Estrogen Deficiency in Severe Postpartum Depression: Successful Treatment With Sublingual Physiologic 17β-Estradiol: A Preliminary Study

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Background: The postpartum period is a time when women are vulnerable to depressive disorders, which can be severe and have long-lasting adverse sequelae. In spite of multiple contacts with health care providers, women with postpartum depression often remain unrecognized and untreated. To evaluate the association between estradiol and postpartum depression, we measured serum estradiol concentration and performed an open-label study of physiologic 17β-estradiol.

Method: Twenty-three women fulfilling ICD-10 criteria for major depression with postpartum onset were consecutively recruited from a psychiatric emergency unit. Serum estradiol concentrations were measured at baseline and weekly during sublingual 17β-estradiol treatment for 8 weeks. The treatment effect was assessed using a clinician-rated depression symptom scale, the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: At baseline, all patients were severely depressed (mean MADRS total score = 40.7; range, 35–45) and had a low serum estradiol concentration (mean = 79.8 pmol/L; range, 23–140 pmol/L); in 16/23 patients, the concentration was even lower than the threshold value for gonadal failure. During the first week of estradiol treatment, depressive symptoms diminished significantly, resulting in a mean MADRS score of 11.0 ($Z = -4.20$, $p < .001$), and serum estradiol concentrations approached those of the follicular phase (mean ± SD = 342 ± 141 pmol/L). At the end of the second week of treatment, the MADRS scores were compatible with clinical recovery in 19/23 patients.

Conclusion: This preliminary study shows that depression symptoms may be rapidly reduced in patients with postpartum depression who have documented estradiol deficiency by treatment with 17β-estradiol and suggests that estradiol can have significance in the pathophysiology of this condition and may be an option in the treatment of women vulnerable to postpartum depression.

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Pregnancy and childbirth represent naturally occurring life events accompanied by profound neuroendocrine and psychosocial alterations. During the postpartum period, the risk for onset of psychiatric illnesses is high, and compared with that of nonchildbearing women, there is a 3-fold increase in the relative risk of depression in the first month postpartum.[1] The rates of depression are 10% to 16% during the 6 to 12 weeks after delivery and up to 22% during the first 6 months postpartum according to controlled epidemiologic studies.[1–4] A woman is about 20 times more likely to require hospitalization for a psychiatric illness in the month after delivery than in any month in the previous 2 years.[5,6] No less than 5% of women with postpartum depression may commit suicide, and the risk of suicide for women admitted to a psychiatric hospital during their first postpartum year is more than 17 times that of the general population.[4,7] Depression may resolve spontaneously within 6 months, but prospective studies show that a quarter of the affected mothers are still depressed at the child's first birthday.[1] Furthermore, clinical and epidemiologic data support the view that untreated maternal depression has a long-lasting adverse impact on the mother, the marital relationship, the mother-child attachment, and the child's emotional, social, and cognitive development.[8,9]

Despite this vast body of information and multiple contacts with medical professionals during the puerperal period, maternal depression often remains unidentified by health care providers and thus undiagnosed and untreated.[10,11] Postpartum psychiatric disorders can also be resistant to conventional psychiatric treatment methods.[5,11] Only limited clinical investigations have been conducted in this population, leaving few options for treatment. Therefore, safe and rapidly effective therapies are needed that have specific etiologic relation to the disor-

der. Antidepressant drugs are assumed to be as effective in the postpartum period[12,13] as at other times, but they cause concerns about the breastfeeding infant. Physiologic estrogen has been reported to be effective in the treatment of postpartum depression[14,15] and puerperal psychosis.[16] High doses of conjugated equine estrogen have been observed to have preventive effects on postpartum affective disorders.[17] The reason for these beneficial effects is unknown, and the pathogenesis of postpartum psychiatric illnesses has remained unexplored.

For this study, we evaluated serum estradiol levels at baseline and prospectively during estradiol treatment in 23 women with severe postpartum depression. The women had documented estradiol deficiency and responded successfully to treatment with 17β-estradiol sublingually.

PATIENTS AND METHOD

Patients

The study was approved by the ethics committees of the Helsinki City Hospital and the Adnex Research Clinic of Gynecology, as well as the National Agency for Medicines. All patients received oral and written study information and gave written informed consent. Consecutive patients were recruited from the emergency outpatient unit of the Department of Psychiatry, Helsinki City Hospital, Helsinki, Finland. The inclusion criteria were ICD-10 criteria for major depression based on structured psychiatric interviews by 2 psychiatrists, a Montgomery-Asberg Depression Rating Scale (MADRS)[18] total score ≥ 22, serum estradiol concentration ≤ 200 pmol/L hypothesized by clinical experience, onset of depression within 6 months postpartum, and a time since parturition of less than 12 months. Patients using hormonal preparations (N = 2) were excluded, as were patients with any history of cervical, uterine, or breast disorder or previous evidence of thromboembolic disease that would contraindicate estrogen treatment (N = 0). One patient was excluded from the study because of irregular use of treatment. The final study population comprised 23 white women with major depression; their mean ± SD age was 29.5 ± 6.5 years. Of the 23 patients, 15 were primiparous, and 2 had had a previous episode of depression, including 1 patient with previous postpartum depression. The mean time from delivery to onset of the psychiatric symptoms was 33.7 ± 31.7 days (range, 3–120 days), and mean duration of symptoms before the baseline measurement was 74 ± 61 days (range, 15–290 days, excluding 1 case in which prominent symptoms had lasted 2 days). Fourteen of the 23 patients had received psychiatric treatment with psychotherapy (N = 10) or antidepressant medication (N = 4) without adequate effect before estradiol treatment. Four patients had a short psychiatric hospital treatment period; 3 of them had attempted suicide. Thirteen patients were breastfeeding, and none of the patients had resumed menstruation at the time of recruitment.

Method

Serum estradiol concentration was quantified by radioimmunoassay at baseline and weekly during the first month and monthly thereafter from morning samples obtained between 7 and 9 a.m. before the first 17β-estradiol dose of the day. The follow-up period continued for 8 weeks. Blood disorders were excluded by laboratory measurements of hemoglobin and red and white blood cell counts; infections, by sedimentation rate and C-reactive protein; and thyroid dysfunction, by thyroxine (T_4) and thyroid-stimulating hormone (TSH). Estrogen treatment was carried out with micronized 17β-estradiol (Estrofem, Novo Nordisk, Bagsvaerd, Denmark), 1 mg sublingually 3 to 8 times daily according to the serum concentration. The goal was to reach a concentration of 400 pmol/L, i.e., about one third to half of the peak level during the regular menses rhythm. The mean daily dose during the first week was 3.9 mg and thereafter was 4.8 mg. Patients were allowed to continue breastfeeding during the treatment with physiologic 17β-estradiol. Breastfeeding patients were informed that estradiol treatment can diminish milk supply. Cyclical progesterone, dydrogesterone, was planned to be added to estradiol treatment after 3 months to combat the risk of endometrial hyperplasia. In a subgroup of consecutive patients (N = 12), transvaginal ultrasonography was performed at baseline and monthly to monitor ovarian function and the endometrium.

The psychiatric symptoms and treatment effect were evaluated at baseline and weekly by the validated, clinician-rated 10-item MADRS[18] (scores 0–6). Treatment response was defined as a 50% reduction in the initial depression score, and recovery was defined as a MADRS total score of 7 or less. If the total score had not declined to 7 within 2 weeks, or if it increased after an initial decline, the patients were offered antidepressant medication as an adjunct therapy. For ethical reasons no untreated group was used as a control group; in serial sampling and repeated-measures design, each patient was her own control.

Statistical Analysis

The treatment effect measured using the MADRS scores was analyzed nonparametrically with the Friedman test, a 2-way analysis of variance (ANOVA). Pairwise comparisons with start point ratings were performed with the Wilcoxon signed rank test. Statistical calculations were made with the SPSS 8.0 software (SPSS Inc., Chicago, Ill.).

RESULTS

The serum concentration of estradiol at baseline was lower than the upper limit for inclusion (200 pmol/L) in

Table 1. Psychiatric Symptoms (MADRS total scores) and Serum Estradiol Concentration During 17β-Estradiol Treatment[a]

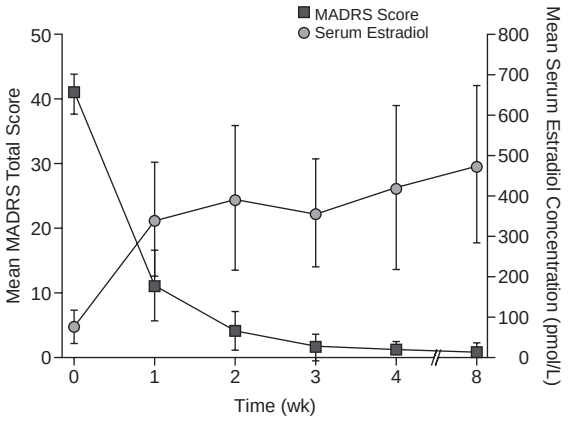
Measure	Week 0	Week 1	Week 2	Week 3	Week 4	Week 8
MADRS total score						
Mean	40.7	11.0	4.2	1.9	1.0	0.8
SD	2.8	5.5	3.0	2.0	1.6	1.8
Serum estradiol, pmol/L						
Mean	79.8	342	393	358	421	478
SD	41.7	141	178	134	200	193

[a]Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

all patients (mean ± SD = 79.8 ± 41.7 pmol/L; range, 23–140 pmol/L), i.e., no patient was excluded because of values over the screening limit. In 16 of 23 patients, the serum estradiol levels were even lower than the indication for gonadal failure (< 110 pmol/L).[19] The values were similarly low in patients with early-onset and later-onset depression, as well as in patients who were or were not breastfeeding. The routine laboratory values, including thyroid function, were within the normal range in all patients. During the treatment with sublingual 17β-estradiol, the serum level of estradiol rose similarly in all patients and approached the values of the follicular phase within a week (mean ± SD = 342 ± 141 pmol/L) (Table 1). The concentration of estradiol continued to increase slightly until week 8, when the mean concentration was 478 ± 193 pmol/L, except in 2 patients in whom the concentration varied between 160 and 230 pmol/L. None of the patients menstruated during the 8-week follow-up. Transvaginal ultrasound examination showed that the thin endometrium at baseline had thickened slightly, but no marked hyperplasia was observed until week 8. No adverse reactions were reported in breastfeeding infants. Sublingual administration was considered easy by the patients and was well tolerated.

All patients exhibited severe symptoms of depression at baseline (mean MADRS total score = 40.7 ± 2.8; range, 35–45) (Table 1). During the first week of the 17β-estradiol treatment, there was a dramatic improvement in the condition of the patients, and the total scores of symptoms decreased significantly to a mean of 11.0 ± 5.5 ($Z = -4.20$, $p < .001$). In 21/23 patients, the decline of symptoms exceeded the responder criteria (50% reduction of symptoms), and in 9/23 patients, the MADRS total score was ≤ 7. Most patients reported feeling that they had "awakened to the world" between the fifth and seventh days of treatment. At week 2, the symptoms continued to decrease, with a mean MADRS score of 4.2 ± 3.0, and in 19/23 patients, the MADRS scores were ≤ 7. There was a concurrent decline of depressive symptoms, which coincided with the rise in the concentration of serum estradiol (Figure 1). At week 3, 2 patients opted for an adjunctive antidepressant; in both cases, the estradiol concentration had remained low during the treatment period (160 pmol/L and 230 pmol/L, respectively). Two patients reported feeling so well at week 4 (MADRS scores = 0 in both cases) that they wanted to stop estradiol medication, which was allowed, and at week 8 they were still symptom-free. At week 8, all patients had a MADRS total score ≤ 7, with a mean score of 0.8 ± 1.8.

Figure 1. Serum Estradiol Concentration and MADRS Total Scores During Treatment With 17β-Estradiol[a]



[a]Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

DISCUSSION

Although depression is twice as prevalent in women as in men,[20] the postpartum period is an especially potent precipitator of severe mood disorders in vulnerable women. The postpartum period, even if typically portrayed as a time of unqualified happiness and excitement, is more realistically often experienced as a time of significant stress. In fact, no other life event brings about changes that rival the neuroendocrine and psychosocial changes associated with pregnancy and childbirth. The research for an etiologic basis of postpartum psychiatric disorders with a focus on postpartum depression has been characterized by many claims but few confirmed findings. Curatively used specific etiology has remained enigmatic.

To our knowledge, this is the first study to show an association between low serum estradiol and clinical response to 17β-estradiol treatment in women vulnerable to postpartum depression. The limitation of this preliminary study is the lack of a control group. For ethical and methodological reasons, the study was performed as an open-label trial. On pretreatment assessments, all patients had a low serum estradiol concentration concomitant with severe depression; in more than half of the patients, the estradiol level was lower than the threshold value of gonadal failure. The decline of depressive symptoms coincided with the rise in the concentration of serum estra-

diol. Our results suggest that there may be a threshold effect of concentration of bioavailable (sublingual-route) estradiol and psychiatric symptoms. A similar effect has been observed in cognition of postmenopausal women.[21]

One striking finding was the rapid effect of sublingual 17β-estradiol treatment on mood improvement during the first week of treatment ($p < .001$), even in patients who had previously undergone psychotherapy or antidepressant treatment without adequate effect. Improvement continued during the second week, and the symptoms declined to a level of clinical recovery in most patients. This dramatic response to estradiol treatment suggests that estradiol may have a causal relation to postpartum depression and efficacy in the treatment of this condition. Furthermore, the finding is in line with the clinical experiment of Bloch et al.,[22] in which blockage of estradiol production with leuprolide resulted in significant mood symptoms in patients with a history of postpartum depression but not in patients without such a history. Our 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 antidepressant medication begins to take effect.

Drastic physiologic events occur after delivery. At the end of the term of pregnancy, serum estradiol levels are very high (about 100,000 pmol/L)[23]; this estradiol is of placental origin. With removal of the placenta at delivery, serum estradiol concentration declines sharply within a few days. Ovarian estradiol production may recover slowly, and thus, postpartum estradiol deficiency can be prolonged and profound, resembling menopause. Our method to examine and to obtain a rapid treatment response in postpartum depression is based on measuring the serum concentration of estradiol and replacing the documented deficiency with physiologic 17β-estradiol sublingually. The serum levels are monitored to ensure adequate dosage and to control the treatment within physiologic levels. The sublingual administration is easy and convenient and avoids such drawbacks as variable bioavailability, the first-pass intestinal and hepatic effects of oral estrogens,[24] and the noncompliance, including poor absorption, associated with transdermal estrogen therapy.[25] The rapid but short duration of action via the sublingual route mimics the natural pulsatile ovarian function,[26] and results in higher physiologic circulation ratios of estradiol to estrone than does oral administration.[27] Several daily doses are needed to maintain the levels because of the rapid absorption and short half-life of 17β-estradiol.[27]

Ovarian steroid hormones are neuroactive steroids and have profound effects on mood and behavior in women.[28] Owing to their lipophilic nature, reproductive hormones can easily cross the blood-brain barrier. Estrogens have their own receptors (ERα and ERβ) in the brain and appear to exert specific and significant modulating effects on several neurotransmitter systems, including serotonin, norepinephrine, and dopamine, which are traditionally associated with regulating mood and behavior.[29–31] The massive postpartum drop in serum estradiol concentration and the clinical response in these patients may be associated with neurotransmitter dysfunction in women vulnerable to postpartum depression, because central levels of estradiol are reported to correlate with plasma levels.[32,33]

The most important issues in the management of postpartum depression are early identification and rapidly efficacious treatment with specific etiologic relevance to the disorder. Further research is warranted to establish optimum treatment duration, dose-response relationships, and central action mechanisms of estrogen.

Drug names: estradiol (Estrace and others), leuprolide (Lupron and others).

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