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Transdermal Estradiol Treatment during Breastfeeding: Maternal and Infant Serum Concentrations

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BACKGROUND

Estradiol (E2) has shown promise as a treatment for postpartum major depression (PPMD). The impact of transdermal E2 treatment was examined in three investigations (Ahokas et al. 2001; Gregoire et al. 1996; K. L. Wisner, personal communication, December 1, 2014). Because E2 is of interest as a treatment for PPMD and 79% of U.S. women initiate breastfeeding (Centers for Disease Control and Prevention 2014), we evaluated the impact of transdermal E2 on breastfeeding success and infant serum concentrations and growth.

The literature on transdermal E2 use in mother-infant breastfeeding pairs is limited. Vaginal E2 treatment significantly increases maternal plasma and breastmilk E2 concentrations (Nilsson et al. 1978), but transdermal E2 doses up to 100 mcg/d did not significantly increase E2 concentrations in plasma (Illingworth et al. 1995; Perheentupa et al. 2000), serum (Perheentupa et al. 2004), or breastmilk (Perheentupa et al. 2004). None of the studies on E2 treatment for breastfeeding mothers included infant serum or plasma concentrations.

Ball and Morrison (1999) reported poor weight gain in an 11-day old infant whose mother was treated with 50 mcg/d transdermal E2 for postpartum depression. The authors hypothesized that the E2 may have lowered milk quantity or quality and consequently caused poor weight gain. A single case cannot establish causality, but suppression of breastmilk production is a potential adverse effect of maternal E2 treatment (Lawrence & Lawrence 2010).

Our aims were to examine: 1) whether transdermal E2 treatment significantly increased serum concentrations of E2 in mothers and their breastfed infants compared to treatment with sertraline or placebo. Due to the exogenous E2 supplementation and potential transfer via breastmilk, we hypothesized that E2 concentrations would be higher in mothers and infants of the E2-treated group compared to the other two groups; 2) whether transdermal E2

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treatment of breastfeeding women significantly reduced infant growth. Because E2 is a prolactin antagonist that inhibits milk secretion (Lawrence & Lawrence 2010), elevated E2 concentrations may reduce breastmilk production. We hypothesized that infant weight, length, and head circumference would be lower in the E2-treated group than in the comparator groups; and 3) the nature and strength of the association between maternal and infant E2 concentrations in breastfeeding mother-infant pairs. We hypothesized that mother and infant concentrations would be significantly correlated due to transfer via breastmilk.

The lab that performed the E2 analyses included assays of estrone (E1) with E2. Because little information is available regarding infant E1 and E2 concentrations, we performed exploratory analyses to examine relationships between infant E1 and E2 and age and sex.

METHODS

E1 and E2 concentrations for 19 mother-infant dyads were included in this analysis. These dyads represent the subset of women from a double-blind randomized controlled trial (RCT) of transdermal E2 for treatment of postpartum depression (K. L. Wisner, personal communication, December 1, 2014). The mothers who were breastfeeding had maternal and infant serum samples drawn on the same date. The RCT used a parallel dose escalation strategy for E2 with doses ranging from 50 mcg/d to 200 mcg/d. The doses were advanced 50 mcg every 2 weeks unless side effects were prohibitive or the subject met criteria for remission of PMDD.

Serum samples were drawn at weeks 4 and 8 on all mother-infant pairs for women who were breastfeeding more than 50% at the time of the visit. For this analysis, if the same mother-infant dyad had serum drawn at multiple visits (which occurred in 42.1% of the sample), the later visit was used because doses were usually higher at later visits and therefore the likelihood of detecting elevated serum concentrations would be higher. At the time points included the majority (73.7%) of women were fully breastfeeding.

Serum samples were frozen and analyzed at the same time in the same laboratory. E1 and E2 were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Agilent Technologies, Inc., Santa Clara, CA 95051). Intra-assay coefficients of variation (C.V.'s) were 11.8%, 7.3%, 6.0%, 1.6%, 1.5% and 1.4% at 0.23, 0.50, 0.74, 35, 151 and 405 pg/mL respectively. Inter-assay C.V.'s were 10.8%, 8.5%, 6.9%, 5.1%, 4.6% and 4.8% at 0.29, 0.50, 0.77, 32, 140 and 382 pg/ml respectively. The assay limit of detection was 2.5 pg/mL. To be conservative, serum concentrations below the limit of detection were recorded as 2.5 pg/ml.

Baseline characteristics were compared using Analysis of Variance (ANOVA) for continuous variables and Chi-Square Cramer's V for categorical variables due to limited sample size. For Aim 1, Analysis of Covariance (ANCOVA) was used to compare maternal and infant E1 and E2 concentrations between treatment arms. Maternal age was included as a covariate because women in the group randomized to sertraline were significantly younger than those in the placebo group. Because there was a significant interaction between maternal age and treatment arm for maternal E2, maternal E2 was also included as a

covariate when evaluating infant E1 and E2. For Aim 2, infant weight, length, and head circumference were compared across treatment groups in three separate ANOVA analyses. Because of the wide range of infant ages at the time of serum sampling (1.57-5.03 months) we also compared average daily weight gain, average daily length increase, and average daily head circumference increase from study entry to the time of serum sample using three ANOVA analyses. For Aim 3, Pearson Product-Moment correlations were used to examine the relationship between maternal and infant E1 and E2.

For our exploratory analyses, the relationship between infant age and E1 and E2 concentrations was explored using Pearson correlations, and infant E1 and E2 concentrations by sex were compared using a chi-squared analysis.

RESULTS

The maternal and infant estradiol concentrations are presented in Table 1.

Baseline characteristics were compared across treatment arms (Table 2); only maternal age differed among the three groups. We specifically compared maternal BMI at the time of the serum draw for women in each treatment group, as overweight/obese status may impact E2 metabolism (Westhoff et al. 2012; Zieman et al. 2002), and found no significant differences.

Aim 1: E1 and E2 Concentrations by Treatment Arm

For maternal E1 we found no significant impact of treatment. The covariate effect was not significant and the treatment by age interaction was not significant. For maternal E2 a significant interaction was observed between maternal age and treatment ($F(2,13) = 7.76$, $p=0.006$) which suggests that mothers' age and treatment status significantly impacted maternal E2 concentrations. Neither infant E1 nor infant E2 differed by treatment, and neither the covariates nor the interactions were significant.

Aim 2: Infant growth outcomes

Infant length, weight, and head circumference did not differ by treatment. Similarly there were no significant differences in average daily weight gain, average daily length increase, or average daily head circumference increase across treatments (all $p>0.05$).

Aim 3: Mother-Infant E1 and E2 Correlations

Maternal E1 was significantly correlated with maternal E2 ($r(17) = 0.622$, $p=0.004$) and infant E1 was significantly correlated with infant E2 ($r(17) = 0.949$, $p<.0001$). However, we found no significant correlations between mother and infant E1 ($r(17) = -0.172$, $p=0.481$) or E2 ($r(17) = -0.095$, $p=0.698$) concentrations.

Exploratory Analyses

Because we found no significant difference in infant E1 and E2 concentrations by treatment, all 19 infants were grouped to analyze potential differences in E1 and E2 by infant age and sex. We found no significant correlations between infant age and either E1 or E2 serum concentrations (all $p>0.05$). Infant E1 and E2 concentrations did not differ by sex.

DISCUSSION

Transdermal E2 treatment (50 to 100 mcg/d) did not significantly impact infant E1, infant E2 or maternal E1 concentrations, which suggests that maternal transdermal E2 treatment at doses up to 200 mcg/d does not impact infant serum concentrations. Transdermal E2 treatment, as compared to sertraline and placebo, did not affect infant growth as assessed by weight, length, and head circumference, from which we conclude that transdermal E2 did not meaningfully alter either the quantity or quality of breast milk. Only 1 of the 19 women (belonging to the E2-treated group) decreased her percentage of breastfeeding (as compared to formula and other supplementation) across the course of the study, which supports the acceptability of E2 treatment to breastfeeding women.

The absence of significant correlations between mother and infant E1 and E2 concentrations suggests that any E1 or E2 transfer via breastmilk is limited.

Limitations and Strengths

Women enrolled in this RCT had serum E1 and E2 concentrations less than anticipated and low enough to merit discontinuation of the trial (K. L. Wisner, personal communication, December 1, 2014). The impact of transdermal E2 treatment on breastfeeding women and their infants needs to be evaluated at higher doses where increased maternal E1 and E2 concentrations are achieved. It is important to note that transdermal E2 has not been established as a treatment option for PPMD and in this report we address only its safety profile for breastfeeding women and their infants.

Despite these limitations, the findings add to the scant literature and expand our understanding of the safety profile of transdermal E2 use while breastfeeding. To the best of the authors' knowledge, this analysis is the only report of E1 or E2 serum concentrations in breastfed infants of mothers receiving transdermal E2 treatment.

Conclusions

Overall, these data suggest that transdermal E2 treatment of breastfeeding women does not affect infant E1 or E2 concentrations or infant growth.

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Table 1

Mother and infant El and E2 concentrations

Treatment Arm	Study Visit Week	Infant Age at Draw (Months)	Infant Sex	Maternai Dose at Draw (mg)	Maternai El (pg/ml)	Maternai E2 (pg/ml)	Infant E1 (pg/ml)	Infant E2 (pg/ml)
Estradiol	8	3.47	M	.20	14	12	BD	BD
Estradiol	8	3.93	F	.15	14	7	BD	7
Estradiol	4	1.57	F	.10	45	98	BD	BD
Estradiol	8	3.90	M	.05	46	26	BD	BD
Estradiol	8	3.63	F	.20	38	73	BD	7.1
Estradiol	4	2.00	M	.10	33	30	BD	BD
Placebo	8	5.03	M	.15	56	47	BD	BD
Placebo	8	1.87	M	.10	17	10	28	17
Placebo	8	4.27	M	.15	22	20	BD	BD
Placebo	8	2.47	F	.15	26	19	BD	BD
Placebo	4	2.30	F	.10	23	11	BD	BD
Placebo	8	4.97	M	.15	29	17	29	16
Placebo	8	4.03	F	.10	27	13	BD	6.1
Sertraline	4	2.07	M	100	16	12	BD	BD
Sertraline	8	3.63	M	100	16	6.7	BD	BD
Sertraline	8	3.07	M	150	55	30	BD	BD
Sertraline	4	3.17	M	100	28	12	BD	BD
Sertraline	4	3.70	F	100	32	13	4.7	7.6
Sertraline	8	2.97	M	150	17	7	5**	5**

* BD refers to values below the 2.5 pg/ml limit of detection

** This result was reported as <5 but the precise value could not be determined. It was treated as 5 for the analyses

Table 2

Socio-demographic characteristics by treatment arm at baseline

		Treatment Arm			Analysis	
Measure	**All (N=19)**	**Estradiol (N=6)**	**Sertraline (N=6)**	**Placebo (N=7)**	**Test statistic**	**p**
Age	29.7 + 5.02	30.5 + 5.32	25.7 + 5.01	32.4 + 2.37	F (2,16) =4.09	0.037
Race					Cramer's V = 0.394	0.206
White	16 (84.2)	6 (100.0)	5 (83.3)	5 (71.4)		
Black	1 (5.3)	0 (0.0)	1 (16.7)	0 (0.0)		
Other	2 (10.5)	0 (0.)	0 (0.0)	2 (28.6)		
Hispanic					Cramer's V = 0.347	0.319
Yes	1 (5.3)	1 (16.7)	0 (0.0)	0 (0.0)		
No	18 (94.7)	5 (83.3)	6 (100.0)	7 (100.0)		
Education (level)					Cramer's V = 0.278	0.816
High school	2 (10.5)	1 (16.7)	0 (0.0)	1 (14.3)		
Some college	8 (42.1)	2(33.3)	4 (66.7)	2 (28.6)		
College	6 (31.6)	2 (33.3)	1 (16.7)	3 (42.9)		
Graduate school	3 (15.8)	1 (16.7)	1 (16.7)	1 (14.3)		
Employed					Cramer's V = 0.274	0.490
Yes	10 (52.6)	4 (66.7)	2 (33.3)	4 (57.1)		
No	9 (47.4)	2 (33.3)	4 (66.7)	3 (42.9)		
Marital status					Cramer's V = 0.394	0.208
Single	5 (26.3)	0 (0.0)	2 (33.3)	3 (42.9)		
Married/cohabiting	13 (68.4)	6 (100.0)	3 (50.0)	4 (57.1)		
Divorced/separated	1 (5.3)	0 (0.0)	1 (16.7)	0 (0.0)		
Parity					Cramer's V = 0.342	0.380
1	5 (27.8)	1 (16.7)	1 (16.7)	3 (50.0)		
2	8 (44.4)	2(33.3)	4 (66.7)	2 (33.3)		
3+	5 (27.8)	3 (50.0)	1 (16.7)	1 (16.7)		
Alcohol Use					Cramer's V = 0.206	0.668
Yes	4 (21.1)	2 (33.3)	1 (16.7)	1 (14.3)		
No	15 (78.9)	4 (66.7)	5 (83.3)	6 (85.7)		
Cigarette Use					Cramer's V = 0.347	0.319
Yes	1 (5.3)	0 (0.0)	1 (16.7)	0 (0.0)		
No	18 (94.7)	6 (100.0)	5 (83.3)	7 (100.0)		
Infant Sex					Cramer's V = 0.291	0.448
Male	12 (63.2)	3 (50.0)	5 (83.3)	4 (57.1)		
Female	7 (36.8)	3 (50.0)	1 (16.7)	3 (42.9)		
Variables obtained at time of blood draw						
BMI	30.3 + 6.82	30.4 + 4.67	28.2 + 3.91	32.0 + 10.1	F (2,16) =0.49	0.622
Breastfeeding					Cramer's V = 0.282	0.554
50-80%	1 (5.3)	1(16.7)	0 (0.0)	0 (0.0)		

		Treatment Arm			Analysis	
Measure	**All (N=19)**	**Estradiol (N=6)**	**Sertraline (N=6)**	**Placebo (N=7)**	**Test statistic**	**p**
>80%	4 (21.1)	1 (16.7)	2 (33.3)	1 (14.3)		
100%	14(73.7)	4(66.7)	4 (66.7)	6 (85.7)		
Infant Age (days)	98.9 + 17.7	93.5 + 30.9	94.0 + 17.7	107.9 + 39.7	F (2,16) =0.445	0.648