnancy and which might also contribute to fewer abnormal moods. It is not possible to investigate these important factors adequately in retrospect, but we are now looking into their impact in a prospective study of pregnant bipolar women. At this point, there is, however, no evidence that these changes have a differential impact on primary mood disorders and other psychiatric disorders.

Further support for our hypothesis would stimulate new multidisciplinary research to clarify the protective mechanisms involved. Such investigations could

also clarify the differentiating physiological features of typical bipolar disorders. Most importantly, such research may lead to the discovery of new, natural, prophylactic agents.

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