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Maternal prenatal cortisol trajectories predict accelerated growth in infancy

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Abstract

Higher maternal cortisol in pregnancy has been linked to childhood obesity. Much of the previous research has been limited in that cortisol in pregnancy is only measured at one time-point, precluding the ability to examine critical timing effects of prenatal maternal cortisol. To fill this gap, this longitudinal study measured maternal plasma cortisol at 15, 19, 25, and 31 weeks of pregnancy, and assessed infant body mass index percentile (BMIP)[1] at birth, 3, 6, 12, and 24 months in 189 mother-infant pairs. Three distinct patterns of maternal cortisol in pregnancy (typical, steep, and flat trajectories) were identified using general growth mixture modeling (GGMM)[2] and then used to predict child growth patterns using multilevel modeling. Infants of mothers who had flat cortisol trajectories, characterized by relatively high cortisol in early gestation that plateaus by mid-gestation, experienced more rapid increases in BMIP from birth to 6 months, and had higher BMIPs at 3 and 6 months, than infants whose mothers had the typical slow cortisol rise over gestation, or steep (rapidly accelerating) trajectories. These results suggest that it is not just the total amount of maternal cortisol in pregnancy that shapes early infant growth, but instead the timing and trajectory of prenatal cortisol exposure. To better understand the early

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[1]Body mass index percentile.

[2]General growth mixture modeling.

origins of obesity risk, future research is needed to investigate the factors that shape mothers' prenatal cortisol trajectories.

1. Introduction

Childhood obesity has tripled in the United States since the 1970s (Fryar et al., 2014), such that nearly 1 in 5 children and adolescents in the US are obese (Hales et al., 2017). Childhood overweight and obesity are risk factors for chronic health conditions such as diabetes, cancer, and cardiovascular disease (Sahoo et al., 2015). Moreover, children with obesity are at greater risk of poor body image and depressive symptoms (Daniels et al., 2005). The underlying causes of this health crisis are complex, influenced by interactions among genetic, nutritional, behavioral, and environmental factors (Sahoo et al., 2015). The current paper focuses on how prenatal risk factors shape children's obesity risk.

Developmental origins of disease models posit that environmental signals during sensitive periods of development, including gestation and early infancy, shape the disease risk of the organism throughout the lifespan (Barker, 2004; Gluckman et al., 2008). It is widely hypothesized that exposure to maternal glucocorticoids (cortisol in humans) represents a primary mechanism programming offspring health and development, including, obesity (Gluckman et al., 2008). In healthy human pregnancy, maternal cortisol levels increase two to four fold across gestation (Dörr et al., 1989). Due to the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) and other regulatory molecules, it is estimated that 10–20 % of maternal cortisol crosses the placental barrier and that cortisol of maternal origin accounts for 40–50 % of circulating fetal cortisol (Gitau et al., 1998). Decades of research with animal models supports the fundamental role of prenatal glucocorticoid exposures in offspring development, including growth and metabolism (Ballard and Ballard, 1972; Seckl and Holmes, 2007). For example, rodents whose mothers are administered glucocorticoids during pregnancy give birth to pups that are smaller at birth, exhibit rapid weight gain during early infancy, and have higher percentages of body fat when they reach adulthood, particularly in food rich environments (Maniam et al., 2014; Reynolds, 2010). Few studies in humans have explicitly tested the role of glucocorticoids in developmental origins of obesity models, and, with few exceptions (Hahn-Holbrook et al., 2016; Laugesen et al., 2022; Stout et al., 2015; Street et al., 2012), research has predominantly overlooked postnatal growth, focusing instead on how cortisol in pregnancy impact infant birth weight alone (Ali Khan et al., 2011; Cherak et al., 2018).

Low birth weight is a well-established risk factor for obesity in later life ((Calkins and Devaskar, 2011; Cianfarani et al., 1999; Nobili et al., 2008). In humans, infants exposed to synthetic glucocorticoids in late pregnancy are smaller at birth (Ali Khan et al., 2011; Davis et al., 2009), and a recent meta-analysis of 9 studies of 1606 maternal-fetal dyads concluded that higher maternal salivary cortisol over the day during pregnancy was associated with

lower birth weight infants (Cherak et al., 2018). Animal models demonstrate that it is not only the absolute amount of prenatal cortisol exposure that programs offspring metabolism, but also the timing of those exposures (Seckl, 2001). Administration of synthetic glucocorticoids to sheep, for example, show that high doses in early pregnancy, which are physiologically atypical, are more detrimental to later metabolic disease risk than are high doses of cortisol administered in late pregnancy when cortisol concentrations normatively are high (Gatford et al., 2000). Consistent with these findings in experimental animal models, there is increasing evidence in humans that relatively high maternal cortisol in early gestation is associated with less optimal fetal and child development (Bergman et al., 2010; Davis and Sandman, 2010; Glynn and Sandman, 2012; Sandman et al., 2013); whereas, elevations later in gestation, which are necessary for fetal organ maturation and preparation for labor and delivery (Ballard and Ballard, 1972), have been linked to salutary influences in the offspring (Davis et al., 2017; Davis and Sandman, 2010; Ram et al., 2019; Thompson et al., 2017). For example, elevated early gestation maternal serum cortisol predicted child fat mass index at 5 years among girls in a large prospective study (Van Dijk et al., 2012). Therefore, it is feasible that, patterns of cortisol across gestation may predict both birth weight and postnatal growth.

It is not birth weight alone that predicts obesity risk, but rather the combination of small size at birth and the velocity of growth after birth (Calkins and Devaskar, 2011; Cianfarani et al., 1999; Nobili et al., 2008). The post-natal 'Growth Acceleration' hypothesis posits that any upward centile crossing (for weight or length), regardless of its cause, raises infants' risk for subsequent obesity and cardiovascular disease (Singhal and Lucas, 2004). In support of this hypothesis, a meta-analysis of 47, 661 participants from 10 studies concluded that a one standard deviation upward centile crossing for weight or length in the first year confers a two-fold higher risk of childhood obesity and a 23 % higher risk of adult obesity (Druet et al., 2012). Thus, studies that identify predictors of early life growth profiles can contribute to understanding of the early origins of obesity risk. One study examined maternal prenatal cortisol with early postnatal growth trajectories in 60 mother-infant pairs and found higher cord blood cortisol was associated with more rapid childhood weight gain across the first 5 years of life (Street et al., 2012). Despite the dearth of research in humans, a comparative analysis of 719 studies of 21 mammalian species concluded that, across mammalian taxa, excessive prenatal exposure to glucocorticoids leads offspring to grow faster at the expense of metabolic processes that promote long-term health (Berghänel et al., 2017).

The present study was designed to test the relation between the maternal prenatal cortisol profiles and early childhood growth trajectory in humans. Plasma cortisol samples were collected from women at 4 time-points during pregnancy and infant growth measurements were obtained at birth and at 3, 6, 12, and 24 months postpartum. We identified patterns of prenatal cortisol using general growth mixture modeling (GGMM), then employed growth curve modeling to assess whether these prenatal cortisol profiles predict child body mass index percentile (BMIP) trajectories. We predicted that infants exposed to atypically high cortisol, particularly during early pregnancy, would be most likely to display accelerated growth.

2. Methods

2.1. Participants

Pregnant women were recruited from obstetrics clinics in Southern California and enrolled prior to 16 gestational weeks (M = 15.47, SD = 0.91) in a longitudinal study examining the influence of the prenatal environment on early development. To be eligible to participate, mothers had to be over the age of 18, English-speaking, have a single intrauterine pregnancy. Women were excluded for use of alcohol, tobacco, illicit drugs, cervical or uterine abnormalities, use of corticosteroid-based medications during pregnancy, and diagnosis of disease influencing neuroendocrine function.

Prenatal cortisol trajectory groups (see Section 3.1 below for details) were determined using the full sample with maternal cortisol data (N = 257). Mother-child dyads were excluded from the growth analyses if they met any of the following criteria: mother dropped out of study prior to or at delivery (n = 8), infant was born preterm (before 37 weeks gestation) (n = 22), were missing child length and/or weight for at least 4 out of the 5 postnatal time points (n = 33), or were classified in cortisol trajectory groups that were too small to use in postnatal child growth analyses (n = 5), leaving a final sample of 189 for the current paper. Sample characteristics are summarized in Table 1. Those participants missing child anthropometric data were of lower socioeconomic status and their children were smaller at birth than those that completed at least one postnatal follow-up. These groups did not differ in race/ethnicity or whether they were cohabitating with the child's biological father.

2.2. Procedures

Maternal plasma was collected at 15 weeks (Mean age = 15.47, SD = 0.91), 19 weeks (M = 19.69, SD = 1.02), 25 weeks (M = 25.69, SD = 0.98), and 31 weeks' (M = 31.09, SD = 0.84) gestation. Child length and weight were assessed at birth, 3 months (M = 3.06, SD = 0.26), 6 months (M = 6.04, SD = 0.29), 12 months (M = 12.08, SD = 0.25), and 24 months (M = 24.12, SD = 0.41) months of age. Information about the pregnancy and birth outcomes were collected from medical records. Maternal demographics and breastfeeding practices were obtained through maternal interviews.

2.3. Maternal measures

2.3.1. Maternal plasma cortisol concentration—Maternal venous blood samples (20 mL) were collected via antecubital venipuncture. Maternal blood samples were collected at least one hour after the participant had eaten and time of day at sample collection was recorded (15 weeks' gestation, Mean time of day = 13:44 h, SD = 1:40, range 9:16–16:26; 19 weeks, Mean = 13:50, SD = 1:49, range 9:27–17:10; 25 weeks, Mean = 13:33, SD = 1:29, range 8:20–17:01; 31 weeks, Mean = 10:10, SD = 17:16). Blood was drawn into Ethylenediamine tetraacetic acid (EDTA) chilled vacutainers treated with aprotinin (500 KIU/mL; Sigma Chemical Company, St Louis, MO, USA) and then was immediately centrifuged at $2000 \times g$ for 15 min. Plasma was extracted and aliquoted in polypropylene tubes and stored at − 70 C until assayed.

Plasma levels of total cortisol were determined using a commercially available competitive binding, solid-phase, enzyme-linked immunosorbent assay kit (IBL America, Minneapolis, MN). The inter-assay and intra-assay coefficients of variance are reported as less than 8 %, and the minimum detectable level of the assay was 0.25 μg/dL. Plasma cortisol concentrations were modestly correlated with the time of day of sample collection at each gestational assessment (15 weeks: $r = -0.223$, $p = .001$; 19 weeks $r = -0.144$, $p = .039$; 25 weeks $r = -0.200$, $p = .004$; 31 weeks $r = -0.147$, $p = .040$).

2.3.2. Maternal anthropometrics—Maternal height and weight (at 15 and 37 weeks) were measured in the laboratory. Maternal weight prior to pregnancy (obtained via self-report) was used to calculate pre-pregnancy body mass index (BMI). Gestational weight gain was calculated by subtracting maternal weight at 15 gestational weeks from maternal weight at 37 gestational weeks.

2.3.3. Demographic factors—Maternal demographic information was collected via structured interview and included age, race/ethnicity, parity, gravida, marital status, annual household income, education level, and cohabitation status with the child's biological father.

2.4. Pregnancy and birth outcomes

Gestational age at birth (GAB) was calculated according to standard American College of Obstetricians and Gynecologists (ACOG) guidelines (ACOG, 2009), which uses a combination of last menstrual period and an ultrasound conducted prior to 20 gestational weeks. Medical record review was conducted to assess birth outcomes, including birth weight and length.

2.5. Child measures

2.5.1. Child anthropometrics—Child weight and length were collected at five time points between birth and 24 months of age – birth, 3, 6, 12, and 24 months (see Table 2 for raw means and standard deviations of child weight, length, and BMIP at each time-point). Mothers undressed their children, then weight was measured on a digital scale (Midmark, Versailles, OH) and length was either determined while the child lay in a supine position (through 12 months of age) or standing (at 24 months). Child BMIP was used as opposed to other anthropometric measures, such as raw BMI or weight-for-length, because it accounts for differences in growth trajectories for boys vs girls. Child BMIP was calculated to index child body composition using an SPSS macro provided by the World Health Organization (WHO). This macro uses the Latent Moderated Structural (LMS) model to fit the child's length and weight to standard WHO growth curves and generates a child's BMI z-score standardized for age and sex (Cole and Green, 1992; Organization, 2006). For ease of interpretation, these z-scores were converted to percentiles.

2.5.2. Breastfeeding and introduction of complementary food—At each postpartum assessment, mothers were asked about the initiation and cessation of breastfeeding and the age at which solid foods were introduced into the child's diet.

2.6. Data analytic strategy

First, GGMM with latent class analysis was used to detect unique patterns of prenatal plasma cortisol trajectories. GGMM allows for the detection of meaningful subgroups that exhibit distinct growth trajectories (in our case, gestational cortisol profiles) without imposing the assumption that the groups are drawn from the same population. 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, 2000). All GGMM analyses were run using MPlus version 6.12.

Second, multilevel growth curve modeling was used to assess whether distinct cortisol trajectories in pregnancy (identified by GGMM) predicted changes in infant BMIP from birth to 2 years of age. Multilevel modeling allows for the determination of between-person differences among within-person trajectories and offers advantages over other statistical tools for the evaluation of longitudinal data because it accounts for shared variance on within-individual measurements and can accommodate missing values (Raudenbush and Bryk, 2002). Cortisol trajectory groups were included as level 2 predictors of BMIP at birth and changes in BMIP over the first 2 years of life (level 1). Shared variance of within-subject changes in BMIP was addressed by using a covariance structure with random intercepts and slopes. All continuous predictors were z-scored ([participant's raw score – population mean]/population standard deviation) before being entered into multilevel models to aid model interpretation. All multilevel modeling analyses were conducted in SPSS 18 using the "mixed" function.

Finally, we conducted follow-up analysis to test whether plausible covariates, such as gestational age at birth, might explain any observed association between cortisol trajectories and infant BMIP. For example, it is possible that cortisol trajectories in pregnancy could predict infant BMIP though gestational age at birth, because cortisol in pregnancy has been shown to predict GAB, which in turn, has been shown to predict infant BMIP. Other potential covariates tested included breastfeeding duration, weight gain in pregnancy, pre-pregnancy BMI, and demographic variables including education, and socioeconomic status (see Table S3 in Supplemental materials for analysis testing the relationship between demographic and health factors and infant BMIP). Any covariate that predicted infant BMIP were included as covariates in follow-up multivariate modeling. In addition, we also statistically adjusted for time-of-day of sample collection.

3. Results

3.1. Identifying distinct cortisol trajectories in pregnancy

GGMM identified five unique gestational cortisol trajectories (see Peterson et al., 2020) and Supplemental materials for details). As can be seen in Fig. 1, the group characterized as typical (n = 151) exhibited the expected steady increase in plasma cortisol throughout gestation. Two groups (i.e., a steep and a flat group) had atypical trajectories. The atypical steep group (n = 24) displayed a more dramatic increase in plasma cortisol throughout gestation relative to the typical group. Cortisol levels in the atypical flat group (n = 14), by contrast, were relatively high in early pregnancy and then plateaued during mid-gestation,

never exhibiting the late gestational peak seen in the typical and steep group. There were too few participants in the other two groups identified to justify statistical analysis (Ns = 2 & 3), therefore, these participants were excluded from further analyzes.

3.2. Modeling infant BMIP trajectories

Consistent with infant growth patterns in the US (Taveras et al., 2011), BMIP increased over the first 2 years of life for infants in this sample. Initial models suggested that a cubic growth curve model best described these changes in infant BMIP. The average BMIP at birth was 54 % (birth intercept: Coef = 0.538, SE = 0.019, t = 27.38, p < .001, 95 % CI = 0.50–0.577) and increased to 69 % by 2 years (intercept at 2 years: Coef = 0.69.1, SE = 0.02, t = 32.72, p < .001, 95 % CI = 0.649–0.732). On average, BMIP in the sample remained relatively stable for the first 6 months of life (linear slope: Coef = − 0.01, SE = 0.01, t = − 1.145, p = .25, 95 % CI = − 0.03 to 0.01) but then increased from 6 months to 1 year (quadratic slope: Coef = 0.0025, SE = 0.0093, t = 2.409, p = .017, 95 % CI = 0.0004–0.004) with growth slowing slightly from 1 to 2 years (cubic slope: Coef = − 0.00007, SE = 0.00029, t = − 2.619, p = .01, 95 % CI = − 0.00013 to 0.000019).

3.3. Do cortisol trajectories in pregnancy predict infant BMIP trajectories?

Prenatal cortisol trajectory group membership did not predict BMIP at birth (ps > .47). However, infants exposed to flat cortisol trajectories during gestation experienced more rapid gains in BMIP from birth to 6 months compared to infants in the typical and steep cortisol groups (see Fig. 2; flat vs. typical group linear slope contrast: Coef = − 0.07, SE = 0.034, t = − 2.19, p = .029, 95 % CI = − 0.14 to − 0.007; flat vs. steep group slope contrast: Coef = − 0.108, SE = 0.041, t = − 2.61, p = .01, 95 % CI = − 0.19 to − 0.026). Infants exposed to flat cortisol trajectories in pregnancy also had significantly higher BMIPs at 3 and 6 months than infants in the typical and steep groups (ps < .05). After 6 months of age, infants in the typical and steep groups experienced greater BMIP gains compared to the flat group (flat vs. typical group slope contrast: Coef = 0.008, SE = 0.037, t = − 2.11, p = .035, 95 % CI = 0.0005–0.0156; flat vs. steep group slope contrast: Coef = 0.01, SE = 0.004, t = 2.47, p = .014, 95 % CI = 0.002–0.020). By 1 and 2 years, BMIP did not differ among the cortisol trajectory groups. The associations between cortisol at each time point in pregnancy and child BMIP are presented in Supplemental materials in Table S2. Higher cortisol in early pregnancy predicted greater increases in BMIP from 0 to 6 months (the association was statistically significant for cortisol at 19 weeks, with a trend in the same direction for cortisol at 15 weeks). Cortisol at 25 or 31 weeks did not predict infant BMIP or changes in infant BMIP.

3.4. Do confounding variables explain the association between prenatal cortisol trajectories and infant BMIP trajectories?

We ran models statistically adjusting for several possible confounds that predicted infant BMIP (see Table S3 in Supplemental materials). Specifically, infants tended to have higher BMIP across development if mothers had higher parity, pre-pregnancy BMI, more gestational weight gain, and higher gestational age at delivery (GAB). It is unlikely that any of these factors accounted for our primary findings because when included in our multilevel models they did not alter the pattern of results. Specifically, infants in the flat cortisol group

still had statistically greater increases in BMIP from 0 to 6 months compared to the infants in the steep and typical groups after statistically adjusting for parity, pre-pregnancy BMI, gestational weight gain, and GAB (adjusted flat vs. typical group linear slope contrast: Coef = − 0.08, SE = 0.035, t = − 2.17, p = .031, 95 % CI = − 0.16 to − 0.007; adjusted flat vs. steep group slope contrast: Coef = − 0.098, SE = 0.044, t = − 2.24, p = .03, 95 % CI = − 0.19 to − 0.012). Finally, time-of-day of sample collection did not differ between the flat, steep, and typical cortisol groups (15 weeks, F = 1.13, p = .327; 19 weeks, F = 0.36, p = .68; 25 weeks, F = 0.79, p = .457; 31 weeks, F = 1.74, p = .18; Means, SDs, and ranges of time-of-day of sample collection are reported in Section 2.3.1) and including time-of-day of sample collection in the growth curve models did not change the pattern of results.

4. Discussion

The current study adds to the evidence that fetal exposure to maternal cortisol may program offspring metabolism and early growth profiles. Specifically, we found that infants whose mothers had aberrant maternal cortisol trajectories characterized by high cortisol levels early in gestation and failure to show the typical cortisol increase later in pregnancy (flat group) were more likely to exhibit accelerated growth between birth and 6 months than infants exposed to the typical gradual or steep increases in cortisol over pregnancy. Because accelerated growth is a well-established risk factor for later disease and obesity risk (Druet et al., 2012; Ong and Loos, 2006; Singhal, 2017), our results suggest that infants whose mothers had atypical cortisol trajectories in pregnancy characterized by high levels early in gestation and failure to show the typical increase late, may be at higher risk for obesity in adulthood. This finding is consistent with previous research in ovine models suggesting early gestation may be a sensitive window for exposures to elevated cortisol. Further, they build on prior work by Van Dijk et al. (2012) showing that early gestational cortisol is associated with a higher child fat mass index at five years. Specifically, elevations in early gestation exerts more profound impacts on metabolic programming than do high cortisol exposures in late pregnancy (Gatford et al., 2000). Further, late gestation cortisol exposure is normative and necessary for typical maturation of the fetus. In line with this view, placental production of 11β-HSD-2, which partially shields the fetus from maternal cortisol by converting it to inert keto-products (Brown et al., 1996), rises with gestational age in humans, dropping off just before birth (Stewart et al., 1995), presumably so cortisol can facilitate organ maturation before delivery (Davis and Sandman, 2010; Glynn and Sandman, 2012; Stewart et al., 1995). Thus, fetuses whose mothers have flat cortisol trajectories may give the infants the experience a double dose of developmental insults, as they are exposed to aberrantly high cortisol in early gestation when they are relatively less protected, then they receive less of the essential peak exposures prior to birth that are necessary for organ maturation and preparation for labor and delivery.

Cortisol trajectories during pregnancy did not predict infant birth weight in this study. Some previous research has reported that maternal prenatal cortisol predicts infant birth weight (Cherak et al., 2018), while other studies report null results, or report that the association between cortisol and birth weight is rendered non-significant after including relevant covariates (see Cherak et al., 2018, for a review). Because the majority of previous studies have utilized simpler correlational methods, rather than GGMM analysis, to identify

unique cortisol trajectory profiles, we performed follow-up correlations to test whether plasma cortisol levels at each individual time-point predicted infant birth weight or BMIP at birth (see Table 3). Again, we observed null relations between plasma cortisol and either infant BMIP or weight at birth. There are several differences between the current and previous studies that could possibly explain the inconsistency. First, we measured total cortisol in plasma, whereas most previous studies have used salivary measures (Cherak et al., 2018). Second, unlike other studies, we did not include premature infants in our sample, which restricted the amount of variation in birth weight. Finally, although we collected multiple measures across gestation to capture overall prenatal exposure, we only measured cortisol once during the day. A recent meta-analysis of saliva cortisol found that studies were more likely to report associations between birth weight and cortisol when they took multiple measures of cortisol over the day (Cherak et al., 2018). Future research should simultaneously investigate the contributions of maternal cortisol to fetal growth on multiple timescales, including both diurnal and gestation-related variations. Future research is also needed to investigate the broader question of why some women have atypical cortisol trajectories in pregnancy. We preformed exploratory analyses to see how the flat, high, and typical cortisol groups differed in terms of demographic and health factors (see Table S4 in Supplemental materials). It was notable that mothers in the flat group were younger, had less income and education, were less likely to be living with the baby's father and more likely to be first-time mothers compared to the mothers in the high or typical groups. One plausible interpretation of these results is that the psychological stress of having fewer resources or being a first-time mother could be a risk factor for flat prenatal cortisol patterns. In line with this view, previous research has shown that mothers who self-report higher (compared to lower) levels of psychological distress in pregnancy are more likely to have abnormally flat cortisol trajectories in pregnancy (Peterson et al., 2020).

It is important to contextualize our findings in light of several limitations. For example, this study was not designed to establish causality; the possibility remains that factors other than prenatal cortisol program infant growth patterns, although animal models have demonstrated a causal link between glucocorticoid exposure and infant growth postpartum in rodents and primates (Maniam et al., 2014; Reynolds, 2010). In addition, although neither mothers' pre-pregnancy BMI nor weight gain in pregnancy accounted for our findings, the present study did not include comprehensive assessment of maternal and infant diet, both of which likely contribute to infant growth trajectories. Finally, this study lacked the statistical power to examine important moderators like infant sex. Future larger studies should examine if the effects of prenatal maternal cortisol on infant growth differ for male and female infants.

5. Conclusion

This research suggests that fetal exposure to atypical maternal cortisol trajectories may be a risk factor for accelerated growth and later metabolic dysregulation. These findings add to the growing body of research suggesting that there are sensitive periods for the effects of prenatal cortisol exposure that contribute to later metabolic program ming and disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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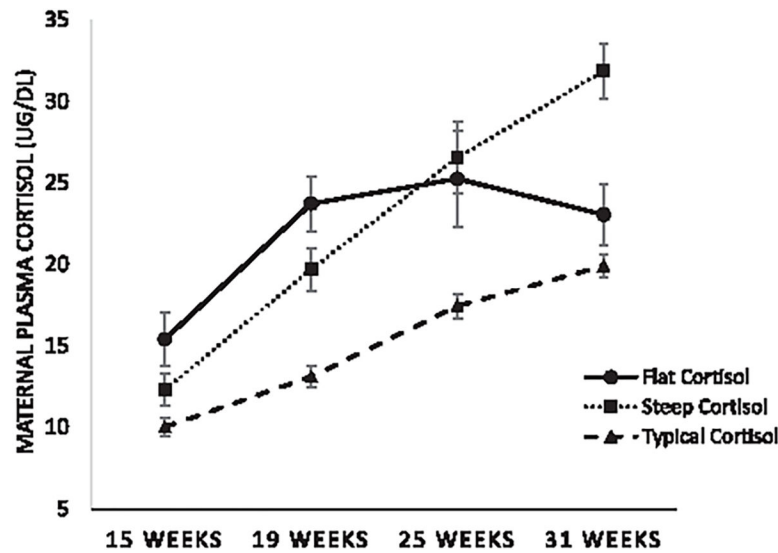
Fig. 1. Prenatal cortisol trajectory groups identified by GGMM analysis.

The group characterized as typical (n = 151) exhibited the expected steady increase in plasma cortisol throughout gestation, and had significantly lower cortisol than the flat and steep groups at all four time points. Two groups, a steep and a flat group, had atypical trajectories. The atypical steep group (n = 24) displayed a more dramatic increase in plasma cortisol throughout gestation relative to the typical and flat groups. Cortisol levels in the atypical flat group (n = 14), by contrast, were significantly higher in early pregnancy compared to the two other groups and then plateaued during mid-gestation. In terms of differences in changes in cortisol across groups between specific time-points in pregnancy, between 15 and 19 weeks, the typical group showed significantly less change from 15 to 19 weeks than the flat and steep groups. From 19 to 25 weeks, the steep group continued to show significantly more change in cortisol than the typical group, while the flat group had less cortisol increases than the typical group. Between 25 and 31 weeks, the steep group persisted in having the most cortisol change relative to the other two groups, while the flat group exhibiting a slight decrease in cortisol relative to the typical group. The lines are plotted with 95 % confidence intervals.
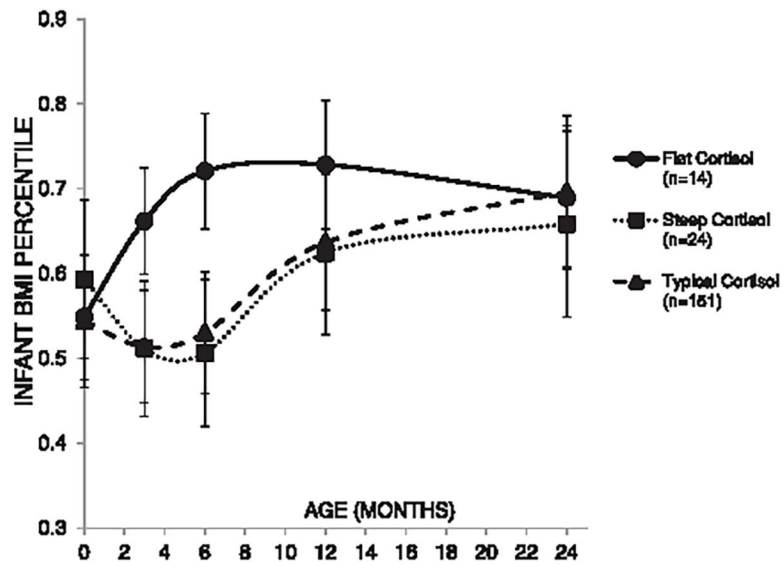
Fig. 2. Infant BMIP trajectories over the first 2 years of life as a function of patterns of cortisol exposure in pregnancy.
Infants exposed to flat cortisol trajectories experienced significantly more rapid increases in BMIP from birth to 6 months, and had significantly higher BMIPs at 3 and 6 months, than infants exposed to the typical cortisol rise over gestation, or steep (rapidly accelerating) trajectories. Lines are plotted with 95 % confidence intervals.

Table 1

Participant characteristics ($N = 189$).

	($M \pm$ SD/%)
Maternal	
Age at Delivery ($M \pm$ SD)	29.5 ± 5.5
Primiparous (%)	47.1 %
Cohabitating with baby's father (%)	87.8 %
Ethnicity (%)	
Non-Hispanic White	46.6 %
Hispanic	28.6 %
Asian	8.5 %
Multi-Ethnic	12.7 %
Other	3.1 %
Household Income ($, $M \pm$ SD)	59,947 ± 35,075
$0–$30,000 (%)	26.7 %
$30,001–$60,000 (%)	23.0 %
$60,001–$100,000 (%)	28.9 %
Over $100,000 (%)	21.4 %
Education (Years, $M \pm$ SD)	15.3 ± 2.4
High School or Less (%)	17.8 %
Some College (%)	41.4 %
College Graduate (%)	40.9 %
Pre-pregnancy BMI	25.1 ± 6.1
Gestational Weight Gain (lbs)	25.2 ± 9.9
Child	
Sex (% Female)	45.5 %
Gestational Age at Birth ($M \pm$ SD)	39.5 ± 1.1
Birth Weight (g)	3457.7 ± 419.7
Apgar score (5 min)	9.0 ± 0.3
Breastfed (%)	96.3 %
Age at breastfeeding cessation (months)[b]	6.7 ± 5.9
Age at first solid food (months)[c]	4.9 ± 1.1

Table 2

Child weight, length, and body mass index percentile (BMIP) through 2 years of age.

	Weight (g) (M ± SD)	Length (cm) (M ± SD)	BMIP (M ± SD)
Birth	3457.67 ± 419.70	50.39 ± 2.28	0.55 ± 0.29
3 months	6243.09 ± 799.21	60.91 ± 2.24	0.51 ± 0.28
6 months	7912.67 ± 978.68	67.07 ± 2.42	0.56 ± 0.29
12 months	9807.18 ± 1259.50	74.92 ± 2.72	0.64 ± 0.27
24 months	13,129.00 ± 1414.13	88.35 ± 3.33	0.69 ± 0.25

Table 3

Correlations between plasma cortisol, birth body mass index percentile (BMIP), birth weight and gestational age at birth.

Plasma cortisol measurement (weeks)	Birth BMIP Pearson's r (*p* values)	Birth Weight Pearson's r (*p* values)
15	−0.046 (p = .516)	−0.018 (p = .801)
19	−0.051 (p = .472)	−0.081 (p = .247)
25	0.036 (p = .600)	0.079 (p = .257)
31	0.024 (p = .743)	−0.051 (p = .481)

Note: Correlation coefficients are statistically adjusted for the time-of-day that samples were collected.