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Abstract

Objective: It is widely assumed that glucocorticoids represent a primary mechanism through which exposures to adversity and maternal psychological distress shape prenatal developmental trajectories of both mother and fetus. However, despite repeated investigations and the fact that prenatal cortisol has been reliably linked to developmental outcomes, the empirical evidence supporting an association between prenatal cortisol and maternal distress are scarce. In this study, a novel approach to assess links between maternal prenatal psychological distress and gestational cortisol profiles, General Growth Mixture Modeling (GGMM), was applied.

Methods: Measures of pregnancy anxiety, perceived stress, state anxiety and depressive symptoms as well as plasma samples (for determination of cortisol) were collected four times during pregnancy from 250 women.

Results: Using GGMM, three cortisol trajectory groups were identified including a typical group (n=199) that exhibits the expected steady increase in cortisol throughout gestation; a steep group (n=31) displaying an accelerated increase in cortisol over the course of pregnancy relative to the typical group; and a flat group (n=20) with relatively higher cortisol levels early in pregnancy that plateau mid gestation. Women reporting the highest distress scores exhibited trajectories expected to be associated with the least optimal developmental outcomes (flatter trajectories characterized by relatively higher levels early in gestation and lower levels late).

Conclusions: These findings suggest that psychological distress during pregnancy is associated with unique prenatal cortisol profiles and support further examination of this link, to enable continued evaluation of a plausible biological pathway by which maternal psychological distress programs fetal development.

*Keywords: Prenatal, Cortisol, Distress, Pregnancy, Fetal Programming, Anxiety, Depression, Glucocorticoids, General Growth Mixture Modeling (GGMM)*

The prenatal period is a sensitive window of neurological development for both mother and fetus, characterized by bidirectional endocrine influences that prime the maternal brain for the demands of motherhood and that simultaneously shape the central nervous system (CNS) of the developing fetus (Glynn & Sandman, 2011). Cortisol (the primary glucocorticoid (GC) in humans) is a steroid hormone and end product of the hypothalamic pituitary adrenal (HPA) axis that is intimately involved in regulating prenatal developmental trajectories. Over the course of a typical human pregnancy, maternal cortisol increases two to four fold, reaching concentrations by the end of gestation similar to those of the hypercortisolism observed in Cushing's syndrome (Mastorakos & Ilias, 2003). These increasing levels play an essential role in maintenance of intrauterine homeostasis, development of vital organ systems in the fetus (including the lungs, liver and CNS), and in the onset of maternal behaviors (Glynn, Howland, & Fox, 2018; Howland, Sandman, & Glynn, 2017; Moisiadis & Matthews, 2014a).

Because of their stress sensitive nature, coupled with their involvement in maternal and fetal development, GCs are hypothesized to represent a primary mechanism through which exposures to adversity and maternal psychological distress could alter timing of delivery and affect developmental trajectories (Challis et al., 2005; Harris & Seckl, 2011; Moisiadis & Matthews, 2014a, 2014b; McGowan & Matthews, 2018). However, the relative lack of evidence demonstrating associations between maternal psychological distress and GCs, has led some to advocate reevaluating the utility of such theoretical models (c.f. O'Donnell & Meaney, 2016). Still, it is possible that the lack of demonstrated concordance may be attributable to limitations of commonly-used methodological approaches in cortisol measurement – specifically to the fact that the vast majority of studies collect a single biological sample (sometimes at multiple gestational time points) and then examine these single values or the average of these values with indicators of distress or adversity (Giesbrecht, Bryce, Letourneau, Granger, & APrOn study Team, 2015; Glynn, Davis, & Sandman, 2013; Schetter & Glynn, 2011). Some have further suggested that more comprehensive approaches (e.g. assessment of diurnal variation or analyses which allow consideration of comprehensive gestational trajectories) may provide corroboration for the role of cortisol in timing of parturition and prenatal programming of fetus and

mother, a view that is gaining increasing empirical support (Cherak, Giesbrecht, Metcalfe, Ronksley, & Malebranche, 2018; Giesbrecht et al., 2015; Glynn, 2010; Kane, Schetter, Glynn, Hobel, & Sandman, 2014; O'Connor et al., 2014; Swales et al., 2018). Building upon these studies and employing more comprehensive and nuanced measurement of prenatal cortisol, in the present study, a novel approach is applied (General Growth Mixture Modeling), which allows the identification of unique subpopulations in prenatal cortisol trajectories, to assess links between maternal prenatal psychological distress and gestational cortisol profiles.

## Methods

### Study Overview

Pregnant women were recruited from clinics in Orange County California, associated with the University of California, Irvine Medical Center based on the following criteria: (1) English speaking, (2) current intrauterine-singleton pregnancy, (3) over the age of 18, (4) no drug use or smoking, and (5) free of any conditions that may dysregulate neuroendocrine functioning. Psychosocial interviews were conducted and blood samples were obtained four times during gestation (T1: $M$ = 15.42 wks, $SD$ = .92 wks, range 13.29 to 18.00; T2: $M$ = 19.70, $SD$ = 1.00, range 17.00 to 22.86; T3: $M$ = 25.69, $SD$ = 1.00, range 23.14 to 29.00; and T4: $M$ = 31.10, $SD$ = .85, range 29.14 to 34.14*).* All study procedures were reviewed and approved by the University of California, Irvine Institutional Review Board. Written and informed consent was obtained from all participants.

### Participants

The final sample of 250 participants used in analyses were ethnically diverse with 43.5% Caucasian, 29.8 Latina, 8.6% Asian, 12.9% multi-ethnic and 5.1% other and had a mean age at delivery of 29.4 years. Five participants were excluded from analyses because their trajectory groups were too small for analysis (both n's < 5; See results and supplement for more details). Two additional participants were not included in the analyses due to missing psychological data. See Table 1 for the demographic profile of this cohort.

### Study Measures

**Plasma Cortisol**. Blood samples (20 ml/draw) were withdrawn by antecubital venipuncture into EDTA (purple top) vacutainers. EDTA vacutainers were chilled on ice immediately and Aprotinin (Sigma Chemical Co., St. Louis, MO) was added at 500 KIU/ml blood. Samples were then centrifuged at 2000 x g (15 min). Plasma was decanted into polypropylene tubes and stored at -80 °C until assayed. Plasma cortisol levels were determined with a competitive binding solid phase enzyme-linked immunosorbent assay as described previously (Glynn, 2010).

**Measures of Psychological Distress**. Maternal psychological distress was measured with widely-used, reliable and valid measures of pregnancy anxiety (Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999), state anxiety (State-Trait Personality Inventory; Spielberger, 1979), perceived stress (Perceived Stress Scale; Cohen, Kamarck, & Mermelstein, 1983) and depressive symptoms (Center for Epidemiologic Studies – Depression Scale; Santor & Coyne, 1997). Because levels of psychological distress are relatively stable across gestation (refer to Table S1 to see means for each of the four measures at each gestational assessment) and because we did not have timing specific hypotheses for relations with cortisol trajectories, we created a prenatal composite variable which constituted the mean across gestation for each of the four measures.

**Obstetric Risk** A dichotomous variable was created based on the presence or absence of at least one prenatal complication (Hobel, Hyvarinen, Okada, & Oh, 1973; Hobel, Youkeles, & Forsythe, 1979). Complications included infection, preeclampsia, oligohydramnios, polyhydramnios, intrauterine growth restriction, anemia, diabetes, vaginal bleeding, placenta abruptio, premature rupture of membranes, and cerclage.

**Statistical Analyses**

General Growth Mixture Modeling (GGMM) using MPlus version 6.12 (Muthén & Muthén, 2012) was used to identify unique prenatal plasma cortisol trajectories. The GGMM framework uses latent class analysis to allow for multiple subpopulations to occur in trajectories of longitudinal data. Group number selection was guided by the Akaike and Bayesian Information Criteria (AIC and BIC) and the *p* value for the Parametric Bootstrapped Likelihood Ratio Test (BLRT; McLachlan & Peel, 2000). Smaller values of AIC and BIC indicate better fit. The BLRT provides a comparison

for a model with k vs. k-1 classes (with k-l model serving as a null hypothesis); thus a significant value indicates the k class model is preferred to the k-1 class model. Non-significant values indicate the k-1 class model is preferred. The present models allowed for quadratic growth, and quadratic variance of the model was constrained to zero. The final solution was accepted only if the best log likelihood was replicated across several starting values.

Based on the AIC, BIC and LRT parameters (Table S2), the five-group solution was selected as optimal (See Figure S1 for group cortisol trajectories for all 5 groups and Table S3 for parameter estimates). Although the BIC increased slightly when moving from a four to a five-group model, the AIC continued to improve, the entropy (.86) is relatively strong (indicating adequate classification of individuals into groups) and the BLRT suggests that adding a fifth group to the model significantly improved fit Table S1). The average latent class probability was adequate, ranging from .74 to 1. The six-group model is clearly not an improvement over the five-group model (See Table S2).

Potential covariates were identified based on previously established predictors of HPA-axis function and included: maternal education, age, race/ethnicity, parity, household income, cohabitation with the baby's father, prepregnancy BMI, obstetric risk and infant sex. Maternal cohabitation status, parity, race/ethnicity and maternal age were included as covariates in further analysis because they related to cortisol trajectory group membership at $p < .10$ (see Table 1). One-way ANOVAs were additionally computed to ensure that trajectory groups were not reflective of time of day of sample collection. There were no group differences in time of sample collection at any gestational assessment (All F's <2.4, *p's* >.09), suggesting that group differences in plasma cortisol and trajectories were not due to time of sampling.

Differences between trajectory groups in cortisol levels at each gestational time point were assessed with analysis of covariance (ANCOVA), adjusting for gestational week and time of sample collection. Multivariate analyses of variance (MANOVA and MANCOVA) was used to examine links

between cortisol trajectory group and psychological distress. All post-hoc analyses were conducted with the Bonferroni correction.

## Results

*Cortisol Trajectory Groups*

Our analyses focused on three unique prenatal cortisol trajectory groups (see Figure 1). The demographic profiles for each group are presented in Table 1. The "typical group" (n=199) is characterized by a cortisol profile which was relatively low early in gestation and rose steadily into late gestation. The "steep group" (n=31), also exhibited relatively low levels of cortisol early in gestation, but had an accelerated rise across pregnancy. The "flat group" (n=20), had relatively high levels of cortisol early in gestation and plateaued in mid gestation. ANCOVAs revealed differences in cortisol among groups at weeks 15, 19, 25 and 31 weeks (all p's < .001, F's > 35.57; see Table 1). Post-hoc tests indicated that the three groups differed from each other at every gestational time point (all *p*'s <.05) with one exception − the steep and flat groups were not different at 25 weeks' gestation (p = .36). Additionally, as expected, for each group there was a statistically significant increase in cortisol levels between the 15 and 31 week assessments (All t's > 64.9, *p's* <.001).

*Cortisol Trajectories and Psychological Distress*

The MANOVA revealed that psychological distress levels differed based upon cortisol group membership (Table 2; Wilks' Lambda $F$ (8, 488)=2.25, $p$<.00). Further, inspection of the univariate $F$ tests indicates that there are group differences observed for each measure of distress (state anxiety ($F$(2,242)=6.76, $p$<.00, $\eta_p^2$=.05; perceived stress ($F$(2,242)=3.46, $p$<.05, $\eta_p^2$=.03; pregnancy anxiety ($F$(2,242)=2.68, $p$=.07, $\eta_p^2$=.02 and depressive symptoms ($F$(2, 242)=5.56, $p$<.00, $\eta_p^2$=.04). As shown in Figure 2, the flat trajectory group exhibited higher levels of distress compared to the steep and typical trajectory group for each of the measures. Adjusting for identified covariates (maternal age, race/ethnicity, cohabitation status and parity) did not alter the pattern of results or conclusions about the

association between psychological distress and cortisol trajectory groups (Wilks' Lamda $F(8, 478)=2.14$, $p<.05$; see Table 2 for full MANCOVA model and Table S4 for ANCOVA models)

## Discussion

Our study identified three unique cortisol trajectory groups that were associated with maternal psychological distress during pregnancy. These findings highlight the potential utility of employing comprehensive methodologies, such as GGMM, that take into account trajectories of prenatal stress physiology. They also raise the possibility that the link between psychological distress and potential physiological processes shaping fetal development (including cortisol) have not been consistently documented previously because of methodological approaches that fail to describe profiles across gestation, and instead focus only on measurements at a single point or averages over several time points. In sum, the findings corroborate the call for more comprehensive approaches to gestational cortisol measurement (Giesbrecht et al., 2015; Howland et al., 2017; Schetter & Glynn, 2011) and are consistent with the broader hypothesis that GCs mediate links between adversity and maternal and fetal development.

The strengths of this investigation include the relatively large sample size, the broad, dimensional assessment of psychological distress and the repeated assessment of maternal cortisol that allowed the analyses of cortisol trajectory groups. Because this study is correlational, causal conclusions cannot be drawn, and it is not possible to ascertain whether or not the differences in prenatal GCs are a reflection of maternal distress, whether GC profiles are determining maternal distress or whether bidirectional influences account for the observed associations. Another point of consideration is that the group differences in distress were largely attributable to the flat trajectory

group, which had a relatively small sample size (n=20); our confidence in the robustness of these findings will be increased when corroborating data from other studies is provided.

This study contributes to our understanding of the ways in which the interaction between maternal adversity and gestational biology relate to health and development of the mother and her child. Findings from both animal models and humans demonstrate that the nature and implications of prenatal GC exposures for both the pregnant woman and her fetus are dependent on the timing of these exposures (Glynn, 2010; Glynn, Howland, & Fox, 2018; Hamada & Matthews, 2019; Moisiadis & Matthews, 2014a). Early in gestation, the fetus is partially protected from maternal cortisol by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which oxidizes cortisol into its inactive form (Beitins, Bayard, Ances, Kowarski, & Migeon, 1973). However, as parturition nears, fetal exposure to cortisol is facilitated by a precipitous drop in 11β-HSD2 levels, allowing more maternal GCs to cross the placenta to ensure maturation of critical development of organ systems, including the CNS (Ishimoto & Jaffe, 2010; Matthews, 2000; Seckl & Holmes, 2007; Shearer, Wyrwoll, & Holmes, 2019). Consistent with this normative pattern of fetal cortisol exposures, there is increasing evidence that relatively high maternal GCs in early gestation are associated with less optimal fetal and child development (Bergman, Sarkar, Glover, & O'Connor, 2010; Davis & Sandman, 2010; Glynn & Sandman, 2012; Sandman, Glynn, & Davis, 2013); whereas, elevations later in gestation have been linked to salutary influences in the offspring (Davis, Head, Buss, & Sandman, 2017; Davis & Sandman, 2010; Ram, Howland, Sandman, Davis, & Glynn, 2019; Thompson, Morgan, Unger, & Covey, 2017). Similarly, elevated late gestational maternal cortisol is associated with benefits for the mother such as enhanced infant-directed affiliation in non-human primates (Bardi, French, Ramirez, & Brent, 2004).

It is notable that the women who experienced the least psychological distress (the steep group) also exhibited the cortisol profiles that would be the most advantageous for maternal and fetal development (relatively low early with a pronounced increase late). In contrast, the women who reported the highest levels of psychological distress (the flat group), exhibited cortisol trajectories that

would be associated with the least optimal developmental outcomes (relatively high early in gestation with a plateau later). Taken together, these observations strongly support further examination of the link between maternal distress and prenatal cortisol trajectory profiles, to enable investigation of a plausible biological pathway by which maternal psychological distress may program fetal development.

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**Figure 1**. *Plasma Cortisol Trajectory Group*

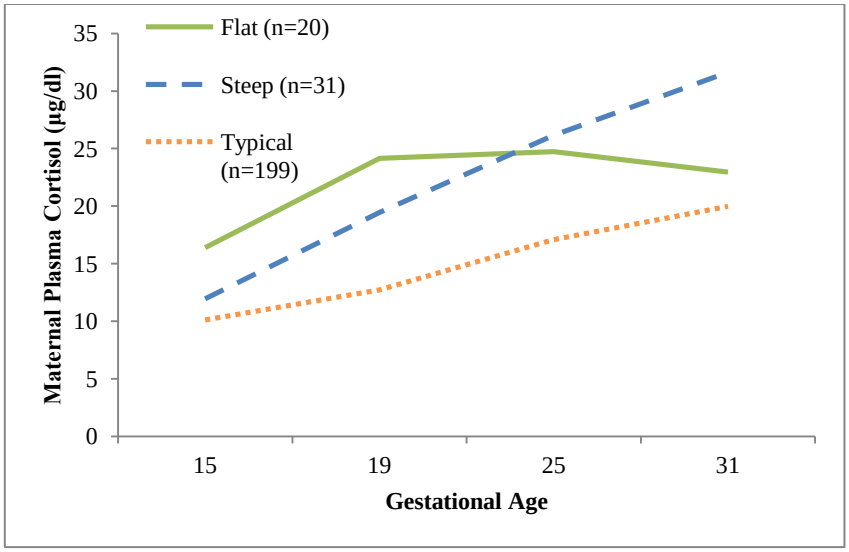


**Figure 2.** *Pairwise comparisons (Bonferroni corrected) revealed differences in psychological distress related to cortisol trajectory group membership. *p<.05 **p<.01 ***p.001*

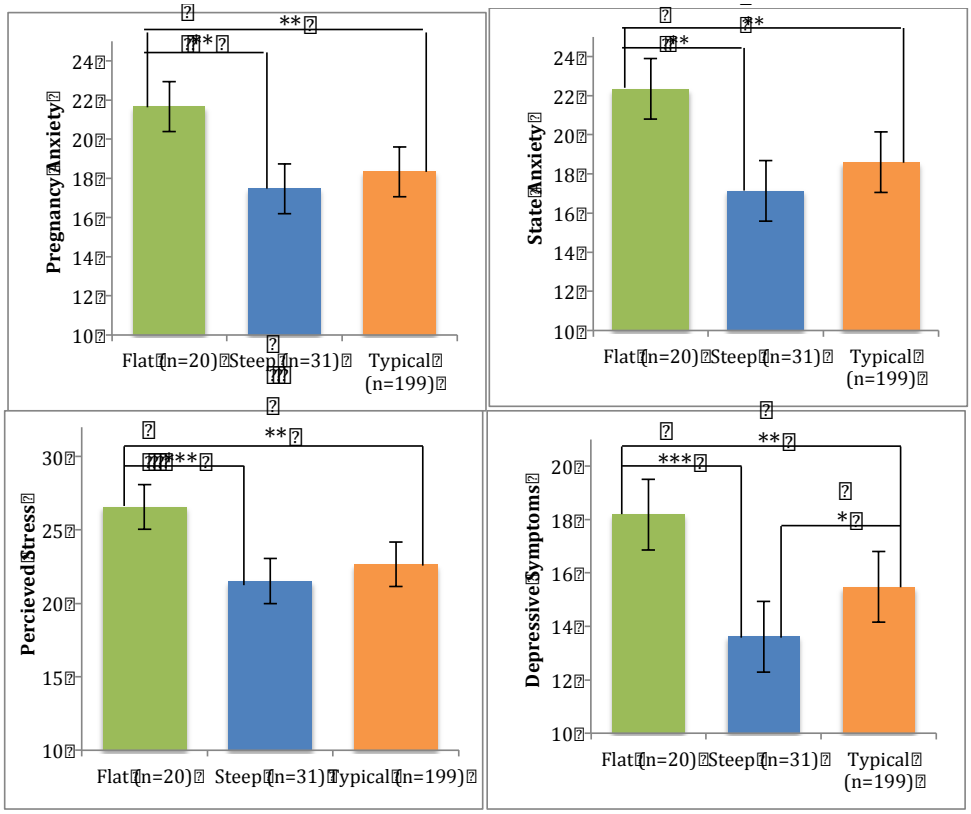


**Table 1**. *Participant characteristics*

| | | *Full Sample n=257* | *Atypical Flat n=20* | *Atypical Steep n=31* | *Typical n=199* | *Group differences p* |
|---|---|---|---|---|---|---|
| Maternal age at delivery (mean years) | | 29.41 (5.52) | 26.05 (5.08) | 29.67 (5.00) | 29.75 (5.55) | .02 |
| Maternal race (%) | | | | | | |
| Caucasian, non-Hispanic | | 43.5 | 30.0 | 46.7 | 44.7 | .01 |
| Latina | | 29.8 | 25.0 | 33.3 | 29.6 | |
| Asian | | 8.6 | 15.0 | 10.0 | 7.5 | |
| Multi-ethnic | | 12.9 | 20.0 | 10.0 | 13.1 | |
| Other | | 5.1 | 10.0 | 0.0 | 5.0 | |
| Maternal education (%) | | | | | | |
| High school or less | | 17.6 | 25.0 | 13.3 | 17.1 | .71 |
| Some college, Vocational degree | | 44.0 | 40.0 | 46.7 | 44.2 | |
| 4-year college degree | | 24.4 | 30.0 | 26.7 | 23.6 | |
| Graduate degree | | 14.0 | 5.0 | 13.3 | 15.1 | |
| Annual household income (mean USD) | | 58,175 (34,421), | 50,921 (37,530) | 65,345 (3,2132) | 57,462 (34,431) | .34 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cohabitation with father (% yes) | | 87.5 | 70.0 | 90.3 | 88.4 | .05 |
| Parity (% primiparious) | | 46.7 | 85.0 | 38.7 | 42.7 | .09 |
| % with any obstetric risk factor | | 29.2 | 15.0 | 35.5 | 29.6 | .28 |
| Child sex (% female) | | 50.2 | 57.9 | 51.6 | 49.2 | .76 |
| Infant birth weight | | 3,319 (594.37) | 3,151 (721.82) | 3,295 (352.54) | 3,349 (603.05) | .36 |
| Gestational age at birth (GAB) | | 39.0 (2.2) | 38.8 (3.5) | 38.7 (1.4) | 39.0 (2.2) | .98 |
| Apgar Score (5 min) | | 8.93 (.48) | 9.0 (.00) | 8.97 (.32) | 8.92 (.52) | .69 |
| Plasma Cortisol (µg/dl) | | | | | | |
| 15 weeks | | 10.81 (3.81) | 16.41 (3.81) | 11.94 (2.24) | 10.11 (3.34) | .00 |
| 19 weeks | | 14.55 (5.23) | 24.15 (3.34) | 19.45 (3.18) | 12.73 (3.88) | .00 |
| 25 weeks | | 19.08 (6.30) | 24.73 (5.14) | 26.15 (5.06) | 17.08 (4.72) | .00 |
| 31 weeks | | 21.79 (5.84) | 22.97 (3.14) | 31.63 (3.42) | 19.97 (3.94) | .00 |
| Psychological Measures | | | | | | |
| PSS | | 2.27 (.60) | 2.66 (.73) | 2.15 (.56) | 2.27 (.58) | .01 |
| Pregnancy Specific Anxiety | | 1.84 (.49) | 2.17 (.49) | 1.75 (.35) | 1.83 (.50) | .01 |
| STAI | | 1.86 (.49) | 2.24 (.64) | 1.71 (.47) | 1.86 (.46) | .01 |
| CESD | | 1.7 (.49) | 2.02 (.60) | 1.51 (.38) | 1.72 (.48) | .01 |

Interpretation of the statistically significant omnibus p-values: Women in the atypical flat group were both younger and more likely to be primiparous than women in the other two groups (all p's < .05). Women in the atypical flat group also were less likely to be cohabiting with the baby's father than those in the typical group ($p < .05$) or the atypical Steep group ($p = .07$). Although the chi-square model was statistically significant for race/ethnicity, this can be attributed to differences among the groups in the overall distribution of race/ethnic group membership – probing for differences with additional chi-square models for specific race/ethnic groups did not yield statistically reliable results. Group differences for plasma cortisol and the psychological measures are described in the results section.

**Table 2.** *Multivariate Analysis of Variance Assessing Associations between Cortisol Trajectory Group and Psychological Distress*

| Variable | *Wilks' Lambda* | *F* | *df* | *p* | $\eta_p^2$ |
|---|---|---|---|---|---|
| **MANOVA** | | | | | |
| (intercept) | .10 | 561.69 | 4 | .00 | .90 |
| Cortisol Group | .92 | 2.60 | 8 | .01 | .04 |
| **MANCOVA** | | | | | |
| (intercept) | .52 | 55.21 | 4 | .00 | .48 |
| Cortisol Group | .93 | 2.14 | 8 | .03 | .04 |
| Cohabitation | .89 | 7.63 | 4 | .00 | .11 |
| Race/Ethnicity | .98 | 1.49 | 4 | .21 | .02 |
| Age | .96 | 2.52 | 4 | .04 | .04 |
| Parity | .90 | 6.59 | 4 | .00 | .10 |