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Prophylactic Lithium in Puerperal Psychosis

The Experience of Three Centres

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At three centres, 21 women at high risk for puerperal psychosis were given prophylactic lithium carbonate late in the third trimester of pregnancy or immediately after delivery. Only two of the women had a recurrence of their psychotic illness while on prophylactic lithium. One woman given lithium during third trimester had an unexplained stillbirth. Although a larger sample in a carefully controlled study is still required, there now seems to be grounds for the use of prophylactic lithium immediately after delivery in women not breastfeeding who have previously suffered from either puerperal psychosis or bipolar disorder.

The risk of psychosis in the post-partum period is approximately 1 in 500, but for women with a history of bipolar affective disorder or post-partum psychosis the risk is increased 100-fold to about 1 in 5 (Brockington *et al*, 1982; Kendell, 1985). A number of investigators have discussed the potential role of lithium carbonate as prophylaxis in these high-risk women (Reich & Winokur, 1970; Targum *et al*, 1979; Kadrmas *et al*, 1979; Abou-Saleh & Coppen, 1983) but there has been no consensus about its clinical utility (Sneddon & Kerry, 1980; Oates, 1986). Following reports of small numbers of women who were at high risk for recurrent puerperal psychosis who were treated prophylactically with lithium carbonate after delivery (Stewart, 1988; van Hulst & Klompenhouwer, 1989), clinicians at three centres (Toronto, Rotterdam, and Edinburgh), experienced in the treatment of post-partum psychoses, agreed to collect and pool systematic data on such patients to obtain a larger sample from which to draw clinical conclusions.

Method

Consecutive high-risk women given prophylactic lithium carbonate by one of the investigators to prevent post-partum psychosis were identified in Toronto, Rotterdam, and Edinburgh. The women were referred by obstetrician gynaecologists, psychiatrists, general practitioners, paediatricians or health visitors to the authors who had a known interest in post-partum psychiatric disorders. To qualify for lithium prophylaxis, the woman must have had at least one previous post-partum psychosis requiring admission and have agreed to take lithium carbonate after delivery or commencing late in the pregnancy, and to have regular serum lithium determinations performed for six months after delivery. Lithium use also required that the woman not breastfeed or become pregnant (Robinson & Stewart, 1986).

In Toronto and Rotterdam, lithium carbonate (900–1200 mg daily) was initiated within 24 hours of delivery and serum levels were determined twice weekly for the first week, weekly for three weeks, and then as clinically indicated. In Edinburgh, lithium carbonate was administered from week 34 of gestation and monitored weekly until delivery, when the dosage was decreased and monitored daily for one week and thereafter as in Toronto and Rotterdam. The women were seen by one of the investigators in hospital after delivery, and followed regularly as out-patients for six months. Lithium was discontinued at that time unless there were clinical reasons for its long-term use.

A standard data form was used to collect information from the charts and/or patients by the clinician investigators in the three centres. The form requested information about all previous non-puerperal, gestational and puerperal disorders using Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978). Frequency and length of hospital admissions and diagnoses for all episodes were recorded, based on patient examination and information in the medical and nursing notes. Onset after delivery (in days) of previous puerperal episodes was recorded. A family history of mental illness (including diagnoses when available), association of such history with pregnancy if known, and total number of illness episodes were obtained. Extensive information was collected about the dosage, timing of administration and serum levels of lithium following delivery. Symptoms of mental illness or psychological distress were recorded over the six months after delivery.

Results

Twenty-one high-risk post-partum women received prophylactic lithium (eight in Toronto, eight in Rotterdam, and five in Edinburgh). Their mean age was 23.1 years (s.d. 3.9, range 15–30 years) at the time of their first mental illness, 25.6 years (s.d. 3.2, range 19–32 years) at their first post-partum psychosis, and 31.2 years (s.d. 3.7, range 25–38) at the time of prophylactic lithium administration. Nineteen were married, one lived in a long-term common-law relationship, and one was single.

The initial puerperal psychosis was the first episode of mental illness for 14 women but by the time of the study 13 had experienced 1 to 12 or more non-puerperal episodes

Table 1
Results of lithium prophylaxis in 21 women with previous puerperal psychoses

Patient no.	No. of family members with history of mental illness	No. of previous non-puerperal episodes in patient	No. of previous puerperal episodes in patient	Mean onset of puerperal psychosis: days after delivery	Mean duration of puerperal psychosis: weeks	Recurrence of puerperal illness on lithium carbonate
1	2	0	2	5	8	Mild symptoms
2	1	2	1	6	8	-
3	2	1	1	3	8	-
4	1	1	1	3	4	Mild symptoms
5	0	0	2	10	72	-
6	2	0	3	6	43	Mild symptoms
7	1	6	1	3	24	-
8	1	0	2	4	94	-
9	2	0	1	3	27	-
10	0	0	1	3	10	-
11	1	0	1	2	12	-
12	4	4	1	13	26	-
13	1	0	2	5	19	-
14	2	1	2	7	13	-
15	0	1	1	2	11	-
16	1	1	1	5	17	-
17	1	2	3	19	20	-, stillbirth
18	3	2	2	5	5	Major depression
19	0	12+	1	8	16	Bipolar I
20	0	5	1	90	8	-
21	1	7	2	43	8	Relapse at 3 weeks after lithium discontinued

(Table 1). Eight women had only puerperal episodes. Seven women (nos 3–7,20,21) had an illness episode during pregnancy. The mean number of previous puerperal illnesses was 1.5 episodes (range 1–3), and their mean duration was 21.6 (s.d. 22.7, range 4–94) weeks. The mean onset of puerperal illnesses after delivery was 11.7 days (s.d. 20.1, range 2–90), but 17 of 21 occurred within ten days of delivery.

The commonest RDC diagnoses for previous episodes of puerperal or non-puerperal illness were bipolar I and major depressive disorder. However, acute schizoaffective (manic or depressed) disorder and unspecified functional psychosis were diagnosed in 14 of 32 puerperal episodes but in only 2 of 45 non-puerperal episodes.

Sixteen women had a family history of mental illness in first- and second-degree relatives. Of the 26 recorded mental illnesses in relatives, 23 were affective illnesses (two of which were puerperal episodes), and three were unspecified. Nine mothers of patients had been in hospital with mental illnesses and ten relatives had "multiple admissions" or were said to be "chronically mentally ill".

Sixteen women started lithium within 24 hours of delivery, four women (nos 17,18,20,21) started at 34 weeks' gestation, and one woman with an unstable bipolar illness (no. 19) took lithium at her request throughout pregnancy, except during the 4th to 12th weeks when the risk of teratogenic effect is high (Weinstein & Goldfield, 1975). The mean lithium dose in pregnancy was 1030 mg (range 750–1200 mg) a day to achieve serum lithium levels of 0.52–1.21 mmol/l. The mean lithium dose after delivery was 900 mg (range 750–1200 mg) a day to achieve a serum level of 0.8 mmol/l (range 0.4–1.0) by post-partum day 7.

There was one full-term stillbirth, cause undetermined, to a woman (no. 17) who received lithium carbonate

Table 2
RDC diagnoses of puerperal and non-puerperal illness episodes

	Puerperal episodes (21 women, 32 episodes)	Non-puerperal episodes (excluding pregnancy) (13 women, 45 episodes)
Bipolar I (bipolar depression with mania)	8	32
Major depressive disorder	9	9
Manic disorder	1	2
Acute schizoaffective (manic)	7	1
Acute schizoaffective (depressed)	4	0
Unspecified functional psychosis	3	1
Schizophrenic disorder	0	0

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750 mg/day from 34 weeks' gestation and whose serum lithium during pregnancy ranged from 0.55 to 0.69 mmol/l.

Seventeen women took lithium for six months or longer as agreed. Of the four others, the three women who stopped lithium between the fourth and sixth month remained well. One woman (no. 21) prematurely discontinued lithium and suffered a psychotic relapse at three months post-partum. Her previous puerperal illness had begun three days after delivery.

Nineteen women suffered no puerperal psychosis while on lithium, although three (nos 1,4,6) had mild brief psychological symptoms treated as out-patients with lorazepam (1–2.5 mg) at bedtime (the only other psychotropic medication to be given). Patient no. 1 experienced mild confusion and insomnia from post-partum day 9 to 15, patient no. 4 complained of insomnia, tiredness and inability to cope during post-partum days 7–12, and patient no. 6 complained of insomnia and mild depressive symptoms from post-partum week 3 to 6 upon discovering that her husband was again having an affair.

Two women on lithium suffered a puerperal psychosis. Patient no. 18 had a major depression without psychotic features starting on post-partum day 6 that required a 13-day hospital admission. Serum lithium levels after delivery were 0.86 (day 2) and 0.74 mmol/l (day 4). This illness was shorter than her previous puerperal illness, which had prominent psychotic features, required an eight-week admission, and was diagnosed as schizoaffective depression. Patient no. 19, who previously had had over 12 episodes of mania or depression from the age of 15, had a recurrence on day 8 after delivery that required a four-month admission and was eventually treated with electroconvulsive therapy. She had taken lithium throughout pregnancy (except between gestational weeks 4–12) and her serum lithium levels between delivery and onset of psychosis were 0.81, 0.79 and 0.69 mmol/l. This illness was longer than previous non-puerperal episodes but the same duration as a previous puerperal psychosis.

Discussion

Pregnant women at high risk for recurrence of post-partum psychiatric disorders present a not uncommon clinical dilemma. It is not surprising that other investigators over the years have attempted to discover helpful interventions. Dalton (1985) has described the "successful" use of progesterone for two months after delivery in a group of women with "a history of postnatal depression that was severe enough to require medical treatment". As fewer than half of this retrospective and geographically diverse sample was admitted to hospital (presumably these were not all psychotic) and only 50% were followed up by the author (rather than by questionnaires to the woman and her family doctor), it is difficult to assess her findings. Other investigators (Brockington *et al*, 1982) have been unable to replicate the beneficial effect of progesterone in a small sample of such women.

Hamilton (1982) has anecdotally described "encouraging" results in high-risk women treated for lactation suppression with a mixture of oestrogen and testosterone in oil, but this work also requires validation. Despite the heuristic appeal of a hormonal causation theory, it is noteworthy that investigators have been unable to demonstrate any significant differences in hormonal levels (including oestrogen and progesterone) between women suffering from post-partum psychiatric mood disturbances and matched post-partum controls (Nott *et al*, 1976; Stewart *et al*, 1988). This report of the prophylactic use of lithium carbonate in women at high risk for puerperal psychosis is an attempt to approach the problem from the perspective of an affective disorder precipitated by the many biological and psychological changes of pregnancy, parturition, and the post-partum period.

The information obtained from these 21 women with previous puerperal psychoses is in agreement with that of other investigators (Platz & Kendell, 1988) who have found that although the puerperal episode is often the first psychiatric illness (14/21 in this study), over time these women frequently develop non-puerperal episodes as well (13 in this study). The early onset of psychotic symptoms (17 within ten days of delivery in our 21 patients) is also a familiar feature of this condition (Dean & Kendell, 1981; Brockington *et al*, 1982; Meltzer & Kumar, 1985). The diagnostic variation between puerperal and non-puerperal episodes highlights the tendency of puerperal psychoses to include confusion, perplexity and schizophrenic features (Kadrmas *et al*, 1979; Brockington *et al*, 1981; Dean & Kendell, 1981) which is reflected in more diagnoses being assigned to the categories of acute schizoaffective or unspecified functional psychoses in puerperal than non-puerperal episodes (14/32 v. 2/45 episodes in this series). The heavy genetic loading for psychiatric disorders (16 of our 21 women had a family history of such disorder), especially affective disorders (23/26 recorded diagnoses), lends support to the theory that puerperal psychoses are basically the same as affective illnesses occurring at other times (Kendell *et al*, 1987; Platz & Kendell, 1988).

The differences in the timing of lithium administration between Edinburgh and Toronto/Rotterdam deserves further comment. The rationale in Edinburgh for initiating lithium prophylaxis at the 34th week of gestation was to achieve a therapeutic serum level of lithium during post-partum days 3–4, when the risk of psychosis is high (Dean & Kendell, 1981). Unless one is prepared to use fairly large loading doses immediately after delivery (when glomerular filtration rates are falling), therapeutic levels are

probably not reached for about five days (Perry *et al*, 1986). On the other hand, in view of possible toxic effects of lithium on the neonate exposed *in utero* (hypotonia, lethargy, poor sucking, shallow respirations, cardiac arrhythmias and cyanosis) (Ananth 1976), the Toronto/Rotterdam centres elected to begin lithium immediately after delivery. Whether this adequately protects women during post-partum days 3–4 is still unknown, but no psychoses recurred during this interval in women from these centres in this small series. The two recurrences of puerperal psychosis were both in women from Edinburgh given lithium before delivery, although one had an unusually unstable history of bipolar illness (over 12 episodes) and the other had a strong family history of affective disorder with two previous puerperal and two non-puerperal episodes of illness herself. When best to commence prophylactic lithium is still uncertain, but given the risks of foetal toxicity (Weinstein & Goldfield, 1975) and the unexplained stillbirth in one of the women given lithium in the third trimester, the safer course is probably to initiate lithium immediately after delivery.

The three women who experienced mild confusion, insomnia, tiredness, and depression after giving birth are of interest, as these symptoms may represent attenuated forms of puerperal illness. This is consistent with the work of Prien (1975) on the reduced severity and intensity of psychosis in bipolar patients treated with prophylactic lithium. Similarly, one of the women with recurrence of puerperal illness (no. 18) had a shorter and non-psychotic illness while on lithium carbonate. The second woman with recurrent puerperal psychosis does not seem to have received any beneficial effect from lithium as judged by the severity or duration of the puerperal psychosis.

In view of the strong family history of affective disorders, the high proportion with bipolar disorder, and the previous occurrence of puerperal psychosis, these 21 women given prophylactic lithium were at very high risk for recurrence of puerperal psychosis. Various predictions, from 20% to 50%, for the risk of recurrence of puerperal psychosis can be found in the literature, depending on the specific risk factor surveyed (Bratfos & Haug, 1966; Reich & Winokur, 1970; Abou-Saleh & Coppen, 1983). However, predictive figures are not available for the multiple risk factors which were present in all but one of our patients (no. 10) given prophylactic lithium. The recurrence rate of 10% in our series thus falls well below the most conservative single-factor estimates of recurrence risks. Although this finding still requires replication in a larger sample in a carefully controlled study, there now seem to be grounds for the use of prophylactic lithium immediately after delivery in women who have previously suffered from either puerperal psychosis or bipolar disorder.

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