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Maternal Prenatal Depression in Pregnancies with Female and Male Fetuses and Developmental Associations with C-reactive Protein and Cortisol

Robert Freedman[a,1], **Sharon K. Hunter**[a], **Kathleen Noonan**[a], **Anna Wyrwa**[a], **Uwe Christians**[b], **Amanda J. Law**[a,c], **M. Camille Hoffman**[a,d]

[a]Department of Psychiatry, Institute for Children's Mental Disorders, University of Colorado Denver School of Medicine, Anschutz Medical Center F-546, Aurora, Colorado, United States 80045.

[b]Department of Anesthesiology, iC42 Clinical Research and Development, University of Colorado Denver School of Medicine, Anschutz Medical Center F-546, Aurora, Colorado, United States 80045.

[c]Department of Cell and Developmental Biology, University of Colorado Denver School of Medicine, Anschutz Medical Center F-546, Aurora, Colorado, United States 80045.

[d]Department of Obstetrics and Gynecology, Division of Maternal and Fetal Medicine; University of Colorado Denver School of Medicine, Anschutz Medical Center F-546, Aurora, Colorado, United States 80045.

Abstract

Background: Prenatal depression has lasting effects on offspring development, including later mental illness risk. Maternal responses to depression include inflammation and HPA-axis stimulation. Effects on development of cerebral inhibitory neurocircuits may differ for female and male fetuses.

Methods: Mothers (N = 181) were assessed periodically, beginning at 16 weeks gestation, on the Center for Epidemiological Studies of Depression Scale (CESD). Maternal prenatal C-reactive protein (CRP) and hair cortisol and cortisone levels were determined. Cortisone was determined in neonatal hair. Development of cerebral inhibitory neurocircuits was assessed in 162 1-month-old newborns by inhibition of P50 electrophysiological responses to repeated sounds.

Results: Maternal depression was associated with decreased newborn P50 inhibition in both sexes. Maternal CRP levels were significantly associated with depression only in male-fetus pregnancies and with decreased newborn P50 inhibition only in males. Maternal cortisol levels

[1]Address correspondence to Dr. Freedman (Robert.Freedman@cuanschutz.edu) 720-224-4638.

were significantly associated with depression only in female-fetus pregnancies and with decreased newborn P50 inhibition only in females. In male-fetus pregnancies compared to female-fetus pregnancies, cortisol was more robustly metabolized to cortisone, which does not activate cortisol receptors.

Conclusion: The study finds sex-specific associations of CRP and cortisol levels with prenatal depression in women and with decreased development of newborn P50 inhibition. Sex-based differences in maternal response to depression with inflammation or cortisol and their developmental effects may reflect evolutionary influences to promote survival in adversity. Decreased newborn P50 inhibition is associated with later childhood behavioral problems, and decreased P50 inhibition is a pathophysiological feature of several mental illnesses.

Keywords

Depression; Pregnancy; Fetus; Hydroxycortisone; C-reactive protein; Inflammation

Introduction

Prenatal maternal depression's effects are implicated in the child's future risk for schizophrenia, attention deficit disorder, autism spectrum disorder, and depression, adding to familial genetic risk (1-4). Cognitive and behavioral effects, as well as brain structural effects, have been characterized in the years after birth (5-11). This study investigated the association of prenatal depression, together with its associated maternal inflammation and cortisol secretion, on the development of a specific inhibitory brain function that is assessed in newborns.

Animal models of prenatal inflammation and cortisol secretion find effects on the development of the hippocampus, neocortex, amygdala, and particularly inhibitory interneurons (12-16). Many of these interneurons develop in human fetuses between 12-20 weeks in gestation (17-18). Optogenetic inactivation of limbic neocortical interneurons decreases the animal's social interactions and its attention (19). The hippocampus is a source for the P50 wave of the human cerebral auditory-evoked response (20). Its analogue in rodent models is generated by hippocampal pyramidal neurons, and its inhibition in response to repeated sounds involves activation of hippocampal inhibitory interneurons (21). Inhibition of the P50 response can be recorded in 1 month-old-newborns and adds to other phenotypes that are assessed before or soon after birth, to gauge prenatal effects on central nervous system development (5-6, 22-29).

The present cohort was recruited from prenatal clinic admissions in a metropolitan community hospital that serves disadvantaged women for a study designed to examine a wide range of prenatal influences on fetal brain development of cerebral inhibition and early childhood behavior. The study included infection, substance use, adversity, depression, and stress as factors to be assessed (Table 1). Depression is associated with both inflammation and increased cortisol (30). CRP is a marker of the mother's hepatic response to inflammation from a range of causes including depression (31). Cortisol levels have been measured in saliva, plasma, and maternal hair during pregnancy (23,32-33). We reported in another cohort that maternal hair cortisol levels mediate the relationship between prenatal

stress and premature delivery (33). In the placenta, 11-β-hydroxysteroid-dehydrogenase-2 (11BHSD2) irreversibly converts cortisol to cortisone, which does not activate cortisol receptors (34). Male placentas have higher 11BHSD2 (35-36). We measured cortisone levels in neonatal hair, to assess cortisol conversion to cortisone during gestation (37).

We have previously shown that both infection and cannabis use decrease development of P50 inhibition in this cohort and that increased maternal CRP from infection in gestation is associated with decreased newborn P50 inhibition in male, but not female newborns (38-40). This is the first report from this cohort to characterize the interaction of maternal depression with fetal sex on both CRP and cortisol levels and the first to characterize the interaction of depression and cortisol levels with fetal sex on newborn P50 inhibition.

The interaction of prenatal depression with fetal sex on maternal CRP and cortisol levels has not been previously reported. A large survey of pregnant women reported that cortisol levels were higher in pregnancies with female fetuses and that CESD rating had no effect, but the interaction between depression and fetal sex was not assessed (41). Another report also found higher basal cortisol response and arousal in women carrying female fetuses, but that study did not address depression (42). Other studies of prenatal depression and CRP levels did not examine the effect of fetal sex and found inconsistent effects (43-44). Asthma and its corticosteroid treatment is a potential model for the interaction of fetal sex, cortisol, and inflammation. Placentas of female fetuses, but not male fetuses, of women who use corticosteroids for asthma during pregnancy had cytokine levels inversely correlated with cord blood cortisol levels (45). A study in depressed women sampling plasma cortisol and cytokines between 16 and 26 weeks gestation reported a similar inverse relationship, but did not assess effects of fetal sex (32). We hypothesized that maternal depression and fetal sex would interact, with higher cortisol levels in female-fetus pregnancies and lower CRP levels reflecting decreased inflammation. The opposite, lower cortisol levels and higher CRP levels were hypothesized in male-fetus pregnancies.

We hypothesized that decreased newborn P50 inhibition would be associated with maternal depression, based on P50 inhibition association with other maternal insults (38-40). We hypothesized 16 weeks gestation to be the critical time period, based on the embryology of inhibitory interneurons responsible for P50 inhibition in this gestational window (17-18). Animal model studies report that hippocampal neurons are more responsive to gestational inflammation in males and to glucocorticoids in females (13-14). Human studies have found greater effects of prenatal inflammation in male offspring and greater effects of maternal cortisol in female offspring (23,26,29,46-48), but other studies have not reported sex effects (49-50). Based on these studies, we hypothesized that male newborn P50 inhibition would be more sensitive to maternal CRP elevation, and that female newborn P50 inhibition would be more sensitive to maternal cortisol elevation.

Methods and Materials

1. Maternal assessment and recruitment

Women (N = 181) were enrolled from a public safety-net prenatal clinic at 14-16 weeks gestation from July 2013 until July 2016. Gestational age at enrollment was assessed by first

ultrasound (51). Exclusions were fetal anomaly, major maternal medical morbidity, and steroid therapy. The Colorado Multiple Institution Review Board approved the study; all mothers, and fathers if available, gave informed consent. Participants were asked to participate in a study of stress on their child's development.

Self-ratings on Adverse Childhood Experiences (ACE), Center for Epidemiological Studies of Depression (CESD), State-Trait Anxiety Inventory-State Version (STAI-S), and the Perceived Stress Scale (PSS) were acquired in structured interviews by trained staff. The CESD is particularly sensitive across multiple socio-economic, ethnic and racial groups, compared to other depression scales (52-54). The 181 women at 16 weeks (range 15-17 weeks) had mean CESD ratings 13.9 (SD 9.5); 19 dropped out within several weeks of enrollment. Mothers who brought their newborns for newborn P50 recording, N = 162, had mean CESD 13.9 (SD 9.3). The most common reason for dropout was the mother's move to another city (Figure S1). Further subject assessments are in the supplement.

2. Maternal and newborn hair cortisol and cortisone

Hair (2.5 cm) was cut from the posterior vertex region as close to the scalp as possible at 28 weeks, which integrates levels from 15-28 weeks of gestation, encompassing the 16-week CESD rating (55). Excessively dyed or shampooed hair was not used (56). The correlation between maternal hair cortisol levels and the Area under the Curve for salivary cortisol, sampled 30 min before waking, before lunch, and 10 hours after waking for 3 days in the 2nd trimester is $r^2 = 0.34$, $P = 0.04$ (57). Hair samples were obtained from 141 neonates. Neonatal hair at birth is formed during the last trimester and measures fetal production of cortisone (37). Cortisone levels were available from only 75 infants for technical reasons. The mass spectrometry-based assay is described in the supplement.

3. Maternal CRP

Plasma CRP at 16 weeks gestation (range 15-17 weeks) was obtained mid-morning and assayed by Beckman-Coulter high sensitivity immunoassays. The lower level of detection was 0.1 mg/L with CV<5%.

4. Neonatal physiological recording of cerebral inhibition

Newborns were studied one month after birth adjusted for gestational age. The mean age was 28.0 days (SD 9.7), range 14-59. Vertex electroencephalogram, electro-oculogram, submental electromyogram, and respiration were continuously recorded while infants napped (22). Recording of the cerebral auditory evoked potential P50, a positive EEG wave 50ms post-stimulus, occurred in the second active sleep episode, the precursor of REM sleep, identified by low voltage desynchronized vertex activity with the absence of K-complexes, change in respiration, and large eye movements with submental atonia (58). The second active sleep episode was reached approximately 45 minutes after sleep onset. In adults, P50 inhibition in REM and waking are equivalent (59).

Two identical binaural auditory stimuli SPL 85dB were delivered 500 ms apart at 10s intervals to elicit $P50_{S1}$ and $P50_{S2}$. Responses to 96 stimulus pairs were averaged, using a Gaussian-based algorithm that accounts for variance or jitter in response latency (60). P50

inhibition is often assessed as amplitude ratios $P50_{S2}/P50_{S1}$ or $(P50_{S1}-P50_{S2})/P50_{S1}$ (61). However, the skew inherent in ratios limits power for correlation with risk factors. $P50_{S2}$ amplitude, covaried for $P50_{S1}$, which is normally distributed, was therefore used as the parameter to assess cerebral inhibition, as validated in a recent meta-analysis (62). Detailed methods have been previously reported (63-64).

5. Statistical analyses

Neonatal $P50_{S2}$ amplitude covaried for $P50_{S1}\mu V$ was the principal outcome. Shapiro-Wilks tests did not find a significant deviation from normal distribution. Hair cortisol levels were skewed and therefore were $\log_{10}$-transformed. General Linear Models and multiple regressions analyzed child sex as a fixed effect and CESD, cortisol, cortisone, and CRP levels as continuous covariates (Table S1). Maternal age was used as a covariate for CESD ratings, CRP, and cortisol levels, to detect confounding maternal socioeconomic influences, including education and occupation, which are correlated with maternal age (38). Gestational age at birth and at newborn P50 recording were covariates to control for maturation differences affecting P50 amplitudes. Previously reported CRP associations were re-analyzed to use the same covariates as other analyses in this study. Spearman's ρ was used for non-parametric correlations. α = 0.05 two-tailed was the measure of significance.

Results

CESD 16-week depression ratings were positively correlated with lifetime history of DSM-5 Major Depressive Disorder (ρ = 0.289, $P < 0.001$) and Bipolar Disorder (ρ = 0.192, $P = 0.014$). CESD ratings   16 are consistent with DSM-5 Major Depressive Disorder and were recorded for 38% of the women. In comparison, 36% of child-bearing age women in a survey of Los Angeles County had CESD ratings   16 (65-66). Women with CESD ratings   16 differed from less depressed women in their rates of infection, substance use, single parenthood, Adverse Childhood Experiences, stress, and anxiety (Table 1). There was no difference in CESD ratings between pregnancies with female and male fetuses (Table S1).

Child sex, maternal CESD depression ratings, and newborn $P50_{S2}\mu V$

Higher maternal 16-week CESD ratings were positively associated with higher newborn $P50_{S2}\mu V$ ($F_{df1,111} = 6.636$, $P = .011$; β = 0.237; Table S2). Maternal PSS stress and STAI-S anxiety ratings were not significant in this analysis. Only the 16-week CESD rating was significant when considered with CESD ratings later in gestation, including CESD rating at 46 weeks gestation (postpartum) (Table 2). No differences noted in Table 1 between women based on their CESD rating were significant when considered with CESD ratings, including gestational infection, use of alcohol, cannabis, or nicotine, obesity (pre-pregnancy BMI 30), absence of father, number of Adverse Childhood Experiences, or African American and Native American ethnicity (Table S3). There was no interaction between child sex and the association of CESD rating on newborn $P50_{S2}\mu V$ (Fig. 1; Table S4).

Child sex, maternal C-reactive Protein (CRP), and newborn $P50_{S2}\mu V$

For CRP level at 16 weeks gestation, there was a significant interaction between maternal CESD rating at 16 weeks gestation and the sex of the fetus, $F_{df1,142} = 4.64$, $P = 0.03$ (Table

S5). For women with male fetuses, CESD rating was positively related to 16-week CRP levels, $\beta = 0.330$, $P = 0.006$, in a multivariate analysis that considered maternal age, obesity (pre-pregnancy BMI 30), and infection (Fig. 2). For women with CESD rating 16 with male fetuses, 16-week gestation CRP levels, 10.1 mg/L (SD 8.0), were higher compared to women with CESD rating <16, 6.2 mg/L (SD 5.8), $P = 0.016$ (Table 1). For newborn $P50_{S2}\mu V$, there was a significant interaction between maternal CRP levels and the sex of the child, $F_{df1,142} = 8.47$, $P = 0.004$ (Table S6). Higher CRP levels were positively associated with greater male newborn $P50_{S2}\mu V$ ($\beta = 0.190$, $P = 0.046$), as previously reported (40).

For women with female fetuses, CESD ratings were not related to 16-week CRP levels in the multivariate analysis, $\beta = -0.013$, $P = 0.9$. Infection reported at 16 weeks gestation was a positive factor, $\beta = 0.273$, $P = 0.024$. For female newborns, higher CRP levels were inversely associated with lower $P50_{S2}\mu V$, $\beta = -0.206$, $P = 0.020$, as previously reported (40).

Child sex, maternal depression and cortisol

For maternal 2nd trimester cortisol levels, there was a significant interaction between CESD rating at 16 weeks gestation and fetal sex, $F_{df\,1,131} = 5.49$, $P = 0.021$ (Table S7). For women with male fetuses, cortisol levels were not related to CESD depression ratings, $\beta = \beta 0.052$, $P = 0.7$. For women with female fetuses, CESD depression ratings were positively related to their 2nd trimester cortisol levels ($\beta = 0.320$, $P = 0.010$; Fig. 3). Maternal age, obesity (pre-pregnancy BMI 30), and infection were not significant factors. For women with CESD rating 16 with female fetuses, 2nd trimester hair cortisol levels were significantly higher 1.06 log pg/mg (0.58) compared to women with CESD rating <16, 0.81 log pg/mg (SD 0.47), $P = 0.045$ (Table 1).

Fetal sex, maternal and neonatal hair cortisol and cortisone

Cortisone levels in 2nd trimester maternal hair relative to cortisol levels were higher in women with male fetuses, exponential association $r^2 = 0.569$, $P < 0.001$, than in women with female fetuses, $r^2 = 0.157$, $P = 0.017$; child sex * 2nd trimester hair cortisol $F_{df1,65} = 43.4$, $P < 0.001$. Neonatal hair cortisone relative to neonatal hair cortisol was higher in males, exponential association $r^2 = 0.660$, $P < 0.001$ than in females, exponential association $r^2 = 0.477$, $P < 0.001$; child sex * neonatal hair cortisol $F_{df1,70} = 4.85$, $P = 0.031$ (Figure 4).

Child sex, maternal cortisol, neonatal cortisone and newborn $P50_{S2}\mu V$

For newborn $P50_{S2}\mu V$, there was a significant interaction between child sex, maternal 2nd trimester hair cortisol, and neonatal hair cortisone levels, $F_{df1,58} = 3.36$, $P = 0.042$ (Table S8). For males the association of 2nd trimester maternal cortisol with newborn $P50_{S2}\mu V$ was not significant, $\beta = -0.037$, $P = 0.8$. Higher male neonatal hair cortisone levels were inversely correlated with lower $P50_{S2}\mu V$, $\beta = -0.499$, $P = 0.002$. Maternal cortisol was positively associated with greater female newborn $P50_{S2}\mu V$, $\beta = 0.312$, $P = 0.020$ (Fig. 3). For females, the association of neonatal hair cortisone with $P50_{S2}\mu V$ was non-significant, neonatal hair cortisone, $\beta = -0.126$, $P = 0.4$. The association of maternal CESD depression ratings with newborn female $P50_{S2}\mu V$ became non-significant when co-varied for maternal 2nd trimester cortisol ($\beta = 0.100$, $P = 0.5$); cortisol remained significant in this analysis ($\beta = 0.290$, $P = 0.048$).

Effects of antidepressants during gestation

Antidepressants were used by 22 women during gestation (14%). Use was significantly positively associated with higher CESD rating at 16 weeks gestation, 18.7 (SD 12.4), compared to no antidepressant use, 13.2 (SD 8.7), $P = 0.012$. As gestation progressed, the association with CESD ratings became non-significant. There were no significant effects of antidepressant use, controlled for CESD rating at 16 weeks gestation, on gestational CRP, maternal hair cortisol, or newborn P50 amplitude (Table 3).

Discussion

Maternal depression at 16 weeks gestation was positively associated with higher amplitudes of the newborn P50 response to a repeated sound stimulus, which indicates poorer development of cerebral inhibitory neurocircuit function. Ratings of maternal stress, anxiety, and adverse childhood experience, as well as depression later in gestation, were not significantly associated when considered with 16-week CESD ratings. The association of maternal depression with either CRP or cortisol levels depended upon the sex of the fetus. Depression in mothers with male fetuses was positively associated with increased CRP levels, and in mothers with female fetuses, depression was positively associated with increased cortisol. These findings are summarized in Table S9. The timing of negative effects of prenatal maternal CRP on male newborn P50 inhibition and cortisol on female newborn P50 inhibition is consonant with other evidence that this period is when both inflammation and cortisol appear to be most pathogenic, when interneuron differentiation is occurring (17-18,49,67).

Evidence for mediation by cortisol of the effects of maternal prenatal depression on female newborn P50 inhibition was observed with Baron and Kenny's criteria (68). A multivariate analysis showed a positive cortisol association with greater $P50_{S2}\mu V$ and loss of significance of the maternal CESD association. The multivariate association was predicated on positive univariate associations of (i) maternal CESD with newborn $P50_{S2}\mu V$, (ii) maternal CESD depression with cortisol levels, and (iii) maternal cortisol levels with newborn $P50_{S2}\mu V$ (68). The corresponding analysis with depression, CRP levels, and $P50_{S2}\mu V$ in male newborns showed similar positive univariate associations between CESD, CRP levels, and $P50_{S2}\mu V$, but the multivariate analysis of effects of depression and CRP levels continued to show significant positive association of depression with $P50_{S2}\mu V$. Unlike cortisol, which is pathogenic itself, CRP is only an indicator of inflammatory response and not a pathogenic agent *per se*, which may account for the failure to find mediation.

The fetal-sex specific association of the mother's depression with either CRP or cortisol, and the sex-specific association of CRP and cortisol with development of cerebral inhibition may be related. Male placentas in early gestation have higher levels of 11-β-hydroxysteroid-dehydrogenase-2 (11BHSD2), which irreversibly converts cortisol to cortisone (34-36). Cortisone does not activate the cortisol receptor and thus effects of maternal cortisol are diminished (34). Higher male neonatal cortisone hair levels, presumably reflecting this irreversible fetal 11BHSD2 activity, were associated with lower $P50_{S2}\mu V$. However, in the mother, cortisone is converted back to cortisol in the hypothalamus by 11-β-hydroxysteroid-dehydrogenase-1 (11BHSD1), which is a reversible enzyme (34). Increased hypothalamic

cortisol in mothers with male fetuses may then suppress the association of cortisol with her depression (34). Depression and stress are associated with increased methylation of 11BHSD2 (25,69). Methylation is associated with decreased placenta 11BHSD2 protein expression in pregnancies with female, but not male fetuses (70), which leaves the female fetus more exposed to maternal cortisol.

CRP levels and depression were positively associated only in mothers with male fetuses. However, there are positive associations of CRP with prenatal infection in mothers with either sex fetus, because viral RNA or bacterial lipopolysaccharide activates a vigorous maternal inflammatory response regardless of fetal sex (38). Inflammation in depression, in the absence of an external antigen, may occur predominantly with male fetuses because of the sex-discordance with the mother, analogous to increased inflammation in female hosts from grafts of male tissue (71). Female placentas are also protected from inflammation by several mechanisms, including higher expression of human chorionic gonadotropin genes, increased expression of X-chromosome genes, differences in serotonin signaling, and differences in torr-receptors (6,72-74).

Possible advantages of the differences between male and female pregnancies in fetal and placental development have been considered from an evolutionary perspective (75-78). Male fetuses are larger, which prepares them to be stronger and support more aggressive behavior. Their development is resistant to the effects of the mother's HPA-axis activation during stress, because of the effects of 11BHSD2 in the placenta. However, their placentas are smaller and their gestation is more vulnerable to other gestational insults that invoke inflammation, which can result in decreased male births in adverse conditions like epidemics (6, 75-78). Female placentas are larger and presumably better able to support the smaller female fetus, perhaps insuring that more females survive adversity in utero to bear their own progeny (79). One mechanism by which the mother limits female fetal growth is to increase cortisol during stressful circumstances (78). The smaller fetus survives but may be more vulnerable to postnatal problems in HPA axis regulation, including those associated with depression (77).

Antidepressant treatment had no direct positive or negative association with newborn P50 inhibition. Any association depended upon the current CESD depression rating (Table 3). The finding corroborates our report in another cohort that newborn P50 inhibition is increased by antidepressant treatment of maternal depression and provides further evidence that this aspect of development is not impeded by antidepressant treatment (80).

Limitations of correlational observations include the possibility of reverse causality and undetected mediating variables. The increased female birth rate in stressed women could explain their higher cortisol response (6). However, there were no differences in CESD ratings in women with female or male fetuses in this cohort. Depression co-existed with many other factors in each woman's pregnancy. These factors, including prenatal infection, substance use, adverse childhood experiences, and postnatal depression have significant impact on fetal development. They were included as variables in the present analyses of the association with maternal depression, which remained significant. The mothers rated their own depression. However, patient self-ratings of depression are found to be more reliable

than clinician diagnoses (81). This study also has limitations in its assessment of inflammatory and corticosteroid effects on the fetus. CRP is only an indirect marker of inflammatory response. We cannot be certain how much cortisol actually reaches the fetus during the 2nd trimester from the mother's level; it is estimated from radiotracers as 25% (82). Neonatal hair cortisone was used to indicate the placenta's 11BHSD2 activity, but this hair is formed in the 3rd trimester when 11BHSD2 levels change in anticipation of parturition (37).

The P50 response is generated in hippocampus, where inhibitory interneurons are responsible for the decrement in its amplitude in response to repeated sounds, which we assessed in this study as P50$_{S2}$μV co-varied for P50$_{S1}$μV (62). In the offspring of mothers with increased prenatal anxiety, the hippocampus was not smaller at birth, but growth decreased in the first 6 months of life related to both pre and postnatal maternal anxiety (27). Another study imaged the fetal hippocampus at 24 and 40 weeks gestation and found decreased volume in fetuses of mothers with anxiety and decreased creatine and membrane choline levels in fetuses of mothers with depression, indicative of decreased cellular development (28). Newborn fractional anisotropy (FA) in the uncinate fasiculus near the hippocampus, associated with axonal development, was decreased in relation to increased prenatal maternal Interleukin-6, but increased more rapidly thereafter (29). Another study had similar findings in mothers related to their prenatal anxiety (26). Sex-specific effects were observed in offspring of mothers with higher prenatal depression and anxiety, with lower FA females and higher FA in males in white matter adjacent to the hippocampus. There are no specific studies of interneuron development with maternal gestation depression. Pathological developmental effects on interneurons in high-risk prenatal conditions, which may or may not include maternal depression, can be observed in post mortem brain tissue from individuals with schizophrenia. Some interneurons fail to migrate from the subplate into the temporal lobe, and they do not fully develop the mature chloride transporter necessary for their inhibitory function (83-84).

Newborn P50 inhibition is a putative translational bridge between pathophysiological associations of maternal depression with fetal development of inhibitory neurons of the hippocampus and later behavioral problems including increased risk for later mental illness. P50 inhibition is a consistent trait in individuals from newborn assessment to 4 years of age (64). The continuity of newborn with adult P50 inhibition is unknown, but decreased P50 inhibition is common in both adult children and siblings of probands with schizophrenia and infants of a parent with schizophrenia, as we and another group have shown (60, 85-86). In this cohort, we previously reported that higher newborn P50$_{S2}$μV, indicative of poor P50 inhibition, was positively associated with behavioral differences at 3 months of age, as assessed by the Infant Behavior Questionnaire-R/SF (40). Female infants with higher P50$_{S2}$μV were less active and quieter. Male infants with higher P50$_{S2}$μV were fussier, harder to engage, and less able to seek comfort from caregivers. In two other cohorts, we assessed children at 3.5 years of age using the Child Behavior Checklist for age 1½-5 years (87-88). Problems with attention and social withdrawal were positively associated with poorer newborn P50 inhibition. Parents whose children developed schizophrenia as young adults report similar levels of attention and social withdrawal problems on the Child Behavior Checklist when their children were as young as 2 years of age (89). Poorer P50 inhibition is

positively associated with problems in attention in adults with schizophrenia as well as in adults without mental illness (90-91). Problems in the self-regulation of temperament and behavior in infancy can thus have enduring consequences as these individuals develop into adulthood (92).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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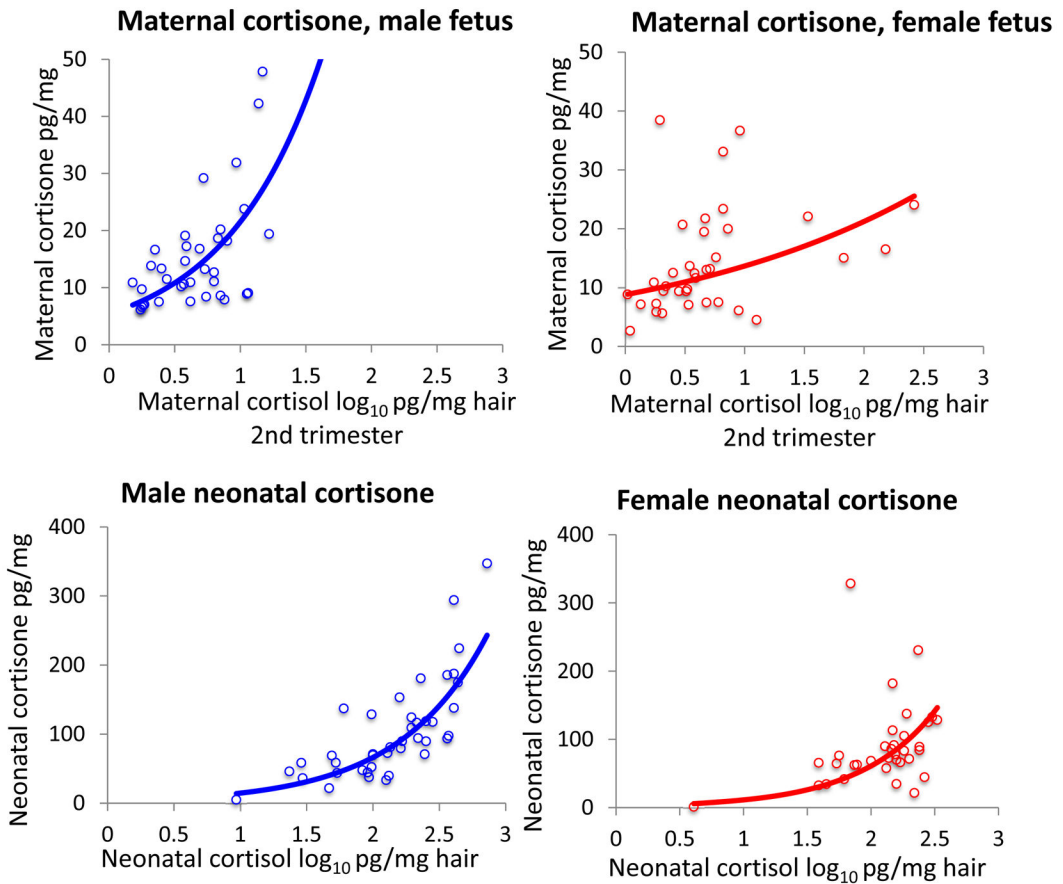
Figure 1.

Left: P50 evoked potentials of an individual 1-month-old female recorded from the scalp vertex in response to paired sounds, 500 ms apart. This child was born full term to a 23-year-old woman with CESD = 18. Maternal 2nd trimester hair cortisol was 34.2pg/mg, the upper 12th%ile for women with female fetuses. Plasma C-Reactive Protein was 12.2mg/L. P50 amplitude (μV) is measured from the most positive peak (mark above wave) to the preceding negativity (mark below wave). The waves are the averaged responses to 96 pairs of stimuli delivered during the newborn's active sleep. This newborn had little suppression of $P50_{S2}\mu$V, compared to $P50_{S1}\mu$V. Her $P50_{S2}\mu$V adjusted for $P50_{S1}\mu$V is 1.35μV, the upper 14th%ile of female newborn amplitudes. Right plots: Significant positive associations for all male and female newborns of maternal depression CESD rating with newborn $P50_{S2}\mu$V adjusted for $P50_{S1}\mu$V, female $\beta = 0.211$, $P = 0.021$, male $\beta = 0.316$, $P < 0.001$.
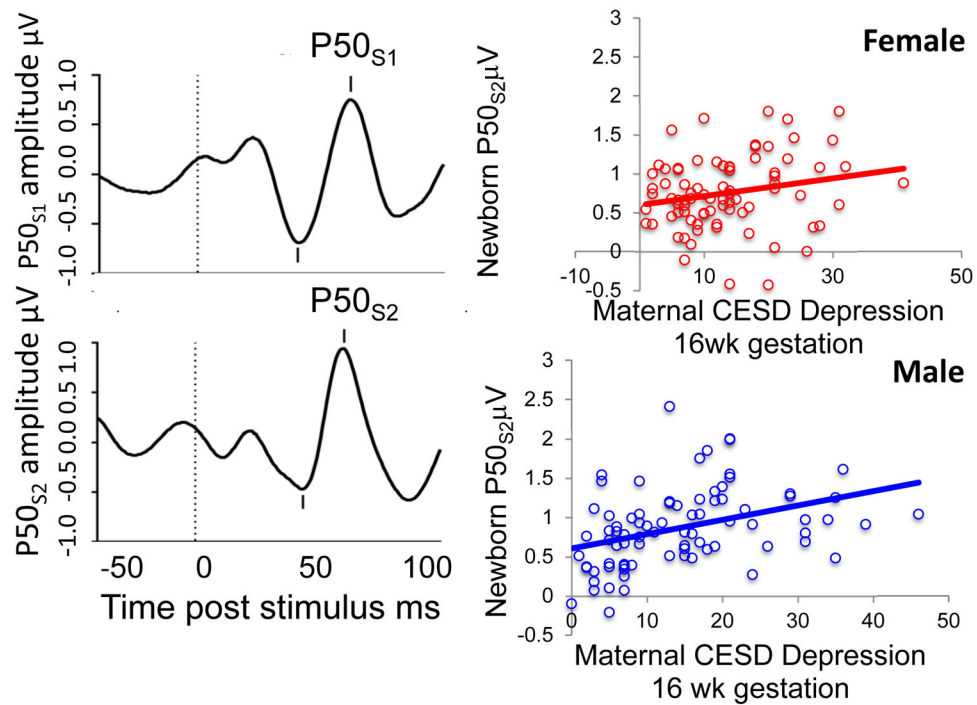
Figure 2.
Top plots. Significant positive association of maternal CESD depression rating and maternal C-Reactive Protein (CRP) at 16 weeks gestation for pregnancies with male fetuses β = 0.330, P = 0.006, but not with female fetuses. Bottom plots: The association of maternal CRP levels with newborn $P50_{S2}\mu V$ adjusted for $P50_{S1}\mu V$ was positive for male newborns β = 0.190, P = 0.046, and negative for female newborns β = −0.206, P = 0.020. The effects of CRP on $P50_{S2}\mu V$ were published previously (40).
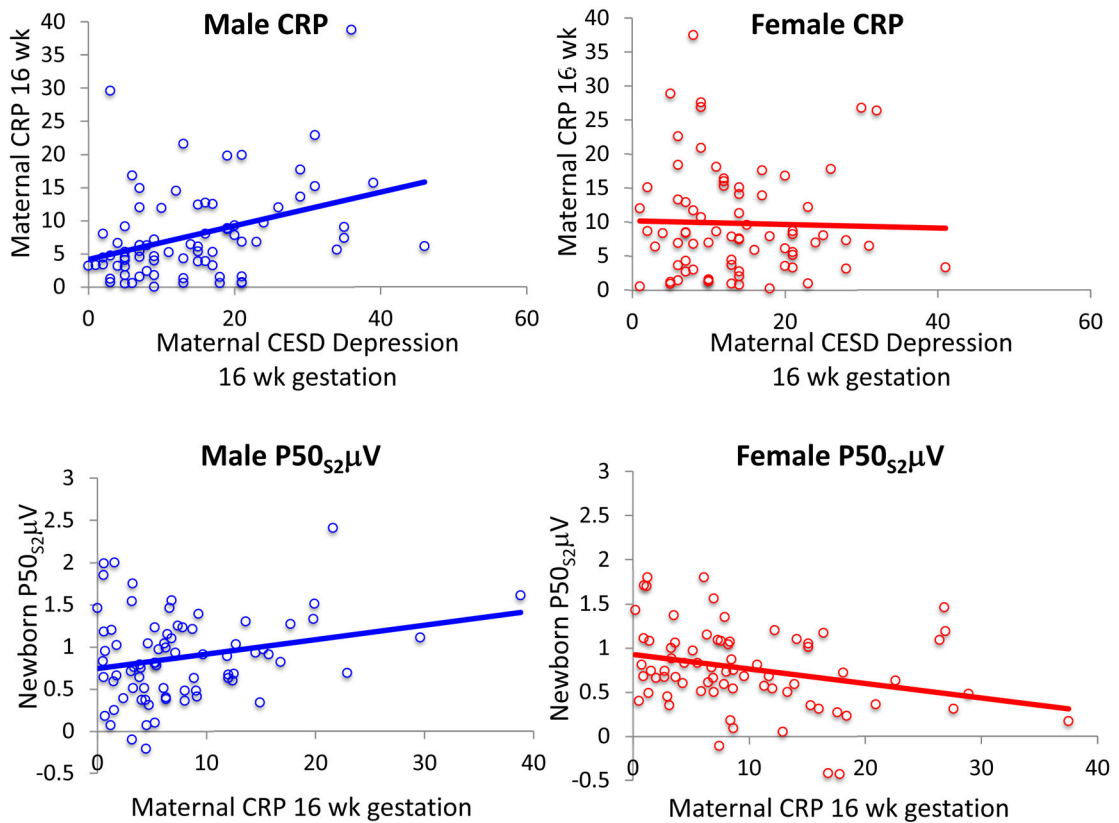
Figure 3.
Top plots. The association of maternal CESD depression rating and 2nd trimester maternal hair cortisol for pregnancies with males fetuses was not significant, but it was positive for pregnancies with female fetuses $\beta = 0.320$, $P = 0.010$. Bottom plots: The association of maternal 2nd trimester hair cortisol with newborn $P50_{S2}\mu V$ adjusted for $P50_{S1}\mu V$ for male newborns was not significant, but it was positive for female newborns $\beta = 0.312$, $P = 0.020$.
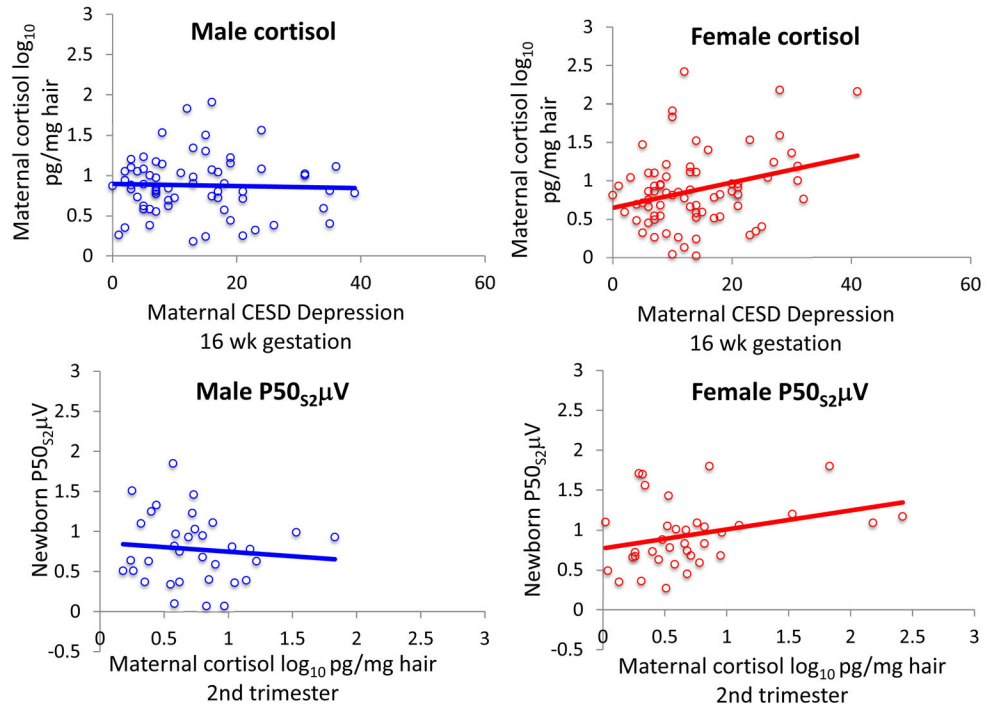
Figure 4.

Relationships of cortisol to cortisone in mothers and neonates. Top: Relationship of maternal 2nd trimester cortisone hair levels to maternal cortisol in women with male fetuses, exponential association, $r^2 = 0.569$, $P < 0.001$) and female fetuses, exponential association $r^2 = 0.157$, $P = 0.017$. Bottom: Relationship of neonatal hair cortisone to neonatal hair cortisol in males, exponential association $r^2 = 0.660$, $P < 0.001$, and in females, exponential association $r^2 = 0.477$, $P < 0.001$.

Table 1.

Differences between mothers and offspring by maternal depression rating.

Center for Epidemiological Studies of Depression (CESD) 16 weeks gestation	CESD ≥ 16 N = 61		CESD<16 N =101		Significance
	N	%	N	%	Fishers *P*
Infection in first trimester, viral or bacterial brought to medical attention or endorsed by mother as moderate to severe	31	51	35	35	0.049
Obesity pre-pregnancy BMI ≥ 30	19	31	28	28	0.7
Alcohol use at 16 wks. gestation	16	25	0	0	<0.001
Marijuana use at 16 wks. gestation	14	23	11	11	0.046
Tobacco use at 16 wks. Gestation	7	11	5	5	0.13
Biological father present	39	64	80	80	0.04
European-American	42	33	84	67	
African-American	12	55	10	45	0.09[1]
Native-American	8	57	6	43	0.09[1]
Hispanic	34	56	48	48	0.3
Antidepressant use	11	18	11	11	0.24
Fetal Sex (male)	34	56	47	47	0.3
	Mean	SD	Mean	SD	t test *P*
Maternal age yr	29.0	6.4	30.3	5.6	0.2
Adverse Childhood Experiences (ACE)	3.42	2.70	2.07	2.05	0.003
Perceived Stress Scale at	29.4	5.9	20.2	7.1	<0.001
16 wks gestation					
State Trait-Anxiety Inventory-State at 16 wks gestation	43.0	10.9	31.3	8.0	<0.001
Male fetus	N = 34		N = 47		
Gestational age at birth d	273.8	13.5	273.8	17.5	0.9
Birth weight g	3260	585	3272	591	0.9
Breast feeding N (%)	29	88%	44	94%	0.7
Maternal C-reactive protein (CRP) 16 weeks gestation	10.1	8.0	6.2	5.8	0.016
Maternal Cortisol log 2nd Trimester log pg/mg hair	0.86	0.39	0.88	0.35	0.7
Maternal Cortisone 2nd Trimester pg/mg hair	14.7	6.0	28.4	39.5	0.2
Neonatal Cortisol log pg/mg hair at birth	2.04	0.38	2.15	0.49	0.3
Neonatal Cortisone pg/mg hair at birth	73.5	49.2	133.0	85.8	0.045
$P50_{S2}\mu V$ adjusted for $P50_{S1}\mu V$ 1 month of age	1.10	0.08	0.70	0.07	<0.001
Female fetus	N = 27		N = 54		
Gestational age at birth d	270.5	12.1	271.6	21.3	0.8
Birth weight g	3004	483	3083	675	0.6
Breast feeding N (%)	25	93%	48	89%	0.7
Maternal C-reactive protein (CRP) 16 weeks gestation	9.3	7.2	10.1	8.4	0.7
Maternal Cortisol	1.06	0.58	0.81	0.47	0.045

Center for Epidemiological Studies of Depression (CESD) 16 weeks gestation	CESD 16 N = 61		CESD<16 N =101		Significance
	N	%	N	%	Fishers *P*
2nd Trimester log pg/mg hair					
Maternal Cortisone 2nd Trimester pg/mg hair	18.5	9.8	10.4	5.2	0.007
Neonatal Cortisol log pg/mg hair at birth	2.11	0.28	2.15	0.34	0.6
Neonatal Cortisone pg/mg hair at birth	65.3	17.9	95.3	48.9	0.08
P50$_{S2}$μV adjusted for P50$_{S1}$μV 1 month of age	0.93	0.09	0.71	0.06	0.04

1 African-Americans and Native-Americans are compared with European Americans. Ethnicity and race are self reported.

Table 2.

Correlations between CESD Depression ratings, newborn P50 parameters, and maternal CRP and cortisol

	CESD Depression Scale 16 wks	Newborn P50$_{S2}$µ adjusted for P50$_{S1}$µ	Newborn P50$_{S2}$µ adjusted for P50$_{S1}$µ Correlation controlled for CESD 16 wks	Maternal C-reactive Protein, male fetus, mg/L 16 wks	Maternal hair cortisol log pg/mg, female fetus 2nd trimester
Prenatal					
CESD 16 wks	--	0.301**	--	0.363**	0.293**
STAI-S 16 wks	0.214**	0.161*	−0.022	−0.014	0.264**
PSS 16 wks	0.212**	0.192*	−0.020	0.230*	0.348**
CESD 22 wks	0.695**	0.224**	−0.060	0.294*	0.061
CESD 28 wks	0.660**	0.172*	−0.042	0.074	0.189
CESD 34 wks	0.648**	0.175*	−0.055	0.288*	0.189
CESD 40 wks	0.585**	0.192*	−0.025	0.111	0.049
Postnatal					
CESD 46 wks	0.524**	0.157*	−0.033	0.012	0.143

Pearson's r

*
$P<0.05$

**
$P<0.01$

Table 3.

Effects of antidepressants on maternal and child parameters.

Measure mean (SD)	Antidepressant N = 22	None N = 139	Significance P =
CESD Depression scale 16 wks gestation	18.7 (12.4)	13.2 (8.7)	0.012
CESD 22 wks	17.0 (11.8)	12.6 (9.1)	0.045
CESD 28 wks	15.4 (9.0)	13.7 (9.6)	0.4
CESD 34 wks	16.9 (11.8)	13.5 (9.8)	0.1
CESD 40 wks	14.0 (7.7)	11.5 (8.8)	0.2
CESD 46 wks (postpartum)	14.4 (8.7)	10.7 (9.2)	0.1
Analyses of antidepressants controlled for CESD 16 weeks gestation, mean (SE)			
$P50_{S2}\mu V$ adjusted for $P50_{S1}\mu V$	0.84 (1.02)	0.82 (0.40)	0.9
Male fetus C-reactive Protein 16 weeks gestation mg/L	9.24 (1.0)	7.49 (0.93)	0.4
Female fetus cortisol 2nd trimester log pg/mg hair	1.14 (0.16)	0.86 (0.06)	0.1