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Saliva estriol levels in women with and without prenatal antidepressant treatment

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Abstract

Objective—Prenatal antidepressant use has been associated with shorter pregnancy duration and an increased risk for preterm birth. This study measured saliva levels of estriol, a hormone which increases exponentially in the few weeks before spontaneous labor, in pregnant women with and without antidepressant treatment.

Method—Saliva estriol levels were obtained across the day at three time points during pregnancy in 77 subjects with either a history of DSM-IV major depressive disorder (MDD) who were treated with antidepressants in pregnancy (Group 1), a history of DSM-IV major depressive disorder who were not treated or had limited exposure to antidepressants during pregnancy (Group 2), and a normal control group (Group 3).

Results—Mean estriol levels in the second half of pregnancy were significantly higher for Group 1 (h/o MDD, on meds) than Group 2 (h/o MDD, off meds) or Group 3 (control).

Conclusions—Prenatal antidepressant use was associated with significantly higher saliva estriol levels in the second half of pregnancy. Whether estriol reflects a causal mechanism by which women on antidepressants have shorter pregnancy duration remains to be further studied.

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Introduction

Preterm birth affects between 7 and 15% of all births in the United States, is a leading cause of perinatal morbidity and mortality, and poses significant financial burdens (1). Though morbidity is most concerning with early preterm births, studies have reported increased rates of neonatal medical problems and increased hospital costs both at delivery and for readmission in the first year of life for premature infants born between 35 and 37 weeks of age (late preterm birth) (2-4). Greater understanding of potential mechanisms involved in prematurity would be beneficial in decreasing infant morbidity as well as major medical costs.

Elevated levels of estriol, the predominant estrogen in pregnancy, have been associated with preterm births, particularly those occurring after 35 weeks (5-8). McGregor et al. (7) found that women who delivered preterm had higher salivary estriol levels earlier in pregnancy than women who delivered after 37 weeks. Heine et al. (6) reported that an estriol measurement of 2.1 ng/ml predicted an increased risk of preterm labor and delivery. Hedriana et al. (5) demonstrated that the late pregnancy rise in estriol showed distinct patterns characteristic of the duration of pregnancy, suggesting that the rate of increase of estriol, rather than the absolute level, may be related to the timing of labor.

A number of studies have reported an increased risk for preterm birth with in utero exposure to antidepressants (9-14). Our group recently found that prenatal antidepressant use, independent of depression, was associated with a lower gestational age and an increased risk of prematurity (15). Subjects in this study included pregnant women with a history of major depressive disorder (MDD) and prenatal antidepressant treatment (Group 1), pregnant women with a history of MDD with minimal to no prenatal antidepressant use (Group 2), and a normal comparison group (Group 3). For Group 1 subjects, the mean gestational age was 38.5 weeks with a preterm birth rate of 14.3%. The mean gestational age and preterm birth rate for subjects in Groups 2 and 3 were 39.4 weeks and 0 % and 39.7 weeks and 5.3%, respectively. Seven of the eight preterm births occurred in Group 1, with a mean gestational age of 35.6 weeks for all eight infants. One of the preterm births was indicated (Group 1), while the rest were spontaneous.

The mechanism by which antidepressants might contribute to earlier birth is not understood. We explored whether antidepressants are associated with altered levels of hormones such as estriol, and thus, via this mechanism, might influence the timing of birth. This study reports findings of saliva estriol levels across pregnancy for three groups of pregnant subjects in our original report. We hypothesized that estriol levels would be elevated in the group with a shorter pregnancy duration.

Method

This study was conducted at the University of California at Los Angeles Neuropsychiatric Institute. Subjects between the ages of 18 and 45 were enrolled in the first trimester of pregnancy. Seventy-one women with a DSM-IV diagnosis of major depressive disorder (MDD) (16) were prospectively followed across pregnancy (15). Forty-nine of the women with MDD chose to be treated with antidepressants during pregnancy (Group 1: h/o MDD, on meds), while twenty-two of these women chose not to be treated, discontinued antidepressants in the first trimester and/or had minimal (< 10 days) exposure beyond the first trimester (Group 2: h/o MDD, off meds). The antidepressants used by subjects in Group 1 are described in our earlier study (15). We additionally followed nineteen women with no psychiatric history (Group 3: controls). Subjects who were actively suicidal, met criteria for another current Axis I disorder, had a positive urine drug screen, or used medications known to adversely affect the fetus were excluded.

Women were instructed to collect five samples of saliva across the day (from 8 am to 8 pm) during weeks 16-18 (Time 1), 24-26 (Time 2), and 34-36 (Time 3) of pregnancy. Women were asked to select a day for collection in which they were not engaged in any increased activity such as exercise. Each subject was instructed to allow saliva to accumulate and collect 2 ml of mixed saliva through a small straw into a polypropylene tube. Subjects were asked to refrain from eating, drinking, or tooth brushing for the hour prior to collection. Subjects immediately froze samples in their home freezer (-20C) and then brought them to UCLA on ice. Once at UCLA, samples were kept frozen at -80C until assay.

Saliva analysis

Saliva samples were assayed by the UCLA GCRC using a competitive immunoassay specifically designed for the quantitative measurement of salivary estriol (Salimetrics; State College, PA). On the day of assay, saliva samples were thawed, vortexed and centrifuged at $1500 \times g$ (@3000rpm). A microtitre plate was coated with rabbit antibodies to estriol. Estriol in standards and unknowns competes with estriol linked to horseradish peroxidase for the antibody binding sites. One hundred μ l of assay diluent was pipetted into five labeled microcentrifuge tubes. The standard was serially diluted 3 times, and the enzyme conjugate was diluted 1:800. The diluted conjugate solution was mixed and 100 μ l was added to each well. The microtitre plate was incubated at room temperature with mixing at 500 rpm. One hundred μ l of tetramethylbenzidine (TMB) solution was added to each well. The plate was mixed at 500 rpm. After incubation, one hundred μ l of stop solution was added. The plate was mixed at 500 rpm and read at 450 nm. Bound estriol peroxidase was measured by the reaction of the peroxidase enzyme on the substrate TMB. Average optical density (OD) was computed for all duplicate wells. The average OD was subtracted for the NSB wells from the average OD of the zero, standards, controls and unknowns. The percent bound (B/Bo) was calculated for each standard, control and unknown by dividing the average OD (B) by the average OD for the zero (Bo). The concentrations of the controls and unknowns was determined by interpolation. The amount of estriol peroxidase detected is inversely proportional to the amount of estriol present.

Data analysis

Comparisons between estriol levels over the three time points in pregnancy for Groups 1, 2, and 3 were conducted via mixed-effects ANOVA. Model parameter estimation was based on residual maximum likelihood. To account for the repeated measures from the same person, the within subject covariance matrix was modeled as a diagonal matrix. The within subject effects of repeated measures per day (5), measurement at different time points during the course of pregnancy (3) and the interaction of these two was set up as a 3×5 full factorial. Scores on the Hamilton Depression Rating Scale-21 item (Ham-D 21) (17) and the Perceived Stress Scale (PSS) (18) were included in the model as time varying covariates. These methods allowed maximum flexibility in the definition of effects, controlled for the effects of multiple measurements on the same participant and ensured that parameter estimates were not biased by missing values.

Results

Seventy-seven subjects (43 women from Group 1, 17 women from Group 2, 17 women from Group 3) provided 890 analyzable samples. As in the original study (15), demographic characteristics were comparable for all three groups. Preterm risk factors were low, and smoking, alcohol, and substance use were uncommon (15).

Marginal mean estriol levels for Groups 1, 2, and 3 at each time point are presented in Table 1. Active depression (Ham-21) and anxiety (PSS) were included as time varying covariates

and did not have a significant effect on estriol (Ham-21: $F(1,287)=2.76$, $p=.10$; PSS: $F(1,291)=.001$, $p=.98$). There was a significant main effect of group ($F(2,79)=10.8$, $p<.001$) and pregnancy week ($F(2,105)=233$, $p<.001$). The group by pregnancy week interaction was significant ($F(4,105)=5.4$, $p=.001$). Post hoc tests using Bonferroni correction showed that mean estriol levels were not significantly different between groups at Time 1 but were higher for Group 1 than Group 2 or Group 3 at Time 2 ($p=.008$, $.012$, respectively) and Time 3 ($p=.01$, $.038$, respectively). While Group 1 subjects had a steeper rise of mean estriol levels across pregnancy (Figure 1), mean levels for Groups 2 and 3 did not differ significantly from each other.

None of the other factors or higher order interactions between the factors were significant. Time of day was included as a factor in the general linear model and was not significant in predicting estriol levels ($p=.92$). Groups 1, 2, and 3 did not differ in the average change in levels of estriol across the day ($p=.49$). The time varying covariates measuring active depression and stress did not show significant interactions with any of the other factors. Because the pregnancy week effect was significant ($p=.01$), we examined data for 72 subjects who provided saliva samples at each of the three time points in pregnancy; the group by pregnancy week interaction for estriol remained significant ($p=.007$).

The relationship between antidepressant dose and estriol levels was examined by dividing subjects into those without antidepressant exposure, those with exposure to low to medium doses of antidepressant, and those with exposure to high doses of antidepressant. The definitions of “low to medium” and “high” dose are described in the original publication (15). Using a repeated measures ANOVA, the main effect of dose was significant ($F(2,75)=5.4$, $p=.006$).

Gestational age at birth for all three groups combined demonstrated a negative correlation with estriol levels that was significant at Time 2 (Pearson correlation $-.245$, $p=.047$). When each group was analyzed separately, the relationship between gestational age at birth and estriol was not significant.

Discussion

Our original study found that women with prenatal antidepressant treatment had babies who were born at a reduced gestational age and were at a higher risk for preterm birth compared to two groups of untreated women. This follow-up study found an association between antidepressants and increased mean saliva estriol levels in the second half of pregnancy, as well as a steeper rise in saliva estriol across gestation. The differences in estriol levels were significant, even when controlling for active maternal depression and anxiety. Our previous study (15) reported a mean gestational age for the preterm infants of 35.6 weeks ($SD=1.1$). Our current findings of elevated estriol levels in antidepressant treated women is consistent with the literature that elevated estriol appears to be predictive of late preterm birth (8). Though preliminary, our data suggests a relationship between antidepressant dose and estriol levels. While our sample size was too small to meaningfully examine the direct relationship between estriol and gestational age for each group, we did find a significant negative correlation between these two variables in the second trimester for all subjects combined.

To our knowledge, this is the first prospective study to demonstrate an elevation in a previously described, biologic marker for preterm birth (8,19) in antidepressant exposed women who subsequently delivered at a shorter gestational age and had a higher rate of prematurity. While the pathophysiologic processes involved in preterm birth are unclear, studies have shown that the pattern of rise in maternal saliva estriol concentrations, which reflect unbound, unconjugated maternal serum levels (20-22), during the latter part of pregnancy correlate with

duration of pregnancy (5). Other biochemical markers that have also been associated with preterm birth include fetal fibronectin and corticotropin releasing hormone (CRH) (23).

Estriol is produced almost entirely from precursors derived from the fetal adrenal gland and liver (24), serving as a direct marker for the activity of the fetal adrenal gland. Levels of estriol demonstrate a characteristic, exponential increase two to four weeks before the onset of spontaneous labor. Goodwin (24) proposed a possible mechanism by which an estrogen dominant milieu could have a positive influence on labor. He suggested that increased estriol in late pregnancy increases the activity of 11 beta hydroxysteroid dehydrogenase, which metabolizes maternal cortisol to inactive cortisone, thereby decreasing the suppression of the fetal hypothalamic-pituitary-adrenal (HPA) axis. The resulting increased DHEAS from the fetal zone of the adrenal gland would lead to increased estriol, further stimulating 11 beta hydroxysteroid dehydrogenase. Further positive feedback could also result as increased cortisol from the definitive zone of the fetal gland competes with progesterone for sites on placental glucocorticoid receptors, removing the potential inhibitory effect of progesterone on placental CRH release (25), and increasing stimulation of the fetal pituitary. The estrogen dominant milieu created by the increase in estriol would result in conditions favoring labor, including the induction of uterine oxytocin receptors, myometrial gap junction proteins, and prostaglandin synthetases (26-28).

The elevation of estriol levels in our study supports literature demonstrating an effect of antidepressants on the duration of pregnancy and suggests a potential endocrine mechanism. How or where antidepressants may interact with the pathways elucidated above remains to be further explored. Our study does not allow us to determine whether treatment with antidepressants increased estriol levels which then resulted in earlier birth, or whether antidepressants shortened gestational age through another mechanism, with higher estriol levels being a marker of this effect. Chronic treatment with antidepressants has been shown to decrease CRH mRNA and CRH concentrations in the hypothalamus of rats (29-31), supporting clinical evidence that successful pharmacologic treatment is associated with normalization of dysregulated CRH levels (32). It is not implausible to consider that antidepressant treatment may also result in changes in estriol levels, though a causal relationship remains to be further investigated.

It is possible that women in this study who chose not to be treated with antidepressants were different in some respect that could reflect on estriol levels. During pregnancy, total and free plasma cortisol levels increase steadily, peaking during the third trimester and maintaining a diurnal variation. For patients with major depression, hyperactivity of the HPA axis has been repeatedly demonstrated (33-35), with increased 24-hour urine free cortisol, elevated plasma and CSF concentrations of cortisol, and nonsuppression of cortisol, beta-endorphin and ACTH following dexamethasone administration. Exogenous corticosteroids have been shown to decrease estriol levels, and, thus, the hyperactivity of the HPA axis in our depressed subjects could have influenced estriol levels. However, a recent study of the effect of depression on the cortisol awakening response during pregnancy did not find a significant difference between women who were depressed and normal controls (36). In addition, both groups of subjects in our study with a history of depression (on and off antidepressants) had a similar degree and duration of depression. Subjects in the antidepressant treated group included those who attempted to decrease or discontinue medication, switched to a different medication, or chose partial improvement with a lower dose. Active symptoms of depression were comparable between these two groups and did not significantly influence estriol results.

Several factors can influence saliva estriol levels, including diurnal variations, corticosteroids, activity, food consumption, and oral lesions or gingivitis. None of the women in our study were taking steroids, and time of day was not a significant variable. While women were given explicit

instructions regarding collection procedures, including food consumption, activity level, and concurrent medication use, oral lesions and hygiene was not assessed.

Despite study limitations, our results suggest an association between prenatal antidepressant use and elevated saliva estriol levels in the second half of pregnancy. Whether the effect of antidepressants on pregnancy duration is mediated by estriol levels or is due to as yet undetermined other factors remains unknown. Further study of the biologic mechanisms involved is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Estradiol levels at three time points in pregnancy for Groups 1, 2, and 3

Table 1

Saliva estriol levels for women with a history of depression taking or not taking antidepressants and healthy comparison women

Time in pregnancy	Group 1: History of depression, taking antidepressants (Mean pg/ml +/- SD) (N=43)	Group 2: History of depression, not taking antidepressants (Mean pg/ml +/- SD) (N=17)	Group 3: Healthy comparison women (Mean pg/ml +/-SD) (N=17)	Analysis
Time 1	167 +/- 13	164 +/- 20	136 +/-20	F(2,204)=.79 p=.45
Time 2	756 +/- 37	537 +/- 62	552 +/- 60	F(2,243)=6.92 P<.01
Time 3	1933 +/- 101	1328 +/- 169	1461 +/- 154	F(2,59)=6.29 P<.01