Positive Treatment Effect of Estradiol in Postpartum Psychosis: A Pilot Study

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Background: Postpartum illnesses with psychiatric symptoms and serious adverse sequelae are highly prevalent during the childbearing years. Despite multiple medical contacts, these illnesses often remain unidentified and untreated. To study the association between estradiol and puerperal psychosis, we measured serum concentration of estradiol and performed an open-label trial of physiologic 17β-estradiol in women with this disorder.

Method: Ten women with ICD-10 psychosis with postpartum onset consecutively recruited from a psychiatric duty unit were studied. Serum estradiol concentration was measured at baseline and weekly during sublingual 17β-estradiol treatment for 6 weeks. The treatment effect was evaluated by a clinician-rated psychiatric symptom scale (the Brief Psychiatric Rating Scale [BPRS]).

Results: The baseline serum estradiol levels (mean = 49.5 pmol/L; range, 13–90 pmol/L) were even lower than the threshold value of gonadal failure, and the patients exhibited high scores on the psychiatric symptom scale (mean BPRS total score = 78.3; range, 65–87). During the first week of 17β-estradiol treatment, psychiatric symptoms diminished significantly (BPRS score decreased to a mean of 18.8, $p < .001$). Until the end of the second week of treatment, serum estradiol concentrations rose to near the values normally found during the follicular phase, and the patients became almost free of psychiatric symptoms.

Conclusion: The reversal of psychiatric symptoms in all patients by treating documented estradiol deficiency suggests that estradiol plays a role in the pathophysiology and may have a role in the treatment of this condition. There was a rebound of psychotic symptoms in the 1 patient who discontinued estradiol treatment. Given the small number of patients, this area deserves further study.

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Postpartum disorders with psychiatric symptoms are underrecognized, undertreated, and classified by syndrome rather than etiology. The incidence of postpartum depression is from 10% to 22% depending on time of symptom onset[1,2] and may result in long-lasting adverse sequelae for the mother, the marital relationship, and the child's psychological development.[3] Prospective studies show that about a quarter of the affected mothers are still depressed at the child's first birthday.[1] The incidence of puerperal psychosis is about 1 per 500 women, but during the month after childbirth there is a 22-fold increase in relative risk of psychosis.[4] Puerperal psychoses are the most severe of the postpartum psychiatric disorders, and they are often resistant to psychopharmacotherapy; no less than 4% of women with puerperal psychosis may commit infanticide.[5] Consequently, safe and rapidly effective therapies that have specific etiologic relevance to the cause of disorder are needed. Estrogen has been observed to be effective in the treatment of postnatal depression,[6,7] and to have a preventive effect on postpartum affective disorder,[8] but for unknown reasons, since the etiopathogenesis of the puerperal psychiatric conditions is poorly understood.

We present 10 women with puerperal psychosis who were admitted consecutively to our hospital, all of whom had documented estrogen deficiency and responded successfully to treatment with sublingual 17β-estradiol.

METHOD

The Ethics committees of the Department of Psychiatry (Helsinki City Hospital), and Adnex Research Clinic of Gynecology approved the study. Patients gave written informed consent after the nature of the study had been fully explained.

Ten consecutive women fulfilling the ICD-10 criteria of psychosis with postpartum onset were recruited from the duty unit of the Department of Psychiatry, Helsinki City Hospital, Finland. No recruited patients were excluded from the study. Their mean ± SD age was 30.6 ± 5.3 years, and the time from delivery to onset of the psychiatric symptoms was 12.3 ± 8.3 days. Mean duration of symptoms before the baseline measurement was 73.0 ± 65.2 days (range, 2–170 days). Anamnestic patients with long duration of symptoms had mild symp-

Table 1. Psychiatric Symptoms (BPRS total scores) and Serum Estradiol Concentration (pmol/L) During Treatment With 17β-Estradiol[a]

		Week				
Patient	Measure	0	1	2	4	6
1	BPRS	79	15	0	0	53[b]
	Serum estradiol	28	280	350	1000	46[b]
2	BPRS	65	16	4	3	0
	Serum estradiol	69	270	340	310	660
3	BPRS	86	34	12	2	0
	Serum estradiol	24	ND	400	420	430
4	BPRS	87	28	9	1	0
	Serum estradiol	13	350	380	840	1100
5	BPRS	84	18	3	0	0
	Serum estradiol	16	160	420	ND	680
6	BPRS	72	12	3	0	0
	Serum estradiol	30	300	590	610	830
7	BPRS	68	14	3	0	0
	Serum estradiol	55	300	330	610	760
8	BPRS	79	20	3	0	0
	Serum estradiol	89	420	600	810	760
9	BPRS	85	15	0	0	0
	Serum estradiol	90	860	ND	440	300
10	BPRS	78	16	4	3	2
	Serum estradiol	81	320	470	500	710
Mean ± SD						
	BPRS	78.3 ± 7.7	18.8 ± 6.9	4.1 ± 3.7	0.9 ± 1.3	0.2 ± 0.7
	Serum estradiol	49.5 ± 30.8	362 ± 199	431 ± 102	615 ± 227	692 ± 229

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, ND = not determined.
[b]Estradiol treatment was stopped 1 week earlier.

toms in the beginning of their illness, which fluctuated and progressed until the patients were referred as floridly psychotic to the psychiatric duty unit. Six of 10 patients underwent psychiatric treatment with psychotherapy (N = 2) or neuroleptic medication (N = 4) before estradiol treatment, without adequate effect. Two of these patients received haloperidol at a daily dose of 8 and 20 mg for 2 and 17 days, respectively; 2 received chlorpromazine, 300 and 400 mg/day, for 14 and 21 days, respectively. None of the patients were breast-feeding any longer, and none had resumed menstruation at the time of recruitment. Blood disorders, infections, and disorders of the thyroid were excluded by laboratory measurements of hemoglobin, red and white blood cells, sedimentation rate, C-reactive protein, and thyroid function (thyroxine and thyroid-stimulating hormone).

Serum estradiol concentration was measured from morning blood samples between 7 and 9 a.m. before the first 17β-estradiol dose of the day by standard radioimmunoassay at baseline and weekly during treatment, which continued for 6 weeks. Estrogen treatment was carried out by micronized 17β-estradiol (Estrofem, Novo Nordisk, Bagsvaerd, Denmark), 1 mg sublingually 3 to 6 times daily according to the serum concentration, with the goal of reaching the concentration level of 400 pmol/L, i.e., about one third of the peak level during the regular menses rhythm. The mean daily dose during the first week was 3.8 mg, and thereafter, 4.7 mg. Four of the patients were receiving neuroleptic medication at baseline, which was gradually stopped during the first week of estradiol treatment. The treatment effect and psychiatric symptoms were evaluated weekly by the validated 18-item Brief Psychiatric Rating Scale (BPRS),[9] on which scores can range from 0 to 6. For ethical reasons, no "non-treatment" group was used as a control; in serial sampling, each patient was her own control. To test the significance of the differences of the BPRS scores, the paired t test was used.

RESULTS

The baseline levels of serum estradiol were lower than the threshold value for gonadal failure (< 110 pmol/L) in all patients (mean ± SD = 49.5 ± 30.8 pmol/L; range, 13–90 pmol/L). The routine laboratory values were within the reference range. During the treatment with sublingual 17β-estradiol, the serum estradiol concentration increased similarly in nearly all patients, approached the values normally found during the follicular phase (362 ± 199 pmol/L; Table 1) within 2 weeks, and continued to rise slightly until week 6 (692 ± 229 pmol/L). No patient menstruated during the 6 weeks of follow-up. One patient (patient 1; see Table 1) discontinued estradiol treatment after 5 weeks, and 1 week later her serum estradiol concentration had declined to near the pretreatment level.

At baseline, all patients exhibited florid psychotic symptoms (mean ± SD BPRS total score = 78.3 ± 7.7; range, 65–87; see Table 1). The total scores of symptoms diminished significantly in a week (18.8 ± 6.9; mean intrapair difference = 59.5, $p < .001$). There was a dra-

matic improvement in the condition of the patients, who, in 2 weeks on treatment, became almost free of psychiatric symptoms (mean ± SD BPRS total score = 4.1 ± 4.7). There was a concurrent rise in the serum concentration of estradiol, which coincided with the decline of the psychotic symptoms (Figure 1). The patient who stopped estradiol treatment exhibited florid psychotic symptoms already by the end of following week (BPRS total score = 53).

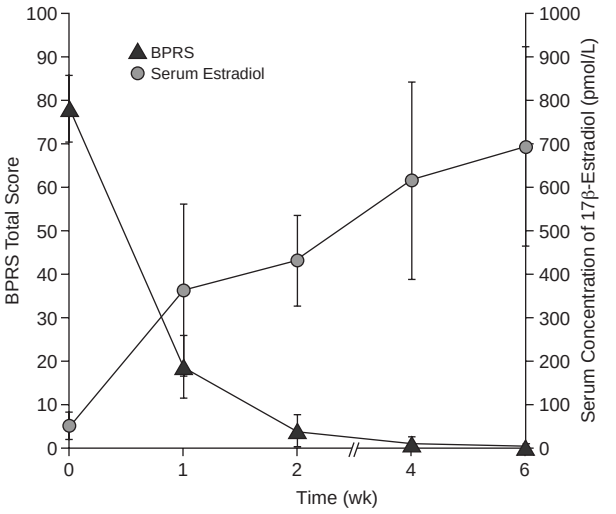
DISCUSSION

Postpartum psychiatric disorders have many unique features that distinguish them from other psychiatric diseases. This was noticed as early as 1858 by Marcé,[10] who claimed that physical and chemical factors interfering with cerebral functions are the cause of the wide variety of symptoms and the mercurial lability in the clinical picture of patients with postpartum psychiatric illnesses. Since the time of Marcé, the area has been the subject of intense epidemiologic, psychological, and endocrinologic studies, but the etiology is still elusive.[2] Only a limited number of clinical studies have been conducted in this population.

To our knowledge, this is the first study to show the connection between low serum estradiol concentration and clinical response to estradiol treatment in women vulnerable to postpartum psychosis. All patients in the present study had estradiol deficiency as documented by laboratory assessments, and the patients responded successfully to treatment with 17β-estradiol. Furthermore, the patient who stopped estradiol treatment exhibited florid psychotic symptoms as early as the end of the following week. This finding suggests that estradiol may be significant in the etiopathogenesis of puerperal psychosis. The observation that psychiatric symptoms diminished very quickly may have important clinical and theoretical implications, because there is a typical delay of about 2 weeks before traditional neuroleptic medication begins to take effect. The limitation of this pilot study is the small number of patients; further research of this area is needed.

Serum estradiol levels are very high (about 100,000 pmol/L) at the end of the term of pregnancy[11]; this estradiol is of placental origin. Parturition is followed by a steep decline in the serum levels within a few days. Ovarian estradiol production may recover slowly, and, hence, postpartum estradiol deficiency can be profound and prolonged, with a wide variety of implications in the actions of the gonadal steroid spectrum. The method to examine and to obtain a rapid treatment response in puerperal psychosis is based on measuring the serum concentration of estradiol and replacing the documented deficiency with physiologic 17β-estradiol. The serum levels are monitored to ensure adequate dosage. The sublingual route avoids first-pass metabolism of oral estrogens and

Figure 1. Serum Estradiol Concentration (mean ± SD) and BPRS Total Scores (mean ± SD) During Treatment With 17β-Estradiol



noncompliance associated with transdermal estrogen therapy.[12] The rapid but short duration of action via the sublingual route resembles the natural pulsatile ovarian function[13] and results in more physiologic circulating ratios of estradiol to estrone than oral administration.[14] Several daily doses are required to maintain the levels because of the rapid absorption and short half-life of 17β-estradiol.[14]

The rapid change in sex steroid homeostasis is important in the context of puerperal physiology since steroid hormones, especially estrogen, exert a powerful effect on mood, mental state, and behavior in women.[15,16] Gender differences in schizophrenia and other psychoses have also been attributed to estrogens.[17] Most of the neuroregulatory effects of gonadal steroids are mediated through their receptors, and a complex and intricate relationship exists between the gonadal steroids and behavior.[18] In ovariectomized animal models, an acute surge of estrogen induces a significant increase in the density of serotonin-2A receptors in the anterior frontal, cingulate, and primary olfactory cortex and in the nucleus accumbens[15,19]—higher centers of the forebrain associated with the control of mood, cognition, emotion, and behavior—suggesting that this may be a key mechanism in the psychotropic effect of estrogen. Ovarian steroid hormones also influence the dopaminergic systems of the hypothalamus as well as the extrahypothalamic regions of the brain in controlling movement and behavior. Studies further indicate that estrogen modulates the dopamine-2 receptors and changes the dopamine transport in the striatum and nucleus accumbens,[20,21] receptors and areas traditionally attributed to the manifestation of psychotic symptoms. These experimental paradigms point to 2 general mechanisms of action of steroids: a rapid, short-term nongenomic membrane effect and a

slower, long-term, possibly genomic effect on dopamine systems.[20,21] The mechanism of antipsychotic effect of estrogen in humans is not known, but the data from experimental models provide evidence that the psychotropic or psychoprotective effects of estrogens may be mediated by coexisting serotonin as well as dopamine receptor mechanisms.[19,20]

The challenges in the management of puerperal psychiatric syndromes, especially puerperal psychosis, are early identification and effective intervention. Postpartum psychoses often resolve within a short time if the symptoms are recognized early and treated quickly. For cases in which the symptoms are not recognized and treated in their initial stage, retrospective data suggest that the duration of symptoms is related to their severity.[5] This carries an increased risk of long-lasting adverse consequences for the mother, infant, and whole family. These findings and the connection between estrogen and the central neurotransmitters serotonin and dopamine may represent a causal relation to puerperal psychosis.

Drug names: chlorpromazine (Thorazine and others), haloperidol (Haldol and others).

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