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Predictors of neonatal hypothalamic–pituitary–adrenal axis activity at delivery

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Summary

Objective—Clinical and preclinical studies indicate that maternal stress during pregnancy may exert long-lasting adverse effects on offspring. This investigation sought to identify factors mediating the relationship between maternal and neonatal hypothalamic–pituitary–adrenal (HPA) axes in pregnant women with past or family psychiatric history.

Patients—Two hundred and five pairs of maternal and umbilical cord blood samples from a clinical population were collected at delivery.

Measurements—Maternal and neonatal HPA axis activity measures were plasma adrenocorticotrophic hormone (ACTH), total cortisol, free cortisol and cortisol-binding globulin concentrations. The effects of maternal race, age, body mass index, psychiatric diagnosis (DSM-IV), birth weight, delivery method and estimated gestational age (EGA) at delivery on both maternal and neonatal HPA axis measures were also examined. Incorporating these independent predictors as covariates where necessary, we evaluated whether neonatal HPA axis activity measures could be predicted by the same maternal measure using linear regression.

Results—Delivery method was associated with umbilical cord plasma ACTH and both total and free cord cortisol concentrations ($T = 10.53$ – 4.21 ; $P < 0.0001$ – 0.010). After accounting for method of delivery and EGA, we found that maternal plasma ACTH concentrations predicted 23.9% of the variance in foetal plasma ACTH concentrations ($T = 6.76$; $P < 0.0001$), and maternal free and total plasma cortisol concentrations predicted 39.8% and 32.3% of the variance in foetal plasma free and total cortisol concentrations ($T = 5.37$ – 6.90 ; $P < 0.0001$), respectively.

Conclusion—These data suggest that neonatal response is coupled with maternal HPA axis activity at delivery. Future investigations will scrutinize the potential long-term sequelae for the offspring.

Introduction

There is considerable evidence that intrauterine environmental influences impact offspring postnatal function, promoting vulnerability for adulthood disorders.^{1,2} The literature broadly refers to this as ‘intrauterine programming’ (IP). Despite the posited role of intrauterine events in long-term health outcomes, the molecular mechanisms underlying this phenomenon remain obscure. Nevertheless, glucocorticoid activity, which generally impedes foetal growth while accelerating tissue differentiation, appears to play an important role.³

The perinatal period is associated with increased maternal hypothalamic–pituitary–adrenal (HPA) axis activity. The placenta releases corticotrophin-releasing hormone (CRH) such that circulating maternal CRH levels increase steadily throughout the pregnancy,⁴ and CRH-binding protein is increased to limit it. Not surprisingly, levels of maternal adrenocorticotrophic hormone (ACTH), cortisol and cortisol-binding globulin (CBG), an extracellular protein that binds circulating cortisol thereby lowering its bioavailability, also increase steadily across pregnancy. Although up to 40% of free cortisol readily crosses the placenta,⁵ CBG, cortisol bound to CBG and ACTH do not.^{6,7}

The impact of maternal stress on HPA axis activity during pregnancy and its relationship to neonatal outcome represents a burgeoning area of investigation, and women with psychiatric illness may be particularly vulnerable to the effects of stress during pregnancy. Elevated plasma cortisol concentrations in chronically stressed mothers are associated with decreased CBG levels⁸ and reduced negative feedback by cortisol on CRH and ACTH release. Despite mechanisms to limit foetal exposure to maternal glucocorticoids,⁹ plasma cortisol concentrations are elevated in depressed mothers and their neonates compared to their euthymic counterparts,¹⁰ and studies support a strong relationship between maternal and neonatal cortisol measures.^{5,11} Similarly, maternal depression and anxiety during pregnancy have been associated with low birth weight,^{12,13} elevated foetal heart rate,¹⁴ premature delivery^{15–17} and preeclampsia.¹⁸ Children of depressed, stressed or anxious mothers score lower on the Brazelton neonatal behaviour assessment scale,^{10,11,13} show reduced mental, motor and emotional development as infants^{19,20} and exhibit social and emotional problems during childhood.^{21–24}

These data suggest that alterations in HPA axis activity may underlie the impact of IP on offspring vulnerability to stress-related illness. We hypothesize that maternal and neonatal HPA axis function will be strongly correlated in a clinical sample at high risk for stress vulnerability.

Methods

Subjects

Subjects were recruited from the Emory Women’s Mental Health Program (WMHP), a referral centre for the treatment of perinatal psychiatric illness. Women with a personal or family history of psychiatric illness ($n = 205$) were enrolled prior to 14 weeks gestation and followed through delivery. All subjects completed an intake questionnaire collecting demographic and clinical data, and 160 (78%) of the subjects completed the Structured Clinical Interview for *DSM-IV* (SCID²⁵). This study was approved by the Emory University Institutional Review Board and was consistent with the guidelines set forth by the Declaration of Helsinki. All participants provided written informed consent prior to study enrolment.

Laboratory measures

Paired maternal and umbilical cord blood samples were collected in chilled EDTA vacutainer tubes, placed on ice and centrifuged (4 °C) within 1 h of delivery. Plasma was harvested, aliquoted at 0.5 ml and frozen at −80 °C until assay. ACTH was assayed in duplicate 200 µl aliquots of EDTA plasma by a two-site immunoradiometric method using materials obtained from DiaSorin (Stillwater, MN, USA). The sensitivity of the assay is 0.22 pM, and inter- and intra-assay coefficients of variation (CV) using an automated sampling method are less than 6%. Total plasma cortisol was assayed in duplicate 10-µl aliquots of EDTA plasma using a solid-phase radioimmunoassay (RIA) obtained from Diagnostic Systems Laboratories (Webster, TX, USA). The sensitivity of the assay is 5.5 nM, and inter- and intra-assay CV using an automated sampling method are <4%. Use of this assay has been described by Ritchie and colleagues.²⁶ CBG was measured in duplicate 10-µl aliquots of plasma using the double-antibody RIA from IBL America (Minneapolis, MN, USA). This is a double-antibody RIA using 125I-CBG as the tracer and a second antibody linked to a cellulose particle. The procedure has an analytical sensitivity of 4.9 nM, and interassay CV are all less than 6% over the entire measurement range (0.079–2.45 µM). Plasma free cortisol was estimated using an equation that accounts for CBG and total cortisol concentrations as well as the protein binding affinity for cortisol.²⁷ Because of sample availability, CBG could only be measured in 55 of the possible 205 pairs, also limiting calculated free cortisol to those 55 pairs.

Statistical analysis

Statistical analyses were performed using Statistical Analysis Software (SAS, Cary, NC, USA). All HPA axis measures were log transformed to limit heteroscedasticity. Maternal age, race, preconception and delivery BMI, education, method of delivery, birth weight, estimated gestational age (EGA) and current psychiatric diagnosis were examined as potential independent predictors of maternal or neonatal HPA axis measures using analysis of variance (ANOVA). To limit spurious associations resulting from small sample sizes, only psychiatric diagnoses represented by five or more mothers were included (Table 1). Any variable associated with a maternal or neonatal HPA axis measure was included as a covariate in subsequent analyses of that measure. Also, we examined the association between maternal use of psychotropic medications prescribed during the third trimester and each neonatal HPA axis measure by class (antidepressants and benzodiazepines) using ANOVA. To determine whether, at delivery, neonatal HPA axis measures were predicted by the mother's HPA axis measures, linear regression was used to evaluate the association of neonatal HPA axis measure with the corresponding maternal HPA axis measure, adjusting for significant confounders.

Results

Table 1 shows the demographic and clinical characteristics of the study sample. Primary psychiatric diagnoses varied, but nearly half of the sample fulfilled criteria for major depressive disorder, and mood disorders overall accounted for approximately two thirds of participants. Most of the remaining sample consisted of women with anxiety disorders. Either antidepressants or benzodiazepines were prescribed in the third trimester to the majority of women. Delivery method was broadly categorized as follows: (i) emergency or (ii) planned Caesarean sections and (iii) assisted or (iv) unassisted vaginal delivery.

Potential independent predictors of umbilical cord blood HPA axis measures were assessed. Maternal and neonatal ACTH, total cortisol and free cortisol concentrations were lower during Caesarean section (planned or emergency) when compared to vaginal delivery (assisted or unassisted) (Table 2; $P = 0.022$ to <0.0001). Also, neonates with a higher EGA

at delivery exhibited increased total cortisol levels ($T = 4.55$; $P < 0.0001$). Because a previous report²⁸ suggests that ACTH and cortisol levels may vary between races (Table 1), a *post hoc* analysis was undertaken to compare HPA axis activity measures between subjects of European and African decent using ANOVA. Plasma ACTH concentrations in mothers of African decent were higher than those of European decent ($P = 0.019$). No significant differences in HPA axis activity measures were observed in neonates of African or European decent. Finally, maternal age, preconception and delivery BMI, education, birth weight and current psychiatric diagnosis or pharmacologic treatment was not associated with neonatal plasma ACTH, total or free cortisol or CBG levels.

Linear regression was utilized to examine whether neonatal HPA axis measures were predicted by corresponding maternal HPA axis measures after accounting for the associations of delivery method and EGA with the neonatal measures (Fig. 1, Table 3). Neonatal plasma ACTH and free cortisol concentrations were covaried for method of delivery while neonatal total cortisol levels were covaried for method of delivery and EGA at delivery. Maternal plasma ACTH concentrations accounted for 23.9% of the variance in neonatal ACTH ($P < 0.0001$). Maternal plasma total and free cortisol levels predicted 32.3% and 39.8% of the variance in neonatal plasma total and free cortisol levels, respectively ($P < 0.0001$). Maternal CBG was not a significant predictor of neonatal CBG.

Recognizing the bidirectional relationship between ACTH and cortisol secretion caused by neuroendocrine feedback mechanisms, we tested whether the associations observed were independent. After accounting for both maternal and neonatal total or free cortisol in the model, maternal ACTH remains predictive of neonatal ACTH ($P < 0.0001$). Similarly, neonatal plasma cortisol levels (total and free) were still predicted by maternal plasma cortisol levels when ACTH is included in the model ($P < 0.0001$).

Discussion

Although maternal HPA axis function is profoundly altered during a healthy pregnancy, the results of this study suggest that neonatal HPA axis activity at delivery is tightly coupled to maternal activity. A report that cortisol levels in maternal plasma and amniotic fluid correlate²⁹ suggests that maternal and foetal HPA function may also be coupled prior to parturition. The observations presented here, taken together with previous findings, suggest that the neonatal HPA axis is not insulated from maternal stress but responds in a manner that parallels maternal HPA axis activity.

Prior studies report that neonatal cortisol levels vary as a function of delivery method.^{30,31} Our findings confirm these prior reports and extend them to a sample of women with psychiatric illnesses. Both maternal and neonatal plasma levels of ACTH, as well as total and free cortisol, were decreased in subjects undergoing planned or emergency Caesarean section. Comparison of mothers who completed unassisted vaginal deliveries with ($N = 122$) and without ($N = 17$) anaesthesia supports increased maternal and neonatal total cortisol levels in deliveries that did not involve anaesthesia, suggesting that maternal pain during labour influenced maternal and neonatal HPA axis responses (data not shown). However, we cannot eliminate other mechanisms underlying this association, such as direct pharmacological effects of anaesthesia.

Previous studies demonstrate that prenatal stress exposure results in lasting behavioural and neuroendocrine alterations in the HPA axis.^{32,33} Surprisingly, we observed no differences in any maternal or neonatal HPA axis measure between different maternal psychiatric diagnoses or treatment with antidepressants or benzodiazepines. *Post hoc* analyses comparing mood to anxiety disorders also did not reveal associations with either maternal or

neonatal HPA axis measures (data not shown). These observations suggest that the effects of delivery *per se* overwhelm possible smaller diagnosis or treatment-related differences in HPA axis response, if any indeed occurred. Clearly, the association of maternal diagnosis, symptoms and treatment with psychotropic medications should be evaluated in a larger population.

A previous report¹¹ suggests that maternal urinary cortisol levels predict neonatal urinary cortisol levels. Our results confirm and extend their findings, although we observe a larger predictive effect of both free and total maternal cortisol on neonatal cortisol. This may be, in part, attributed to our larger sample size, that we measured plasma rather than urine cortisol, that the samples were gathered at delivery rather than in the postdelivery period, or because we accounted for potential confounding factors such as method of delivery.

One of our most intriguing findings is the association between maternal and neonatal ACTH levels, despite reports that ACTH does not cross the placental barrier. A porcine study indicates that maternal ACTH challenge decreases ACTH receptor density in the foetus,³⁴ but the mechanism by which this occurs remains undiscovered. Although this observation implies the existence of direct or indirect maternal and foetal ACTH signalling pathways, it may also reflect independent but parallel responses to a common stressor, such as delivery. Further research into the molecular or cellular mechanisms underlying this association is clearly warranted.

This study is limited by small group of control subjects with no axis-1 diagnosis, which may reduce our power to detect associations with maternal psychiatric diagnosis. However, it is noteworthy that there were no significant variations between eight disorders examined that suggest a lack of specific relationships between diagnostic groups and differences in HPA axis function. It is also possible that women with psychiatric disorders have HPA axis abnormalities that are obscured by the changes that occur during pregnancy. Another limitation is that we calculated free cortisol using CBG in a subset of 55 of 205 paired samples instead of measuring it directly. While maternal and neonatal free cortisol measures were associated, we did not observe the association between CBG levels. This may be attributed to limited power or because the method of calculating free cortisol from CBG levels does not perform well during pregnancy,³⁵ suggesting that follow-up studies should measure free cortisol directly. Despite these limitations, analysis of multiple HPA axis measures in umbilical cord samples allowed us to gain a more complete picture of HPA axis dynamics during parturition than afforded by prior studies, and our sample size provided statistical power to detect associations while controlling for effects of potential confounding factors.

The strong correlation between the maternal and neonatal HPA axis at delivery persists amongst the methods of delivery, supersedes maternal psychiatric diagnosis and suggests that the neonatal response is coupled with maternal hypothalamic–pituitary–adrenal axis activity. Our results raise important questions with respect to the capturing of obstetrical outcome data as it may be related to neuroendocrine alterations in the offspring. Future studies will be required to replicate these findings and to determine whether the effects of increased stress hormones *in utero* or at delivery have a lasting effect on the development of the neonate.

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Conflict of interest

In the past year Charles B. Nemeroff, MD, PhD has served on the scientific advisory boards of AFSP, CeNeRx BioPharma, NARSAD, NovaDel Pharma, Inc., PharmaNeuroBoost, and ADAA and has served of the board of directors of AFSP, NovaDel Pharma, Inc. He received research/grants support from NIH and AHRQ. He is a stockholder of CeNeRx BioPharma, Corcept Therapeutics, Nova- Del Pharma., PharmaNeuroBoost, Revaax Pharma, and Xhale. He holds patents for transdermal delivery of lithium (US 6,375,990B1) and assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters using an ex vivo assay (US 7,148,027B2). He is a consultant with Xhale and Takeda. Dr Ritchie has received research support from NIH, BeckmanCoulter and Abaxis. Dr Newport has received research support from Eli Lilly, GSK, Janssen, NIH, NARSAD and Wyeth, has served on speakers or advisory boards for Astra-Zeneca, Eli Lilly, GSK, Pfizer and Wyeth and has received honoraria from Astra-Zeneca, Eli Lilly, GSK, Pfizer, and Wyeth. Dr Stowe has received research support from NIH, GSK, Pfizer and Wyeth, has served on speakers or advisory boards for Pfizer, Eli Lilly, Wyeth, BMS, and GSK, and has received honoraria from Eli Lilly, GSK, Pfizer, and Wyeth.

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Fig. 1. Distribution of maternal (horizontal axis) and neonatal (vertical axis) measures of log-transformed adrenocorticotrophic hormone, total cortisol, cortisol-binding globulin and free cortisol.

Table 1

Demographic and clinical characteristics of mothers

Measure	N	Mean $\pm$ SD
Age, years	205	31.88 $\pm$ 5.38
Preconception BMI	177	24.33 $\pm$ 5.54
Education, years	200	15.58 $\pm$ 2.17
Race	N (%)	Hispanic (%)
Asian	6 (2.9)	0 (0.0)
African American	18 (8.8)	1 (5.6)
European American	177 (86.3)	2 (1.1)
Native American	4 (2.0)	2 (50.0)
	N	%
Current psychiatric diagnosis (N = 160)		
Major depressive disorder (MDD)	72	45.0
Dysthymic disorder	1	0.6
Depressive disorder NOS	3	3.8
Mood disorder caused by GMC	1	0.6
Bipolar 1 disorder	24	15.0
Bipolar 2 disorder	5	3.1
Bipolar disorder NOS	1	0.6
Total mood disorders		67.5
Generalized anxiety disorder (GAD)	9	5.6
Posttraumatic stress disorder (PTSD)	7	4.4
Anxiety disorder NOS	6	3.8
Obsessive compulsive disorder (OCD)	5	3.0
Panic disorder	4	2.5
Specific phobia	2	1.2
Agoraphobia w/o panic	1	0.6
Social anxiety disorder	1	0.6
Total anxiety disorders		22.5
No axis I diagnosis *	10	6.3
Cannabis use disorder	2	1.2
Schizoaffective disorder	1	0.6
Binge eating disorder	1	0.6
Adjustment disorder	1	0.6
Total other diagnoses		10.0
Maternal medication – third trimester		
Antidepressants (N = 137)	118	86.1
Benzodiazepines (N = 46)	35	77.8
Method of delivery		
Emergency C-section	19	8.9

Measure	N	Mean $\pm$ SD
Scheduled C-section	40	18.7
Assisted vaginal	13	6.1
Unassisted vaginal	142	66.4

* Five (50%) of this group had seizure disorders.

Mean adrenocorticotrophic hormone (ACTH), total cortisol and free cortisol vary by method of delivery, but cortisol-binding globulin (CBG) does not change

Table 2

	<i>N</i>	Planned C-section	Emergency C-section	Unassisted vaginal	Assisted vaginal	<i>F</i>	<i>P</i>
Maternal (mean ± SD)							
ACTH, pM	205	5.25 ± 0.53	4.42 ± 0.37	6.81 ± 0.56	10.95 ± 0.46	3.29	0.022
Total cortisol, nM	205	512.9 ± 47.7	640.6 ± 40.8	731.7 ± 55.2	635.9 ± 47.7	4.15	0.007
Free cortisol, nM	55	12.42 ± 38.35	39.5 ± 13.0	21.5 ± 47.2	22.1 ± 47.2	4.68	0.006
CBG, uM	55	2.70 ± 0.024	2.26 ± 0.025	2.46 ± 0.023	2.08 ± 0.028	0.84	0.48
Umbilical cord (mean ± SD)							
ACTH, pM	205	14.36 ± 0.41	14.43 ± 0.49	24.31 ± 0.40	32.21 ± 0.52	6.80	0.0002
Total cortisol, nM	205	72.0 ± 54.9	99.0 ± 52.4	129.4 ± 53.0	165.8 ± 49.9	10.53	<0.0001
Free cortisol, nM	55	6.1 ± 48.0	24.8 ± 49.4	13.2 ± 43.0	22.6 ± 60.4	4.21	0.010
CBG, uM	55	0.54 ± 0.023	0.516 ± 0.028	0.560 ± 0.0258	0.414 ± 0.028	1.11	0.35

Differences observed between mothers and neonates from planned Caesarean section (*N* = 37), emergency Caesarean section (*N* = 18), unassisted vaginal (*N* = 137) and assisted vaginal (*N* = 13) deliveries (ANOVA; *P* < 0.05).

Table 3

Regression analyses of maternal adrenocorticotrophic hormone (ACTH), total cortisol, free cortisol and cortisol-binding globulin (CBG) measures as predictors of paired neonatal measures

	<i>N</i> , pairs	<i>R</i> ²	<i>T</i>	<i>P</i> -value
ACTH	205	0.239	6.76	<0.0001
Total cortisol	205	0.323	6.9	<0.0001
Free cortisol	55	0.398	5.37	<0.0001
CBG	55	0.010	−0.75	0.458