Estrogen Administration Does Not Reduce the Rate of Recurrence of Affective Psychosis After Childbirth

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Background: High rates of postpartum relapse occur in women with histories of bipolar or schizoaffective disorder. These relapses may be triggered by the postdelivery fall in circulating estrogen through alteration of central neurotransmitter (especially dopaminergic) systems. This study tested the hypothesis that estrogen administration after childbirth would prevent postpartum relapse and would alter dopamine receptor sensitivity.

Method: Twenty-nine pregnant women with a Research Diagnostic Criteria diagnosis of hypomania (bipolar II), mania (bipolar I), or schizoaffective disorder participated in an open clinical trial. Three transdermal dose regimens of estrogen (17β-estradiol) were tested. Starting doses were 200 (N = 13), 400 (N = 3), and 800 (N = 13) μg/day, beginning within 48 hours after delivery and reduced by one half every 4 days for a total of 12 days. On the fourth day after starting estradiol therapy (before relapse occurred), subjects participated in a neuroendocrine challenge test that measured the sensitivity of the central nervous system (tubero-infundibular) dopaminergic system (plasma prolactin and growth hormone responses to apomorphine).

Results: Estradiol at all dose regimens did not reduce the rate of relapse. However, of the 12 women who relapsed, those who had taken the highest dose of estradiol (800 μg/day) needed less subsequent psychotropic medication (fewer chlorpromazine equivalents) and were discharged sooner than those who had taken either of the 2 lower doses. No differences in neuroendocrine responses to apomorphine were detected between women receiving the high-dose and the lower-dose regimens.

Conclusion: The results do not support the hypothesis that a fall in circulating concentrations of estrogens precipitates relapse in subjects at risk of postpartum affective psychosis. The use of prophylactic estrogen in such circumstances is therefore highly questionable.

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Women with histories of affective and schizoaffective psychosis are at high risk of postpartum relapse,[1,2] and identification of pregnant "at-risk" subjects and the development of protocols to prevent and/or manage such illnesses are clinical priorities.[3] Lithium prophylaxis, which is useful in bipolar disorder, has positive, but limited, efficacy in preventing postpartum recurrence of affective psychosis.[4,5] It has been suggested that the massive, rapid postdelivery fall in circulating female sex-steroid concentrations, particularly estrogen, triggers relapse in vulnerable subjects through interactions with central neurotransmitter systems.[6–8] Three main sources of evidence, discussed below, support investigation of the potential role of estrogen in preventing relapse.

Prophylactic Effects of Estrogens in the Recurrence of Postpartum Psychosis

Hamilton and Sichel[8] anecdotally described a series of 50 patients with a history of postpartum psychosis treated with injections of estrone (10 mg in oil) immediately after delivery, followed by oral conjugated estrogen for 14 days. Instead of an expected recurrence rate of 25% to 50%, no patients relapsed. Sichel et al.[9] treated 4 women who had histories of mania and 3 who had histories of major depression with oral conjugated estrogen (5 mg b.i.d.), starting after delivery and reducing doses over the next 14 days; 2 women received additional intravenous estrogen (25 mg t.i.d.) for the first 2 days. Only 1

of the 7 women relapsed. However, there is no evidence of abnormalities in female sex steroid concentrations in subjects at risk of, or currently suffering from, postpartum affective disorders.[10,11]

Psychoactive Properties of Estrogen in Other Clinical Settings

Estrogen enhances mood in postmenopausal women[12] and is superior to placebo in the treatment of clinically significant perimenopausal depression.[13] Klaiber et al.[14] reported that high doses of oral estrogen were effective in ameliorating resistant major depression, and Gregoire et al.[15] showed that transdermal 17β-estradiol (200 μg/day) was superior to placebo treatment of major depression of postnatal onset. In the latter study, a rapid therapeutic response was also observed in some subjects, suggesting that there are actions of estrogen that are unlike the slower changes in neurotransmitter systems that may underlie therapeutic responses to antidepressant and antipsychotic drugs. Ahokas et al.[16] reported improvement within 7 days in all 10 patients in their study who were suffering from postpartum psychosis and who were treated with sublingual estradiol (3–6 mg/day). Less direct evidence for psychoactive actions of estrogen comes from epidemiologic studies of sex differences in the onset of schizophrenia[17] and from reports of possible protective effects in Alzheimer's disease,[18,19] exacerbations of schizophrenia or affective psychosis that were linked with menstrual cycle phase,[1,20,21] and acute psychotic reactions following withdrawal of estrogen therapy.[22]

Interactions Between Estrogen and Neurotransmitter Systems

Estrogen is reported to alter dopamine synthesis,[1,8,23] increase its turnover,[24] and modulate dopamine receptor sensitivity.[25–27] There are, however, differences in the ways that nigrostriatal and tubero-infundibular systems respond[28,29] and evidence that dopamine receptors in the striatum and prefrontal cortex are differentially affected by sex steroids,[30] which support the notion that it is possible to uncouple the effects of sex steroids on dopaminergic systems involved in regulating sensorimotor activity from reproductive and parental behaviors. Serotonergic (5-HT_{2A}) receptors exert tonic inhibition on dopamine release in the medial prefrontal cortex,[31] and brief treatment with estradiol reportedly increases the density of 5-HT_{2A} receptors in the cortex and nucleus accumbens in rats.[32] Analogous interactions may occur in humans, as there has been a preliminary demonstration of increased 5-HT_{2A} receptor ligand binding in postmenopausal women treated with 17β-estradiol (200 μg/day for 7 days).[33]

Our study tested the hypothesis that estradiol administration soon after childbirth would mitigate, in a dose-related manner, the impact of the precipitous falls in circulating estrogen concentrations and thus prevent relapse in subjects with histories of bipolar and schizoaffective disorders. It was also hypothesized that estradiol would exert its prophylactic effects by antagonizing dopamine receptor hypersensitivity, which is suspected to underlie relapse.[6,7]

METHOD

Subjects

Subjects (N = 29) were pregnant women who had a history of hypomania (bipolar II), mania (bipolar I), or schizoaffective disorder as defined by Research Diagnostic Criteria.[34] They had been referred by colleagues or were former patients of the Mother and Baby Unit (MBU), Bethlem Royal Hospital, London, United Kingdom. The subjects were aware of the high risk of recurrence of illness and wished to prevent relapse. All were in remission, none had received psychotropic medication during pregnancy, and none relapsed before delivery. Subjects with a history of thrombophlebitis, embolism, or hypertension or who had a cesarean section were excluded. The trial was approved by the Ethical Committee of the Bethlem Royal and Maudsley Hospitals Trust and the Institute of Psychiatry, Kings College London. All subjects provided written informed consent prior to the start of the trial.

Protocol

All participants and their infants were admitted to the MBU from the obstetric services within 48 hours of delivery and remained in the MBU for a minimum of 14 days. Where possible, estradiol treatment was started on the first day after delivery and, by the latest, within 48 hours of delivery. Given the small but possible risk of thromboembolism associated with estrogen,[35,36] all subjects received heparin at reducing doses (2500–5000 units/day subcutaneously for 12 days). During estradiol treatment, breastfeeding was not permitted because it was not known whether estradiol or heparin would be present in the milk in significant quantities, but the women were encouraged to express breast milk to maintain lactation and to recommence breastfeeding after the 12 days of hormone treatment. The clinical team was independent of the researchers, and clinical assessments were made daily by trained nurses and at regular intervals by ward doctors. If at any time it was felt by the clinical team that there were significant symptoms or signs of relapse of illness, estrogen treatment was discontinued and "conventional" pharmacotherapy was started.

Estradiol Treatment Regimens

Starting doses of transdermally administered 17β-estradiol (Estraderm, Novartis, Camberley, United King-

dom) for the 3 regimens were 200 (N = 13), 400 (N = 3), or 800 (N = 13) μg/day, and these doses were reduced by half every 4 days for a total of 12 days. Undesirable consequences of oral synthetic estrogens or of extracts of conjugated forms of estrogen from equine urine, e.g., first-pass hepatic metabolism,[37,38] were therefore avoided. As this study was exploratory, with no placebo, the protocol was such that the lowest dose (200 μg/day) was used in the first subjects. The first 13 subjects recruited were thus treated with the lowest dose, and 3 relapsed. Because the relapse rate was approaching those reported in untreated samples, the next 3 subjects recruited were treated with the intermediate dose (400 μg/day). All 3 subjects receiving this intermediate dose relapsed, and thus all subsequent subjects were given the highest dose (800 μg/day).

Psychiatric Assessments

Psychiatric assessments were carried out by a psychiatrist using a semistructured interview (the Schedule for Affective Disorders and Schizophrenia-Lifetime Version[39]). Psychiatric history up to the time of interview was assessed in pregnancy at the time of recruitment to the trial, and postnatal psychiatric outcome was assessed at 3 months postpartum. The latter interview also covered the time period between the antenatal recruitment interview and delivery. A postpartum relapse was defined as an episode of illness according to Research Diagnostic Criteria that occurred within 90 days following delivery.

Neuroendocrine Measures

On the fourth day of estradiol treatment (the fourth to sixth day after delivery), subjects missed breakfast, and at approximately 9 a.m., an indwelling intravenous cannula was inserted. The subjects were not breastfeeding, and nurses cared for the babies during the test. The subjects remained at rest in their rooms for 1 hour, and then 5 to 10 mL of blood was withdrawn at two 15-minute intervals to provide baseline values. The dopamine agonist apomorphine HCl was then administered (0.005 mg/kg subcutaneously), and blood (10 mL) was taken at 15-minute intervals over the next 90 minutes (see Wieck et al.[7] for details).

Hormone Assays

Estradiol, progesterone, growth hormone (GH), and prolactin were assayed, and baseline plasma concentrations of GH and prolactin and the response of these hormonal markers to apomorphine were measured. No subjects had baseline plasma concentrations of GH that exceeded 6 mIU/L, and therefore no exclusions were necessary (e.g., in case of feedback of raised GH on the secretory response to apomorphine). Responses to the agonist were expressed as the mean of the 6 measures (15–90 minutes) calculated as changes from the baseline (area under the curve [AUC] for GH and area over the curve [AOC] for prolactin).

Data Analyses

Comparisons of (1) preexisting psychiatric morbidity, (2) clinical outcome, and (3) sex steroid concentrations and dopamine activity were carried out between women who relapsed postpartum and those who remained well, between the 3 treatment dose groups, and between the highest-dose group and the 2 lower-dose groups combined. Where data were not normally distributed, nonparametric tests were used; for categorical data, chi-square tests were used; and for ordinal data, Kruskal-Wallis analysis of variance (ANOVA; 3-group comparisons) or the Mann-Whitney U test (2-group comparisons) was used. Where data were normally distributed, parametric ANOVAs or independent-group t tests were used. All analyses were performed using Stata Statistical Software 6.0 (Stata Corporation, College Station, Tex.).

RESULTS

Clinical Outcome

Twelve of 29 women experienced an episode of illness according to Research Diagnostic Criteria in the 90 days following childbirth. A comparison of women who relapsed and those who remained well revealed no differences in age, weight, parity, number of previous episodes of illness, or time (months) elapsed since last episode. No differences were observed between dose groups in these variables.

Three of 13 women who received the lowest-dose regimen of estradiol (200 μg/day) relapsed, 3/3 who received 400 μg/day relapsed, and 6/13 who received 800 μg/day relapsed. The diagnoses attached to the women who relapsed in the 2 lower-dose groups were manic disorder (N = 3), schizoaffective disorder (N = 2), and depression (N = 1); in the high-dose group, they were manic disorder (N = 5) and depression (N = 1). Onsets of illness were all between 7 and 14 days after delivery, with 2 exceptions: 1 case of depression in which illness began 77 days postpartum (subject 8, 800 μg/day, Table 1) and 1 case of manic relapse in which illness began 75 days postpartum (subject 3, 200 μg/day, Table 1). None of the women in the high-dose group suffered a recurrence of illness during the follow-up from 90 days to 1 year postpartum. One subject, who received a starting dose of 200 μg/day, had a further relapse 4 months after leaving the hospital and committed suicide before she could be readmitted. There were no other recurrences of illness in the 2 lower-dose groups. None of the 17 women who had remained well during the first 3 months after delivery experienced a recurrence in the subsequent 9 months.

An unexpected difference was observed between the women in terms of their responses to pharmacotherapy.

Table 1. Duration of Admission and Amounts of Antipsychotic and Mood-Stabilizing Medication Prescribed During Admission to Subjects Who Relapsed

Subject	Estradiol Dose Regimen (μg/d)	Duration of Admission (d)	Chlorpromazine Equivalents (g)	Carbamazepine (g)	Lithium (g)
1	200	162	130.8	18.4	72.8
2	200	63	36.7	…	…
3	200	55	0.5	22.5	…
4	400	133	67.9	…	27.4
5	400	73	5.0	10.6	…
6	400	93	14.4	…	70.0
7	800	25	1.8	…	16.0
8	800	0	…	…	…
9	800	36	10.2	10.8	…
10	800	32	3.2	8.0	…
11	800	35	6.2	…	…
12	800	26	3.8	5.6	…

Table 2. Baseline and Apomorphine-Induced Responses of Plasma Growth Hormone and Prolactin in Subjects Who Remained Well and Who Relapsed, Following 4 Days of Treatment With Estradiol (200, 400, or 800 μg/day)

		Growth Hormone, mIU/L (± SE)		Prolactin, mIU/L (± SE)	
Group	N	Baseline	AUC	Baseline	AOC
Estradiol, 200–400 μg/d					
Well	10	1.22 (0.30)	5.66 (2.13)	2249 (351)	670 (134)
Relapsed	6	1.19 (0.13)	3.33 (1.06)	1977 (170)	382 (94)
Estradiol, 800 μg/d					
Well	7	2.51 (0.31)[a]	6.31 (1.87)	2843 (435)	642 (181)
Relapsed	6	1.30 (0.28)	7.35 (2.97)	2834 (496)	880 (214)

[a]Baseline growth hormone was significantly greater ($t = 2.59$, $df = 11$, $p < .05$) in the women treated with estradiol, 800 μg/day, who remained well in comparison with those who relapsed.
Abbreviations: AOC = area over the curve, AUC = area under the curve.

The speed of recovery (time to final discharge) of the relapsing subjects was significantly faster in the women receiving the highest-dose regimen of estradiol (median number of days admitted = 29) compared with those receiving the 2 lower starting doses (400 μg/day, median = 93 days; 200 μg/day, median = 63 days; Kruskal-Wallis test, $\chi^2 = 8.42$, $df = 2$, $p = .015$). Although the durations of admission in the high-dose group may seem quite long (Table 1), it was the normal policy of the clinical team to allow increasing and extended periods of home leave before finally "signing off" the patient as discharged. Thus, toward the end of the admission, it was normal for mothers to be spending up to a week at home and then reporting back overnight before final discharge.

Chlorpromazine and haloperidol were prescribed for 11 of the 12 women who relapsed; 2 women in the lower-dose groups received droperidol and clopixol as well, and subjects in both groups also received mood stabilizers. The amounts of neuroleptic medication, expressed as chlorpromazine equivalents,[38] were calculated (Table 1). Women in the high-dose group received fewer chlorpromazine equivalents (median = 3.5) compared with women in the lower-dose groups (400 μg/day, median = 14.4; 200 μg/day, median = 36.7), but these differences were not significant (Kruskal-Wallis test, $\chi^2 = 3.15$, $df = 2$, $p = .21$).

Estradiol and Progesterone Concentrations in Plasma

Postpartum concentrations of plasma estradiol differed according to the treatment dose. There appeared to be a dose-response relationship, but with only 3 subjects at the intermediate dose (plasma estradiol mean = 2478 pmol/L), the conclusive difference is between the subjects who received 200 μg/day and those who received 800 μg/day (plasma estradiol mean = 1049 pmol/L and 3788 pmol/L, respectively; $t = 5.44$, $df = 24$, $p < .0001$). We have data of untreated subjects showing that at 4 days postpartum, despite the marked fall that follows placental expulsion, the estradiol concentration in blood (mean = 1267 pmol/L) is still some 2- to 3-fold higher than would be expected in the luteal phase of the menstrual cycle (I.C.C., M.N.M., A.W.; unpublished data, February 2000). Therefore, 200 μg of estradiol daily for 4 days did not elevate plasma levels above those reported in untreated subjects. There were no increases in progesterone concentrations to parallel the rise in estradiol. Subjects who subsequently relapsed and those who stayed well did not differ in terms of postnatal plasma estradiol or progesterone concentrations.

Growth Hormone and Prolactin Response to Apomorphine

When the values from the total dose groups (well and relapsed) were compared, baseline (pre-apomorphine) GH concentration after 4 days of treatment with estradiol, 800 μg/day, was elevated compared with the concentrations found following treatment with 200 and 400 μg/day (mean GH concentration of 1.99 mIU/L [N = 13] vs. 1.21 mIU/L [N = 16]; $t = 2.54$, $df = 27$, $p < .02$).

Table 2 summarizes comparisons within treatment dose groups of those who remained well with those who relapsed. At the 2 lower doses of estradiol, there were no differences between well and relapsing subjects in baseline GH or prolactin level or in the responses of these markers to apomorphine. At the highest estradiol dose, subjects who remained well had significantly greater baseline plasma GH concentrations than those who relapsed, but the GH response to apomorphine (AUC), the baseline prolactin values, and the inhibition of prolactin secretion by apomorphine (AOC) did not differ significantly between subjects who remained well and those who relapsed (Table 2). A comparison of baseline prolactin values across all

subjects (ignoring outcome) showed, as expected, that the 800-μg daily dose of estradiol elevated prolactin level to a greater extent than did the 2 lower doses (mean = 2839 vs. 2113 mIU/L; $t = 1.94$, $df = 27$, $p < .05$; 1-tailed test).

DISCUSSION

Plasma concentrations of female sex steroids increase dramatically throughout pregnancy as a result of placental production. It has been reported that this increase is accompanied by an increase in the number of dopaminergic receptors in the rat corpus striatum; that is, elevated female sex steroid concentrations are associated with the development of increased sensitivity in central dopaminergic systems.[40] On the other hand, it is well established that many antipsychotic drugs are dopamine receptor antagonists. Observations such as these provided the rationale for the study.

The main finding of our study was that at the doses of estrogen used, i.e., up to 800 μg/day, the hormone did not reduce the rate of recurrence of psychosis in the 90 days after delivery. Elevated baseline GH concentrations were found for the high-dose estrogen regimen, but only in women who remained well, and there were no differences between the lower- and high-dose regimens in the GH response to apomorphine. There were also no differences between the high- and lower-dose regimens in the inhibition of prolactin secretion by apomorphine.

It can be argued that the doses used in this study were not sufficiently high to elicit a prophylactic or therapeutic response. However, the objective of the protocol was to prevent a precipitous postpartum fall in circulating estrogen rather than to achieve concentrations equivalent to those present immediately antenatally. Additionally, the trial had to be conducted such that thrombosis was not a significant risk factor. For these reasons, the high dose was restricted to 800 μg/day. This dose was not as high as has been used in some studies, but it maintained plasma estrogen concentrations some 3 times above those in nonpregnant women. These high concentrations would be expected to alter central dopaminergic systems, as we have data which show that the modest changes in plasma estrogen concentrations that occur in the luteal phase of the menstrual cycle are associated with significant increases in dopaminergic receptor sensitivity.[41] In addition, it can been seen that the neuroendocrine measures of baseline GH and baseline prolactin provide evidence of dose-related effects of the estrogen regimens in the central nervous system (CNS).

We conclude that in subjects at risk of affective psychosis, administration of estrogen to prevent a precipitous fall in circulating levels in the immediate postpartum period does not alter the rate of relapse. Furthermore, the associated neuroendocrine data show no evidence to support the hypothesis that in postpartum affective psychosis, relapse is associated with increased central dopaminergic sensitivity. It is noted, however, that the present observations do not contradict recent studies which indicate that estradiol is an effective antidepressant, especially in perimenopausal and postmenopausal women.[13,42,43]

Women treated with the high-dose estrogen regimen (800 μg/day for 12 days) had shorter hospital admissions, suggesting that the high dose enhanced the action of the antipsychotic drugs that were taken by women who relapsed. The data are consistent with those of Kulkarni et al.,[44] who reported transient improvements in psychopathology in schizophrenic women who were given 0.02 mg of ethinyl estradiol in addition to neuroleptic drugs. One advantage in comparing the high- and lower-dose regimens of estradiol was that both groups received the same ward treatment, and, thus, it was unlikely that any differences in clinical outcome can be ascribed to differences in nonpharmacologic management. It is also important to note that all clinical decisions were made independent of the research team. However, subjects who received the lower doses entered the trial first because of the stepwise design of the study, and this could have been a confounding factor.

The fact that women receiving high doses had shorter admissions does not seem to be primarily due to effects of estrogen on dopamine receptors, because there were no differences between the lower- and high-dose regimens in the GH response to apomorphine, which is substantially mediated via dopaminergic activity. There were also no differences in the inhibition of prolactin secretion by apomorphine, although interpretation of prolactin responses may be confounded by the fact that estradiol itself elevates prolactin secretion, probably by increasing its synthesis or through antagonism of the effects of dopamine on lactotrophs[45] (hence the elevated baseline prolactin level).

Estrogen may sensitize various other CNS systems to the therapeutic effects of antipsychotic drugs. Comparisons of the lower- and high-dose regimens show that the high-dose estrogen regimen elevated baseline GH concentrations, but only in women who remained well. The elevated baseline GH may occur via an action of estradiol on other neurotransmitter systems such as 5-HT or norepinephrine, which can also influence GH secretion.[46,47] Thus, in a future study of the prophylactic or synergistic effects of estradiol with antipsychotic drugs, it would be of interest to investigate interactions with serotonergic systems.[48,49]

Maternal psychotic illness in the postpartum period has implications not only for the sufferer, but also for her family. It is associated with increased rates of psychiatric illness in the partner[50] and has a negative impact on the infant's cognitive and emotional development.[51,52] There is, therefore, a need to develop interventions to reduce these effects. This study shows that estrogen administra-

tion in the immediate postpartum period reduces the rate of fall in circulating estrogen, but does not reduce the rate of relapse. These findings question its use as a prophylactic compound in women at risk of postpartum psychosis and do not support hypotheses which propose that the postpartum fall in estrogen is etiologically important in postpartum psychosis. However, the data showing that, in women who relapsed, the high dose of estrogen enhanced the effectiveness of antipsychotic drugs warrant further systematic investigation. These data are of particular interest because estrogen was administered only for a maximum of 12 days immediately postpartum, and, thus, its relationship to the longer-term treatment with psychotropic drugs is unclear.

Drug names: carbamazepine (Tegretol, Carbatrol, and others), chlorpromazine (Thorazine and others), droperidol (Inapsine and others), estradiol (Estraderm, Estrace, and others), estrogen (Premarin, Cenestin, and others), haloperidol (Haldol and others).

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