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Transdermal estradiol for postpartum depression: A promising treatment option

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Abstract

Postpartum depression (PPD) is the most common complication of childbirth and affects one out of seven childbearing women. While conventional pharmacological and psychotherapeutic antidepressant treatments are effective for PPD, a natural alternative may be preferred by postpartum women, especially those who breastfeed their infants. The treatment of PPD with synthetic forms of naturally occurring estrogen is mechanistically appealing because PPD occurs in the context of estrogen withdrawal at parturition. Preliminary evidence suggests that PPD is a disorder of hormone-related mood dysregulation (similar to perimenopausal depression) that can be effectively treated with estrogen. This review provides the basic science and clinical background as well as safety considerations to support the application of transdermal estradiol as a treatment for PPD. We conclude that estradiol treatment for PPD requires confirmation of efficacy in a randomized clinical

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trial prior to routine clinical use as monotherapy. Additional data regarding maternal tolerability of cyclic progestins, long-term safety of estradiol treatment, estradiol passage into breastmilk and infants, and interdisciplinary collaboration among psychiatrists and gynecologists is also needed before estradiol is used in women who decline or fail to respond to first-line antidepressant treatments, or as an augmentation of conventional antidepressant treatment.

Keywords

postpartum depression; transdermal estradiol

Postpartum depression –its public health impact, treatment, and the demand for novel therapeutics

Postpartum depression (PPD) is a major public health concern (Healthy People 2010, Objective 16-5c; (Wisner et al 2006a)). PPD (which includes both major and minor depression) affects at least 14.5% (one out of seven) of women in their first three months postpartum (Gaynes et al 2005) with rates that rise to 23% - 59% among inner-city (Hobfoll et al 1995) and adolescent mothers (Trad 1995). Suicide is a leading cause of death in new mothers, and suicidal thoughts and non-fatal self-harm behaviors are prevalent in this population (Lindahl et al 2005). The sequelae of PPD include not only maternal low mood and anxiety (Hendrick et al 2000; Wisner et al 1999), but also deleterious effects of impaired maternal caregiving (England 1994; Kendler et al 1993) on child development (Grace et al 2003; Murray and Cooper 1997).

Randomized clinical trials (RCT) have demonstrated that pharmacologic and psychotherapy antidepressant treatments are as effective for PPD (Appleby et al 1997; O'Hara et al 2000; Wisner et al 2006b) as they are for major depressive disorder that occurs in non-postpartum women (Walsh et al 2002). Nortriptyline and sertraline treatment of PPD were both associated with approximately 60% rates of response and 50% rates of remission (Wisner et al 2006b). Twelve-week interpersonal psychotherapy was associated with a 37.5% remission rate relative to 13.7% in the waiting list control group (O'Hara et al 2000), an index of efficacy that is similar to that demonstrated in non-postpartum populations (de Mello et al 2005). Replicated studies reveal negligible passage of sertraline, paroxetine, and nortriptyline into the sera of nursing infants (Weissman et al 2004), thus making psychotropic treatment in PPD more widespread for breastfeeding mothers. These landmark clinical studies have demonstrated that conventional antidepressant treatments are effective for women with PPD.

Notwithstanding progress made in PPD treatment, antidepressant remission rates of 30-50% in PPD and in major depressive disorder (MDD) (Trivedi et al 2006) leave a large void to be filled with novel treatments. Estradiol treatment is one such novel therapy that shows promise for the achievement of more rapid and higher rates of remission in PPD (Ahokas et al 2001a; Gregoire et al 1996b) similar to what has been demonstrated in perimenopause-onset depression (Schmidt et al 2000; Soares et al 2001). The robust antidepressant effect of estradiol is putatively related to estradiol-mediated normalization of hormonally-sensitive neural circuits of depression that are activated during PPD and other reproductive hormone-related mood disorders (Berman et al 1997; Bloch et al 2000; Dreher et al 2007). In addition to being potentially more efficacious than conventional antidepressant treatment, estradiol might also be more acceptable to women with PPD who perceive that hormonal treatments more directly address the etiology of their disorder. Estradiol may also be regarded as a natural therapeutic that overcomes the stigma of conventional treatments (Kelly and Jorm 2007).

Epidemiological, clinical research, and basic science evidence which support estradiol as a therapeutic for PPD

Epidemiological studies converge to powerfully suggest that female gonadal steroid fluctuations can lower the threshold for emergence of mood disorder symptoms and episodes (Rubinow 2006). This theory is substantiated by the 2-3.5-fold increase in risk for psychiatric hospitalization due to incident PPD in the 5 months after childbirth (Munk-Olsen et al 2006), the 2-5-fold risk for MDE and depressive symptoms in perimenopausal compared to premenopausal women (Cohen et al 2006; Freeman et al 2006), and the 1.7-fold increased risk for major depression in women relative to men during childbearing years that begins during puberty (Kessler 2000; Kessler et al 2007). Furthermore, susceptibility to depressed mood during one reproductive transition (ie: premenstrual dysphoric disorder) confers vulnerability for future reproductive hormone-related mood disorders (Freeman et al 2004; Parry 1995; Payne et al 2007).

As evidenced by hormone manipulation experiments, the ovarian hormones estradiol and progesterone are potent modulators of individual risk for reproductive hormone-related mood disorders. In women with premenstrual dysphoric disorder, mood symptoms remitted in 66% of women following ovarian suppression with the gonadotropin releasing hormone agonist leuprolide. Symptoms re-emerged after add-back of estradiol and progesterone in concentrations that approximated the mid-luteal phase (Schmidt et al 1998). Similar findings emerged in a perinatal simulation study in which leuprolide-suppressed women were given and then withdrawn from estradiol doses that simulated peak menstrual cycle concentrations and progesterone doses that simulated mid-gestation concentrations. Among women with a history of PPD, 63% experienced depressive symptom increase during **addition** of combined estradiol and progesterone which peaked during **withdrawal** of these hormones (Bloch et al 2000). In both studies, women without reproductive hormone-related mood disorders experienced no significant mood symptoms during hormonal manipulation. These experiments point to important neuromodulatory effects of both estradiol and progesterone in vulnerable women. We focus on estradiol in this manuscript.

Estradiol appears to function as an antidepressant through mechanisms inherent in traditional psychotropics (Duman et al 1997; Manji et al 2001) in widespread regions of the cortex and limbic brain (Gundlah et al 2000). Estradiol promotes neurite outgrowth and neuronal survival in hypothalamus, amygdala, hippocampus, dopaminergic neurons, and prefrontal cortex (Lee and McEwen 2001). Pro-monoaminergic effects of estradiol include enhancement of norepinephrine, dopamine (McEwen and Alves 1999), cholinergic (Gibbs and Aggarwal 1998), and serotonin systems (Bethea et al 2000; Osterlund et al 2000; Pecins-Thompson and Bethea 1999). Estradiol also mitigates against oxidative stress, glutamateric excitotoxicity, and β-amyloid toxicity (Amantea et al 2005). A potential role for estradiol to modulate feedback regulation of the hypothalamic-pituitary-adrenal (HPA) axis (Cizza et al 1997) is yet another mechanism by which estradiol may act as a psychotropic.

Clinical trials of Estradiol for the Treatment of PPD: efficacy, safety, and future directions

PPD is a disorder that is particularly well-suited for estradiol treatment because it occurs after 100-fold decreases in ambient estradiol between late pregnancy and 48 hours post-parturition. Two published trials suggest that PPD treatment response to estradiol (~80%) exceeds that of standard antidepressants [50.1%± 9.0%; (Walsh et al 2002)]. Gregoire et al (Gregoire et al 1996a) enrolled 61, non-breastfeeding women who presented within 18 months of delivery. Subjects had severe depressive symptoms, reported as mean Edinburgh Postnatal Depression

Screening Scale (EPDS)(Cox et al 1987) score of 21.6 ± 3.0. The EPDS is a widely used screening scale for PPD in which scores of 10 or higher are highly sensitive for the presence of postpartum major depression (Cox et al 1987; Peindl et al 2004). An EPDS score of 21 roughly corresponds to a Hamilton Rating Scale for Depression 17-item score of 28 (Wisner et al, unpublished). Women were randomized to 6 months of treatment with placebo or high dose transdermal 17β-estradiol (200 mcg/day). The mean estradiol concentration of actively treated women was 680 pmol/L (nearly twice the mean estradiol concentration across the menstrual cycle, which is ~ 370 pmol/L). Within one month of treatment, EPDS scores of the estradiol-treated group were 4 points lower on average compared to the placebo-treated group. Because assessments were done once a month, the time course of symptom improvement in the early weeks of treatment is unknown and may be substantially earlier. At 3 months of treatment, 80% of the estradiol group had EPDS scores <14, whereas only 31% of placebo group had scores <14 (corresponds to a Hamilton Rating Scale for Depression 17-item score of <15) (Wisner et al, unpublished). By study completion (6 months), EPDS scores in both groups had decreased; however, the EPDS scores for only the estradiol-treated subjects (score range was 6-9; 4.38 points lower than the placebo group) were consistent with resolution of the major depressive episode (Hanusa et al 2008; Peindl et al 2004).

Ahokas et al. (Ahokas et al 2001b) treated 23 postpartum, severely depressed (mean Montgomery-Asberg Depression Rating Scale score; MADRS= 40) women who presented within 12 months of birth. Thirteen participants were breastfeeding. The women were hypogonadal (mean estradiol=80 pmol/L) and half met criteria for gonadal failure. They were treated openly with sublingual 17β-estradiol (4.8 mg/day) for 8 weeks. The subjects' mean estradiol concentration by study completion rose to 478 pmol/L. Within one week of treatment, 21 of 23 subjects had 50% symptom score reductions and by two weeks, 19 of 23 (83%) subjects achieved remission (MADRS score ≤7). An inverse relationship between estradiol concentration and MADRS score was noted.

Estradiol treatment was well-tolerated in both studies as judged by low attrition. A suicide occurred in the randomized trial after estradiol was replaced with progesterone during a psychiatric hospitalization (Gregoire et al 1996a). Women with contraindications to estradiol treatment, such as histories of thromboembolic events or uterine and breast disease were excluded, and no reports of adverse events were reported in the cited studies. During scheduled endometrial curettage at the study conclusion (6 months), endometrial changes were found in 3 participants, despite co-administration of dydrogesterone[1] (10mg/day, 12 days per month in the final 3 months of the estradiol trial), which resolved at follow-up (Gregoire et al 1996a). Breast tenderness, headache, nausea and vomiting led to estradiol discontinuation in 3 of 6 women who were treated transdermally with 100 mcg/day in a study of non-depressed women (Perheentupa et al 2004). In contrast, low attrition in the estradiol trials for depression suggests that depressed women may have fewer estradiol side effects than non-depressed women.

While these studies support the treatment of PPD with estradiol, study design limitations weaken the evidence base for adding estradiol to the therapeutic armamentarium for PPD. In the randomized trial, the inclusion of women who took concurrent antidepressant medications (47% and 37% in the estradiol and placebo arms, respectively) limits the ability to discern an estradiol-specific treatment effect versus an augmentation effect. The EPDS is a self-report scale; the validity of the findings would be increased if they were confirmed with a clinician interview-based measure. The exclusion of breastfeeding women and the inclusion of severely depressed women (mean baseline EPDS=21 which corresponds to a 17-item Hamilton Rating Scale for Depression Scale score of 28) but not women with mild or minor depression also

[1]Dydrogesterone (9B, 10α-pregna-4, 6-diene-3, 20-dione) is an orally active progestogen with a molecular structure almost identical to that of natural progesterone.

limit the study's generalizability. In both studies, women who presented for treatment up to 12-18 months postpartum were included. This time frame is far removed from the estradiol withdrawal at delivery that theoretically contributes to PPD risk and is a primary rationale for estradiol treatment. Because epidemiological and translational research (Okun et al In press; Sanjuan et al 2008) converge on an early postpartum timeframe for depression vulnerability, this might also be an ideal time to treat. Whether higher rates of estradiol treatment response and remission can be achieved in women with PPD onset proximal to delivery (ie: within a month postpartum) remains to be tested. Results of ongoing RCT of estradiol for PPD (http://clinicaltrials.gov/ct2/show/NCT00744328?term=wisner&rank=4; http://www.clinicaltrials.gov/ct/show/NCT00059228?order=1) will buttress the evidence base for this potential therapy.

Selection of an estrogen formulation for PPD treatment

Of fundamental importance is the fact that not all estrogens are alike. Estrogen types confer benefits and risks based upon their unique pharmacology and route of administration. Of the b*ioidentical estrogens*, 17β-estradiol has greater estrogen receptor affinity relative to estrone and estriol. *Transdermal* 17β-estradiol administration closely resembles physiologic ovarian estradiol production because its metabolism results in a 1:1 ratio of estradiol to estrone concentrations. Conjugated equine estrogens, the most common form of estrogen therapy in menopausal women, are a *biologic* estrogen produced from the urine of pregnant mares. Conjugated equine estrogens contain up to ten different estrogens, many of which possess higher affinity than estradiol for the estrogen receptor. The synthetic estrogen e*thinyl estradiol* differs from 17β-estradiol on the basis of an added ethinyl group at position C-17. As a distinct compound than estradiol, ethinyl estradiol cannot be measured by estradiol assays and has no known bioequivalency to estradiol. Ethinyl estradiol has higher affinity for the estrogen receptor relative to 17β-estradiol. The potency and oral availability of ethinyl estradiol have made it the most widely-used synthetic oral estrogen for contraception. All estrogens, except for transdermal 17β-estradiol, are predominantly metabolized to the less potent, less lipophilic, and therefore less brain-available (Guazzo et al 1996) estrogen, estrone sulfate.

A critical pharmacologic advantage of transdermal estradiol delivery is that it bypasses the enterohepatic circulation. This route of delivery avoids induction of hepatic coagulation factors and triglyceride synthesis and therefore does not appear to increase risk for venothrombolic embolism (Canonico et al 2008). In contrast, orally administered estradiol, ethinyl estradiol, and conjugated equine estrogens have the disadvantage of greater hepatic effects and increased venothrombolic embolism risk (odds ratio of 2-5) (Scarabin et al 2003). Transdermal 17β-estradiol has been advocated as the best available depression treatment in the puerperium and perimenopause because it most closely resembles physiologic ovarian estradiol production, it penetrates the brain the best, and it is not associated with venothromboembolic risk.

What serum concentration of estradiol is therapeutic for PPD?

Estradiol concentrations achieved in transdermal estradiol treatment trials for perimenopause and postpartum depression ranged from 260 – 700 pmol/L, which, like menopausal hormone therapy, simulates mean menstrual cycle concentrations. Notably, such concentrations are 100-fold lower than late third trimester pregnancy estradiol concentrations (60,000 pmol/L) (Tulchinsky et al 1972). Because no correlation between estradiol concentration and depression symptoms was observed in prior studies (Ahokas et al 2001a; Gregoire et al 1996a; Soares et al 2002), we lack evidence that higher estradiol concentrations more effectively treat depression. In addition, whether women with estradiol concentrations in the hypogonadal range (as occurs during lactational amenorrhea) stand to benefit more from estradiol treatment than

non-hypogonadal women with PPD is an area of debate than deserves further study (Ahokas et al 2001b; Soares et al 2002).

In general, endogenous estradiol production is curtailed by exogenous estradiol negative feedback on gonadotropins. Therefore, the administered dose of estradiol translates directly into the serum concentration obtained. Pharmacokinetic studies of the Climara® estradiol transdermal system indicated an approximate 1:1 ratio of administered estradiol concentration (in mcg) to serum estradiol concentration (pg/ml) obtained. Converted from picograms per milliliter to picomoles per liter (pmol/L), transdermal estradiol doses from 25 - 200 mcg/day roughly produce serum estradiol concentrations of 90 – 730 pmol/L. Inter- and intra-individual variability in patch application compliance and estradiol absorption and metabolism yields a wide range of serum concentrations per dose administered. For example, among postmenopausal women, 50 mcg estradiol patches changed every 3 days (rather than twice per week (Schmidt et al 2000)) yielded higher serum concentrations than 100 mcg patches changed twice weekly (Soares et al 2001) (Table 1). The 50 mcg estradiol patches changed every 3 days (Schmidt et al 2000) also yielded nearly the same serum concentrations as 200 mcg estradiol patches changed twice weekly in postpartum women (Gregoire et al 1996b) (table 1). Research is needed to determine the lowest transdermal estradiol concentration that is efficacious for the treatment of depression and to examine how inter-individual variability in estradiol metabolism moderates the estradiol dose-treatment response relationship.

Side effects and risks of transdermal estradiol

Common side effects of estrogen treatment include nausea, vomiting, bloating, stomach/abdominal cramps, headaches, migraines, changes in vaginal secretions, breast tenderness, episodes of vaginal bleeding and/or spotting, and hair loss. Other side effects include high blood pressure, edema, enlargement of uterine fibroids, and vaginal yeast infection. Oral estrogens are more commonly associated with hypertension and vaginal yeast infections. Transdermal estradiol formulations were well tolerated by postpartum and menopausal women with and without depression (Gregoire et al 1996b; Perheentupa et al 2000; Perheentupa et al 2004; Schmidt et al 2000; Soares et al 2001; von Holst and Salbach 2000).

Transdermal estradiol as dosed within the standard clinical range (≤ 100 mcg/d) does not pose risk for venous thromboembolism (Canonico et al 2008; Scarabin et al 2003). Whether supratherapeutic (>100 mcg/d) doses of transdermal estradiol confer thromboembolism risk is unknown. Doses up to 200 mcg/d have been used for the treatment of PPD without reported thromboembolic events (Gregoire et al 1996b). Medical factors that warrant careful monitoring or withholding of high dose postpartum estradiol treatment include heavy smoking, a past thromboembolic event, thrombophlebitis, hypercoagulability or family history of such, untreated hyperlipidemia, uncontrolled hypertension, arterial vascular disease, heart disease, complicated migraine headaches, obesity (>35% ideal body weight), preeclapmsia, or eclampsia (Brandes 2006; Gillum L 2000).

Estradiol, like other hormones, can act like a carcinogen by increasing cell proliferation in target organs. Increases in cell divisions confer risk for random DNA copying errors and reduce time for repair of DNA damage, thus potentially resulting in the propagation of genetic errors. Endometrial hyperplasia is a condition of endometrial cell proliferation that is commonly related to estrogen use in the absence of a progestin. This estrogen-related simple and nonatypical hyperplasia progresses to endometrial cancer in 1% of cases and is earlier in stage and lower in grade relative to endometrial cancer in non-estrogen users. The risk of endometrial cancer posed by estrogen treatment in postpartum women is extremely low. Protective factors for endometrial hyperplasia in postpartum women include parity (wherein high progesterone production negates estrogen-induced hyperplasia), common use of progestin-containing IUDs

or progestin-only oral contraceptives, and lactational amenorrhea-associated hypoestrogenemia. Abnormal uterine bleeding may be a clinical sign of endometrial hyperplasia or cancer and should therefore invoke gynecologic evaluation with possible transvaginal ultrasound and endometrial biopsy (Dubinsky 2004; Espindola et al 2007). Progesterone administration for a minimum of 10 days every 3 months is required to prevent estrogen-related endometrial hyperplasia (Voigt et al 1991). Progestin-releasing intrauterine devices are also highly effective for the prevention of endometrial hyperplasia. In women who develop endometrial hyperplasia, treatment consists of a 21-day course of high dose progestin or endometrial ablation.

Because 75% of breast cancers are estrogen receptor positive, both endogenous and exogenous estrogens can potentiate growth of such cancers. Nevertheless a large study found no increased risk of breast cancer in women with past or present oral contraceptive use, regardless of estrogen dose and duration of use (Marchbanks et al 2002). This finding was also true for a subset of women with a positive first degree family history of breast cancer. Other studies conclude that exogenous estrogen-associated risk of breast cancer is at most 2-3% per year of use or 1-2-fold increased after 5-10 years of use (Prentice et al 2008). More recent evidence suggests that long term, continuous co-administration of the progestin medroxyprogesterone acetate (with estrogen) confers additional risk for breast cancer (2002; Rossouw et al 2002).

Epithelial-type ovarian cancer incidence is not heightened with exposure to reproductive hormones. In fact, parity and oral contraceptive use (clinical variables that suppress ovarian function) are protective factors for ovarian cancer.

Oral contraceptives that contained high dose oral ethinyl estradiol (50 mcg/d) were associated with new onset liver disease (benign hepatic lesions, hemangiomas, biliary stones, and cholestatic jaundice (Eisenfeld and Aten 1987)). In contrast, adverse liver effects are rare for oral estradiol, which has lower affinity for hepatic estrogen receptors relative to ethinyl estradiol, and for transdermal estradiol, which bypasses the enterohepatic circulation.

Breast milk production may be diminished by estrogens if administered prior to well-established lactation, which occurs at 6-8 weeks postpartum. In such situations, the reduction in milk supply is typically rapid (within a week after initiation; D. Bogen, M.D., personal communication) and is characterized by increased infant crying between feeds, less satisfaction after feeding, fewer wet and soiled diapers and weight loss. Discontinuation of the exogenous estrogen treatment can often restore milk production. Extant data reveal negligible passage of estradiol into breast milk for doses up to 100 mcg/d (Perheentupa et al 2004).

Transdermal estradiol has not been widely tested nor has it been approved as a contraceptive. Investigators have demonstrated that transdermal estradiol 50-100 mcg/day treatment suppressed ovarian folliculogenesis and pituitary secretion of FSH and LH (Perheentupa et al. 2000; Perheentupa et al. 2004); however, additional study is warranted in larger samples and in non-lactating women.

Selection of a progestogen to be used in concert with transdermal estradiol for PPD treatment

The administration of estradiol necessitates co-administration of a progestogen, which induces secretory transformation and shedding of the endometrial lining to protect against endometrial hyperplasia and cancer. Commonly used progestogens have oral, subcutaneous, or intra-uterine administration. Intra-uterine administration results in lower systemic progestogen absorption and thus potentially fewer side effects. Oral progestogens can be administered continuously or sequentially (every 3 months).

Similar to estrogens, not all progestogens are the same. The progestogen class is comprised of diverse members that have in common the ability to induce secretory changes in the endometrium. Progesterone is the bioidentical hormone and dydrogesterone is the compound most like progesterone. The highly potent pregnane progestogens (ie: medroxyprogesterone acetate, megestrol and cyproteron acetate) are synthetic derivatives of progesterone with modifications at the C-17 and C-6 sites. The synthetic 19-nortestosterone-derived group of progestogens are derived from testosterone and include norethisterone, norgestrel, and desogestrel. The synthetic progestogens have come into widespread use due to ease of oral administration, ability to be prepared in parenteral, long-acting and depot formulations, and high progesterone receptor potency.

What are the risks of progestin treatment?

The mineralocorticoid activity of the progestogens is responsible for associated weight gain, bloating, and edema side effects. These effects are minimized with the anti-mineralocorticoid progestogen drospirenone. The 19-nortestosterone group possesses dermatologic side effects typical of androgens, including acne, greasy skin, and darkening of facial hair. These androgenic progestogens may also confer adverse metabolic effects including lowering of HDL and decreased insulin sensitivity (Panay and Studd 1997). The pregnane and norpregnane derivatives are considered to have more intermediate effects on cardiovascular metabolic risk factors. The pregnane medroxyprogesterone acetate has been associated with vasospasm risk (Paris et al 2000) and warrants additional study. Progesterone and dydrogesterone have the fewest associated adverse metabolic, vascular, and dermatologic effects relative to other progestogens.

Progestogen effects on mental health are variable. Endogenous progesterone metabolites (ie: allopregnanolone) are potent agonists of the GABA-A receptor and thereby reduce anxiety and positively modulate mood (Uzunova et al 2006). Synthetic progestin components of hormonal contraceptives and hormone therapy have been alternatively associated with increased (Elovainio et al 2007; Kulkarni 2007; Lawrie et al 1998; Pazol et al 2004) or decreased risk for depression (Cagnacci et al 2004; Dalton 1985; Dalton 1989; Dalton 1995; Gupta et al 2001; Joffe et al 2003; Pazol et al 2004; Westhoff et al 1998a; Westhoff et al 1998b; Young et al 2007). In a randomized clinical trial of postpartum healthy women assigned to the injectable progestin norethisterone enanthate (which is closely related to the progestin-only oral contraceptive commonly prescribed to lactating women) or placebo within 48 hours post delivery, depression scores were higher in the progestin group at six weeks postpartum (Lawrie et al 1998). Progesterone itself, in contrast, has shown promise in the prophylaxis and/or treatment of postpartum depression in several open studies (Dalton 1985; Dalton 1989; Dalton 1995), and might be a preferred progestin for women with mood worsening during treatment with synthetic progestins. The levonorgestrel containing intra-uterine device (Mirena©) is an increasingly used contraceptive in postpartum women because of its low systemic absorption, convenience, tolerability, and cost-effectiveness. Continued study of cardiovascular and mental health effects of progestin compounds is needed.

Breastmilk production may be diminished by progestins if administered prior to well-established lactation. Intramuscular medroxyprogesterone acetate treatment of mothers resulted in low breast milk concentrations (1 mcg/L) and nondetectability in infant urine samples (Hale 2002). Because medroxyprogesterone acetate is less bioavailable when given orally, even lower breast milk accumulation and passage to infants would be expected.

Conclusions

A convergence of epidemiological, preclinical, and clinical research suggests the utility of transdermal estradiol for the treatment of PPD. Robust and rapid response to estradiol in two clinical PPD trials, few side effects, and minimal breastmilk passage to the infant make estradiol a promising PPD treatment. Estradiol cannot be considered as a first line agent among conventional antidepressant treatments for acute treatment of PPD until additional efficacy data are available. Additional safety data are also needed before estradiol can be considered as a treatment option for women who do not respond to or decline conventional treatments or who wish to use estradiol as an adjunct to conventional antidepressants. Outcomes related to maternal tolerability of cyclic progestins, long-term safety of high dose estradiol treatment, and high dose estradiol passage into breastmilk and infants are of particular interest. The utility of continuation and maintenance treatment with estradiol has not been investigated with respect to PPD and warrants study.

Lack of robust efficacy data of estradiol as a therapeutic for PPD has been the main obstacle for its clinical use. Studies to obtain this efficacy data in PPD have been challenged by the nonavailability of masked estradiol patches for use in RCTs. The Women's Health Initiative study also raised concerns about estrogen and progesterone-associated health risks that have discouraged additional study; however, such risks are minimal in young, reproductive aged women. Another obstacle is the concern that estradiol could interfere with breastmilk production, given the public health emphasis to increase lactation rates. A major obstacle is that estradiol treatment traditionally falls within the purview of obstetrics-gynecology, while depression traditionally falls with the purview of psychiatry. Isolation of psychiatrists from obstetrical practitioners make each clinician unfamiliar, inexperienced, and unwilling to assume full responsibility for estradiol treatment of PPD. As interdisciplinary practice of medicine grows (Katon and Unutzer 2006), models of interdisciplinary collaboration, such as colocation of Gynecology-Psychiatry clinics, will be poised to increase the application of hormonal treatments for mood disorders and benefit the mental health of postpartum women.

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Table 1

Index of estrogen doses and concentrations produced endogenously or administered exogenously, across the lifespan and for depression treatment

	Dose	Estradiol concentration (pmol/L)	Reference
PHYSIOLOGIC CONCENTRATIONS			
Prepubertal		40	Adashi text 1996
Menstrual cycle range	Ovarian follicle secretes 70 – 500 mcg/d, phase-dependent	180 - 1100	Adashi text 1996
Mean menstrual cycle		370	Adashi text 1996
End first trimester gestation		9,200	Adashi text 1996
End second trimester gestation		37,000	Adashi text 1996
End third trimester gestation		60,000	Adashi text 1996
Lactational amenorrhea		70	Peerhentupa 2004
		150	Peerhentupa 2000
		152 (n=49) breastfeeding	Lawrie 1998
Postpartum – 6 weeks - bottlefeeding		340 (n=9) bottle feeding	Lawrie 1998
Hypogonadal/postmenopausal		< 110	Adashi text 1996
REPRODUCTIVE ENDOCRINE TREATMENTS			
Postmenopausal hormone therapy	Estradiol 25 – 200 mcg/d	250 – 600	Physicians' Desk Reference
DEPRESSION TREATMENT			
Postmenopausal depression treatment	50 mcg/d (changed q3days)	550	Schmidt 2000
	100 mcg/d (changed 2x/wk)	260	Soares 2001
Postpartum depression treatment	200 mcg/d (changed 2x/wk)	680	Gregoire 1996
	3-8 mg/d sublingual	Mean=500 (range 320-710)	Ahokas 2001
HPO AXIS RESEARCH			
Lactation, 20-22 wks postpartum	Estroderm 50(changed 2x/wk)	100	Perheentupa 2004 (data estimated from graphic)
	75	80	
	100 mcg/d	170	
Lactation, 6-1 wks postpartum	Estroderm 50(changed 2x/wk)	Ranged from 100-200 over 12 wks	Perheentupa 2000 (data estimated from graphic)