Published in final edited form as:

Soc Psychiatry Psychiatr Epidemiol. 2012 March ; 47(3): 455–464. doi:10.1007/s00127-011-0353-0.

Impact of Fetal Versus Perinatal Hypoxia on Sex Differences in Childhood Outcomes: Developmental Timing Matters

Michael Anastario, Ph.D.¹, Carolyn M. Salafia, MD², Garrett Fitzmaurice, ScD³, and Jill M. Goldstein, PhD^{4,5}

¹Work was conducted while at Connors Center for Women's Health and Gender Biology, Division of Women's Health, Department of Medicine, Brigham and Women Hospital. Currently at Cicatelli Associates Inc., New York, NY (MA)

²New York University, New York City, NY

³McLean Hospital, Belmont, MA, and Harvard Medical School, Department of Psychiatry

⁴Brigham & Women's Hospital (BWH), Division of Women's Health, Connors Center for Women's Health & Gender Biology

⁵BWH and Harvard Medical School Departments of Psychiatry, Boston, MA

Abstract

Purpose—To examine how the timing of hypoxic exposure results in specific childhood outcomes and whether there is a differential effect by sex.

Methods—A sample of 10,879 prospectively followed pregnancies was drawn from the Boston and Providence sites (New England-NE) of the National Collaborative Perinatal Project. Based on placental pathology, we developed and validated a measure of probable chronic fetal hypoxia (CHP) and contrasted the effects of acute perinatal hypoxia on age 7 emotional, behavioral, and cognitive outcomes.

Results—Perinatal hypoxia had a significant impact on multiple behavioral and cognitive outcomes in boys *and* girls by age 7, in contrast to probable CHP which had a differential effect on girls and boys such that there was decreased verbal IQ and increased inhibition in females alone.

Conclusions—Findings underscore the importance of considering the timing of obstetric complications and offspring sex in investigations of the impact of fetal and perinatal hypoxia on offspring's outcomes throughout the life course.

Keywords

fetal programming; fetal hypoxia; sex differences; inhibition

Introduction

There are a number of adult onset psychiatric and neurologic disorders that have origins beginning in fetal development [1–15]. Fetal and perinatal hypoxia have been implicated as etiologic factors for a number of these disorders in adulthood and associated behavioral and cognitive deficits in childhood (e.g., [3, 5, 16–19]). Further, hypoxia has been associated with damage to brain regions which regulate behavior and emotions [3, 19]. However, it is

unclear how the developmental timing and duration of fetal and/or perinatal hypoxic exposure result in specific behavioral, cognitive, and emotional sequelae in childhood and adulthood.

One window into examining the differential effects on childhood outcomes associated with the developmental timing of hypoxic exposure is to investigate differential outcomes dependent on sex of the exposed offspring. The reason for the use of “sex of the exposed offspring” as a window into understanding the differential effects of gestational timing is based on the fact that the hormonal regulation of the sexual differentiation of the brain occurs primarily during mid-to-late gestation of development (e.g., [20–22]). Thus, we hypothesized that if an obstetric complication, such as hypoxia, occurs during this period, as distinct from birth or perinatal period, then *sex differences* in outcomes will be more prominent than those occurring outside of this critical period of the sexual differentiation of the brain. There is ample evidence that early hypoxic exposure in general is associated with psychiatric sequelae in childhood and adulthood (as referenced above). However, we know from previous animal and human work that the timing of exposure has differential consequences for male and female offspring. For example, in rats, fetal hypoxic exposure led to more severe consequences for learning behavior in male offspring, whereas postnatal exposure to anoxia did not differ between sexes [23]. While the rat brain is less developed at birth than the human brain, low birthweight in humans has served as an indicator of a fetal insult and has been associated with greater neurologic deficits in males than in females [24–26]. However, there are no studies in humans that have linked the timing of the obstetric exposure to specific sex effects in outcomes later in childhood. Thus in this study of obstetric hypoxic conditions, we hypothesize that fetal hypoxic exposure occurring during mid-to-late gestation, a key period of sexual differentiation, compared with perinatal exposure will result in *sex differences* in psychiatric outcomes and associated cognitive or behavioral outcomes in childhood. We have a rare opportunity to test this hypothesis in a human population sample (the National Collaborative Perinatal Project (NCPP) in which mothers were prospectively followed through their pregnancies and the offspring were followed through age 7 regarding behavioral, emotional, and cognitive outcomes.

Methods

Sample

The sample was originally ascertained between 1959 and 1966 from a community cohort of pregnancies drawn from the Boston and Providence sites of the National Collaborative Perinatal Project (NCPP) of the National Institute of Neurological and Communicative Disorders and Stroke [27]. The New England sites were part of a larger, nationwide sample of ~66,000 pregnancies in 12 cities across the United States [27]. In New England, 17,741 pregnancies were followed prospectively, and events of gestation, labor, delivery, and the neonatal period were systematically assessed. Children’s mental, motor, sensory, and physical development were also assessed at 4 and 8 months, and 1, 4, and 7 years of age, including standardized measures of general intelligence at age 7. Placental readings were systematically recorded. This study used these readings to evaluate indicators of hypoxic exposure (see below).

To test the impact of probable CHP on outcomes in this population, we combined subjects in the Boston and Providence CPP cohorts who had data for placental pathology *and* age 7 follow-up. The final New England CPP sample represented all subjects without missing data on probable chronic placental hypoxia (CHP, defined below) or covariates (total missing $n=4,832$, final sample $n=10,879$). Preliminary analyses showed that neither probable CHP nor perinatal hypoxia (defined below) predicted missing data on age 7 variables, nor did either hypoxic exposure interact with sex to predict missing data ($p=0.71$ for CHP interaction, and

$p=0.37$ for acute hypoxia interaction). The analytic sample consisted of 51% male and 49% female exposed individuals, primarily Caucasian (86%) and middle to lower social class, with mothers on average in their mid-twenties. Offspring exposed to probable chronic placental hypoxia were slightly higher in socioeconomic status (SES) and were more likely sampled from the Boston site (see Table 1).

Hypoxic Exposures of Interest

Chronic placental hypoxia (CHP)

For the purposes of this study, we attempted to classify subjects with fetal hypoxia who could be distinguished from subjects with later perinatal hypoxia in order to test for the effects of timing of exposure in relation to age 7 outcomes. There are admitted difficulties in attempting to link placental lesions that are considered to be effects of malperfusion to actual fetal hypoxia. However, quantitatively abnormal maternal blood flow infers overall reduced intervillous perfusion [28] and reduced fetal growth [29]. In addition, specific placental lesions, many of which were coded in the original NCPP data set (see Table 2) have been associated with fetal hypoxia. These can be grouped into lesions of the uteroplacental circulation, lesions of the fetoplacental circulation, or other CHP indicators. The placental pathology features considered to reflect probable CHP were carefully selected among the many scored variables in the NCPP data.

1. **Lesions of the uteroplacental circulation, reflecting compromised uteroplacental oxygen provision:** Uteroplacental thrombosis, villous lesions reflective of uteroplacental vascular pathologic mechanisms, including placental infarcts and villous fibrosis, have been associated with fetal hypoxia [30–43]. Macrophages in amnion/chorion and/or decidua containing hemosiderin reflect remote tissue bleeding, associated with risk of fetal hypoxia [44] and increased risk of cerebral palsy [45].
2. **Lesions of the fetoplacental circulation, compromising placental-fetal perfusion:** Single umbilical artery is associated with both intrauterine hypoxia and perinatal mortality among single live births without malformations [46] and with “fetal distress” [47–48].
3. **Other CHP indicators:** Amnion nodosum develops when there is inadequate amniotic fluid volume to maintain the amniotic debris in solution. Inadequate amniotic fluid volume (oligohydramnios) is associated with increased risk of prenatal ischemic white matter injury [49] and placental dysfunction [50].

Chronicity of these lesions can be difficult to determine with great specificity. We limited the categorization of infarcts to those old enough to be tan-white, and thus have complete hemolysis, a process generally considered to require days to complete. These lesions are generally considered to operate in the mid-late gestational age range [51–56]. Single umbilical artery has its genesis early in the first trimester. Villous fibrosis is conventionally considered to require days to develop, and its association with reduced placental weight is also consistent with a chronic and longstanding process rather than processes operating close to delivery [38, 41], and is among lesions considered to be indicative of maternal malperfusion effects [57]. Hemosiderin metabolism from hemoglobin is also considered to require a minimum of 24–48 hours. Amnion nodosum in general requires protracted reduction in fetal urination resulting in days of oligohydramnios, and in the absence of renal agenesis is almost exclusively a mid-late to late gestational phenomenon [58]. Based on Robbins [59], an acute inflammatory response predominates in the first 6–24 hours of stress (such as infectious tissue injury, or other). After 24 hours, the cell signals change and the response is termed “chronic” [59].

The presence of any one of the eight CHP items (in Table 2) qualified a subject as having been exposed to probable CHP (1= present, 0=absent). A measure of probable CHP severity, represented by number of lesions, was also created. Given that blood gases/acidosis were not collected in the 1960's to test for fetal hypoxia and thus we created a new variable based on placental pathology, we cross-validated our definition of probable CHP exposure by assessing whether probable CHP was associated with the following outcomes: small for gestational age (SGA), low birth weight, death prior to age 7, standardized age 7 height and weight, and 48-hour hematocrit levels at birth (i.e. a significantly high hematocrit at birth would indicate oxygen deprivation) (see Results). While we cannot speak to the sensitivity and specificity of our measure of probable CHP, symptoms chosen for this measure were distinct from symptoms defining acute perinatal hypoxia.

Acute perinatal hypoxia

To test whether age 7 outcomes were associated with perinatal hypoxic exposure, we developed a propensity score (a conditional probability) representing severity of probable *perinatal* hypoxic exposures. Items in the general linear model were: method of delivery (yes/no vertex; breech); abruptio placenta (yes/no); prolapsed cord (yes/no); cord pathology (tight cord around neck, yes/no); duration second stage of labor in hours; and shock (yes/no: anesthetic, hemorrhagic, septic, positional (vena cava syndrome). The model predicted low Apgar scores (<7) at one and five minutes after birth. The propensity model approach was adapted from a model of perinatal mortality by Done and colleagues [60]. In order to create a dichotomous outcome, those in the upper 85th percentile of the distribution were defined as "exposed", (i.e., those most likely to have been exposed to perinatal hypoxia). Approximately 12% of probable CHP exposed offspring also showed signs of probable perinatal hypoxic conditions. Therefore, probable CHP exposed offspring who also experienced probable perinatal hypoxia were classified as having probable CHP. Thus, *only* those experiencing exclusively acute perinatal hypoxia measures were included in the acute perinatal hypoxia definition. This created independent hypoxic exposure groups for further analyses.

Age 7 Cognitive, Behavioral, and Emotional Outcomes

Pediatric neurological exams, psychological assessments, and diagnostic physician summaries composed the measures to define cognitive, behavioral, and emotional outcomes at age 7. In a previous study to derive the emotional and behavioral scales, a variety of behavioral components observed by a trained examiner were factor analyzed and produced a four-factor solution [61]. Behavioral inhibition, distress proneness, attention, and inappropriate interpersonal self regulation composed the age seven scales representing behavior and emotion. Aggression and conduct were measured as separate scales based on positive scores for certain behavioral observations. The aggression scale was a sum of the following positive observations: extreme negativism or resistance (cooperation), extreme assertiveness, willfulness, or forcefulness (assertiveness), and/or very hostile behavior. The conduct scale was a sum of the following positive observations: extreme negativism or resistance (cooperation), extreme assertiveness, willfulness, or forcefulness (assertiveness), very hostile behavior, variable mood or extreme instability, quite upset or extreme acting out, and/or impulsive behavior. The attention scale included items that described the child's ability to stay focused on a task and persist in problem solving, attributes that have been labeled similarly in other research [62]. The Inappropriate Interpersonal Self-Regulation scale (IISR) consisted of items that reflected unrestrained interpersonal behavior [61]. Although the IISR scale is somewhat unusual relative to more traditional domains of temperament and personality, it emerged as a strong interpretable factor and has implications for research on personality and adult emotional functioning. Thus, we chose to retain it for analytic purposes [61]. The cognitive outcomes were derived from a factor

analysis of the neuropsychological battery for age 7 offspring [63] and included normalized scales for academic achievement, verbal conceptual ability, perceptual motor ability, and full scale Wechsler I.Q. All outcome scales were standardized with a mean of 0 and standard deviation of 1 in the entire NCPP sample [61], prior to analytic sample restriction and use in further analyses.

Potential Confounders

Potential confounds of the association between early hypoxic insults and behavioral and cognitive outcomes were examined. They included race (defined as Caucasian, non-Caucasian), family socioeconomic status, site of study (Boston or Providence), and maternal age, and they were controlled in the general linear model. In a multivariate regression model for which inhibition was the outcome, African American subjects showed increased inhibition ($\beta=.05$, $p=.012$); Boston site subjects showed increased inhibition ($\beta=.081$, $p<.001$); increased SES was associated with decreased inhibition ($\beta=-.045$, $p<.001$); and higher maternal age was associated with increased inhibition ($\beta=.0061$, $p<.001$). While SES and site were correlated (note, SES is only .83 of a standard deviation higher in Boston), we tested for evidence of multi-collinearity in the multivariate model. In this case, the variance inflation factor statistics for inhibition were 1.18 for site, 1.16 for SES, 1.04 for race, and 1.01 for maternal age. While SES varied by site, there was minimal evidence of multi-collinearity and thus both were retained in the multivariate model. Race, sex, and site of study were treated as dichotomous variables, and maternal age and family socioeconomic status were treated as quantitative variables.

Statistical Methods

We were primarily interested in whether CHP or acute perinatal hypoxia would show differential effects on outcomes in girls and boys. In order to control for testing multiple outcomes, one overall multivariate F test (from a multivariate analysis of covariance (MANCOVA) model) was conducted to provide a “protected test” of the impact of probable CHP, perinatal hypoxia, sex, and two-way sex by hypoxia interaction terms on multiple outcome variables. The outcome variables for the multivariate tests included cognitive (verbal conceptual), behavioral (conduct), and emotional (self regulation, inhibition) variables. General linear models were then used to separately test for associations between individual outcomes and hypoxic exposures, adjusted for the effects of study site, race, socioeconomic status, and maternal age. Two-way interactions between hypoxia and sex were examined for probable CHP and perinatal hypoxia. In the case that one’s sex modified the effects of a fetal or perinatal hypoxic exposure, the main effects of hypoxia on a particular outcome cannot be interpreted since they would not be meaningful in the presence of a significant interaction. Secondary analyses of these data were approved by Harvard and Brown University’s Institutional Review Boards.

Results

The sample consisted of 964 (8.86%) subjects who were exposed to probable CHP and 1,198 (12.2%) exposed to probable perinatal hypoxia. To cross-validate the measure of probable CHP and probable perinatal hypoxia, we tested their associations with low birth weight, small-for-gestational age (SGA), death prior to age 7, age 7 height and weight, and standardized 48-hour hematocrit levels. Both groups of hypoxic-exposed offspring compared with non-exposed controls had lower birth weight and age 7 height and higher prevalence of SGA and death prior to age 7. In addition, as expected, standardized 48-hour hematocrits were significantly higher in probable CHP exposures ($\text{mean}=.12$, $SD=1.0$) versus healthy controls ($-.007$, 1.0) ($t=-3.8$, $p=.001$), indicating fetal hypoxic exposure most likely occurred. Low birthweight occurred in 10.7% of probable CHP positive cases versus

7.8% of probable CHP negative cases ($\chi^2 = 10.1$, $p = .01$) and 18.5% of perinatal hypoxia positive cases versus 6.3% of perinatal hypoxia negative cases ($\chi^2 = 219.7$, $p = .001$). Thus both hypoxic exposed groups had a significantly increased risk for LBW (probable CHP: adjusted OR=1.5, SE=.04, $p = .001$ and perinatal hypoxia: OR=3.4, SE=.29, $p = .001$). SGA occurred in 12.8% of probable CHP positive cases versus 10.8% in probable CHP negative cases ($\chi^2 = 3.5$, $p = .06$) and 15.7% of perinatal hypoxia positive cases versus 10.1% of perinatal hypoxia negative cases ($\chi^2 = 34.1$, $p = .001$). Neither probable CHP nor perinatal hypoxia had an effect on weight at age 7. The prevalence of death prior to age 7 was 12.5% in probable CHP positive cases and 3.7% in probable CHP negative cases ($\chi^2 = 231.6$, $p = .001$) and 12% in perinatal hypoxia positive cases and 2.3% in perinatal hypoxia negative cases ($\chi^2 = 41.9$, $p = .001$). Thus both probable CHP and perinatal hypoxia significantly increased the risk for death (respectively, adjusted OR=1.9, SE=.05, $p = .001$ and OR=5.7, SE=.057, $p = .001$). Further, an examination of potential confounders showed that probable CHP exposure was significantly associated with family SES and site (see Table 1), but not with race or maternal age.

The protective F test for multiple dependent variables related to probable CHP was significant and included a significant interaction effect of probable CHP with sex [Overall model: Wilk's $\lambda = 0.98$, $F(4, 10,709) = 49.6$, $p < .001$; probable CHP by sex interaction: Wilk's $\lambda = .99$, $F(4, 10,707) = 2.39$, $p < .05$]. For perinatal hypoxia, only the main effect of hypoxia was significant [Wilk's $\lambda = 0.99$, $F(4, 9,768) = 2.4$, $p < .05$]. The interaction of perinatal hypoxia and sex was not significant, thus dropped from the model.

An examination of the specific (univariate) outcomes affected by hypoxia exposures revealed the following. As seen in Table 3, probable perinatal hypoxia was significantly associated with a multitude of outcomes for boys and girls, including a decline in verbal IQ ($\beta = -.06$ (SE = .03); $F(1, 9790) = 4.3$, $p = .05$), lower perceptual motor performance ($\beta = -.13$ (SE = .03), $F(1, 9784) = 18.7$, $p = .001$), decreased IQ ($\beta = -1.1$ (SE = .39); $F(1, 9876) = 8.2$, $p = .01$), and decreased attention ($\beta = -.06$ (SE = .03); $F(1, 9890) = 4.8$, $p = .05$). The main effect of probable CHP was significantly associated only with a decline in perceptual motor skills ($\beta = -.07$) [$F(1, 10736) = 4.8$, $p = .05$].

In fact, the significant effects of probable CHP on age 7 outcomes were evident primarily as modified by sex (represented by the significant overall interaction effect of probable CHP with sex). As seen in Table 3 and Figures 1 and 2, sex specifically modified the effect of probable CHP on two outcomes, verbal conceptual ability and inhibition at age 7. For conceptual verbal IQ, probable CHP lowered standardized scores in girls ($\beta = -.09$) [$F(1, 10732) = 4.7$, $p = .05$] and was associated with a slight increase ($\beta = .04$) in boys' scores. Adjusted least square mean scores for conceptual verbal IQ were lowest in probable CHP females (-.38) compared with unexposed females (-.29), unexposed males (-.16) and exposed males (-.12) (see Table 3 and Figure 1). The effect of probable CHP on verbal IQ in girls was associated with 35% (three tenths) of a standard deviation below the population average, whereas the probable CHP effect in boys was associated with only 8.5% (one tenth) of a standard deviation below the population average. For inhibition at age 7, probable CHP significantly increased inhibition in girls by age 7 compared with little effect on inhibition in boys by age 7 [$F(1, 10871) = 3.7$, $p = .05$]. Adjusted least square mean scores for inhibition were highest in probable CHP exposed females (-.06) when compared with unexposed females (-.01), unexposed males (-.004) and exposed males (-.006) (see Table 3 and Figure 2). The effect of probable CHP on inhibition in girls was associated with approximately 85% (eight tenths) of a standard deviation above the population average, whereas the probable CHP effect in boys was associated with only 14.4% (one tenth) of a standard deviation below the population average. There was no evidence that one's sex significantly modified the effect of perinatal hypoxia on any of the outcomes at age 7. When both probable CHP

and probable perinatal hypoxia were treated as severity (continuous) versus dichotomous measures, results did not change.

A post-hoc analysis was conducted in order to examine whether the interaction between probable CHP and sex was sensitive to the inclusion of individuals classified with exposure to both probable CHP and perinatal hypoxia. When this subgroup was removed, the gap in adjusted least square mean scores was widened for inhibition, where exposed females showed greater inhibition ($-.07$) and exposed males showed less inhibition ($-.03$). For the verbal outcome, scores increased globally, however the differences observed in the exposure group widened from $\Delta=|.26|$ to $\Delta=|.31|$, with exposed females continuing to perform lower ($-.26$) than exposed males ($-.05$).

Discussion

The aim of this study was to test whether the timing of a fetal or perinatal hypoxic insult was associated with *sex-specific* outcomes in childhood by age 7. Findings showed that exposure to probable chronic fetal hypoxia (CHP) had a differential impact on boys and girls at age 7, whereas exposure to probable perinatal hypoxia affected boys and girls similarly. Females exposed to probable CHP showed greater inhibition and lower verbal IQ at age 7 than boys, suggesting that females were particularly vulnerable to probable CHP.

Probable CHP also showed a significant effect on perceptual-motor abilities in both sexes. This is not surprising given that the definition of perceptual-motor abilities contained functions that are both male associated (such as motor functions) and female associated (perceptual speed) [64]. However, our results also contributed unique evidence that, dependent on the specific outcome domains assessed, the effect of probable CHP was also dependent on offspring sex, which was not true for perinatal hypoxic risk factors. We suggest this may reflect insufficient levels of oxygen available to the central nervous system during critical periods of the sexual differentiation of the brain resulting in differential outcomes in boys and girls. This may implicate one pathway for understanding differential vulnerabilities for sex differences in adult psychiatric or neurologic disorders with known developmental origins.

In contrast, perinatal hypoxia has been associated with a more general constellation of outcomes in childhood, and our findings confirm previous reports of similar abnormalities [18, 65–68]. The nature of a perinatal hypoxic insult may lead to hypoxic-ischemic encephalopathy, a condition where the brain's compensatory ability during hypoxemia fails and causes greater damage associated with the severity of the insult [69]. This may explain the observed cross-domain effects for perinatal hypoxia found in age 7 boys and girls.

Our development of a unique chronic fetal hypoxic measure, defined using a systematic assessment of placental pathology to indicate an adverse fetal environment, may not capture all chronic hypoxic insults which occurred in utero, and may not be specific to hypoxia. A single cross-section of the cord was obtained, with one membrane roll and one histologic sample of the disk. It is possible that missing a lesion due to sparse sampling could have resulted in misclassification, with a case being falsely referred to as “normal” in which a lesion was simply missed in sampling. False negatives are unavoidable in this data set for which the placentas no longer exist. However, this type of misclassification should attenuate specific effects of probable CHP. Further, the amount of missing follow-up data may be attributable to unobserved spurious factors. These points may somewhat limit the generalizability of our findings, but would not negate the internal validity of the observed associations.

Fetal hypoxia is a particularly difficult variable to infer from placental measures, as the organism whose hypoxia is of interest is the fetus, and the placenta derives its oxygen from the maternal circulation by which it is directly bathed. However, a misclassification bias would be more likely to result in a Type II Error, as the misclassification would attenuate significant differences between probable CHP and probable acute perinatal hypoxia. Further, it is possible that the observed sequelae reflect a duration effect (i.e. fetal hypoxia extending into the perinatal period), rather than exclusive timing effects. To best counteract this possibility, we eliminated “cross-over” exposures from the perinatal hypoxia group definition and comparison group. Given that this study was conducted in the 1950’s/60’s, blood gas acidosis measurements were unavailable as were Doppler-based screening measurements for waveform velocity. However, we had several measures associated with probable CHP, including significantly higher hematocrits, which contributed to the validation of identifying probable CHP exposure. Finally, there was an even distribution of sex among the exposed individuals reducing the concern that there was a selection bias by sex. Additionally, our measures of childhood behavior and emotion were derived from examiner observation and thus were more prone to reflect biases in clinical opinion than are the cognitive measures. However, the behavioral and emotional variables have been validated in previous studies [61], and one would not expect differential misclassification by sex.

Verbal ability and inhibition are domains in which girls generally tend to predominate over boys [64]. Thus, the lower score among probable CHP-exposed females may be attributable to a sex-specific sensitivity reflecting the underlying development of brain regions implicated in inhibition and verbal ability, which are normally sexually dimorphic brain regions [70–71]. Inhibition in childhood has been linked to anxiety and mood disorders in adulthood [72], disorders that have higher incidences in women than men [72–76]. Our large sample size provided the ability to detect behavioral differences of a relatively smaller magnitude, producing outcomes that may have been subclinical at age 7. The presence of these differences early in the life course may result in more observable differences in adulthood. For example, a recent study documented a link between emotional causes of pain in primary and secondary school and anxiety in adulthood [77]. Further, fetal risk factors, particularly occurring during mid-gestation, have been implicated in major depressive disorder [7, 9–10, 78], which may be associated with birth outcomes, such as low birth weight or neonatal intensive care unit admission, and their association with depression in adulthood [2, 78]. In fact, animal studies of fetal risk factors in stress response circuitry (i.e. brain circuitry associated with depression and anxiety disorders) have demonstrated greater hyperactivity in females compared to males [79–81]. Thus, as mentioned, our findings may suggest one pathway to investigate fetal antecedents to sex differences in major depressive and anxiety disorders in adulthood.

Abnormalities in motor, cognitive (IQ, verbal, academic achievement), behavioral (attention) and executive functioning have been linked with early hypoxic-ischemic encephalopathy [82–85], perinatal anoxia [66], and perinatal hypoxia [67–68]. However, consistent with our findings, there is some work in animals and humans suggesting that perinatal acute hypoxic insults have different effects on male and female offspring than chronic fetal hypoxia [23–26]. It is also possible that the observed differences may reflect other underlying genetic, hormonal and/or environmental factors, necessitating further research to identify the biological mechanisms underlying the sex-specific observations in this study.

Conclusions

In summary, we found that exposure to a hypoxic insult during the fetal mid-to-late gestational period resulted in sex differences in inhibition and verbal IQ at age 7 (with girls exhibiting greater deficits in these domains than boys), whereas hypoxia during the perinatal period showed effects that were not sex-specific. In contrast, exposure to perinatal hypoxia was significantly associated with a variety of childhood outcomes in boys and girls, displaying less domain specificity and no evidence of effect modification by sex. These findings may provide insights into how the timing of hypoxic exposure results in sex differences in certain neurodevelopmental disorders. Although our findings require replication, further research on the hormonal and genetic mechanisms underlying the effects of fetal hypoxic exposure during the sexual differentiation of the brain [22, 71] will help us better understand sex differences that are observed in adult onset psychiatric disorders known to have fetal and neonatal origins.

Acknowledgments

The work was supported by National Institute of Mental Health Office of Research on Women's Health (P50 MH082679 to JMG) and National Institute of Mental Health (RO1 MH56956 to JMG). M.A.'s work was supported by the Connors Center for Women's Health & Gender Biology at Brigham and Women's Hospital. The authors would like to thank Stephen Buka, Sc.D. for his help on previous versions of this work and his substantial commitment to using the New England cohorts of the NCPP to understand fetal and early antecedents to disorders throughout one's lifetime. We would also like to thank the Co-PI's of P50 MH082679 (Stuart Tobet, Ph.D. and Robert Handa, Ph.D.) for their insightful comments on the findings in this study.

References

1. Cannon TD, Yolken R, Buka S, Torrey EF, Goldstein JM, Seidman LJ, Tsuang M, Hadley T, Bearden CE, Rossso J, Dhavale D. Decreased neurotrophic response to birth hypoxia in the etiology of schizophrenia. *Biol Psychiatry*. 2008; 64:797–802. [PubMed: 18486103]
2. Mallen C, Mottram S, Thomas E. Birth factors and common mental health problems in young adults: a population-based study in North Staffordshire. *Soc Psychiatry Psychiatr Epidemiol*. 2008; 43:325–330. [PubMed: 18196185]
3. Cannon TD, van Erp TG, Rosso IM, Huttunen MO, Lonnqvist J, Pirkola T, Salonen O, Valanne L, Poutanen V-P, Standertskjold-Nordenstam CG. Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry*. 2002; 59:35–41. [PubMed: 11779280]
4. Buka SL, Lipsitt LP, Tsuang MT. Pregnancy/delivery complications and psychiatric diagnosis: A prospective study. *Arch Gen Psychiatry*. 1993; 50:151–156. [PubMed: 8427556]
5. Zornberg GL, Buka SL, Tsuang MT. Hypoxic-ischemia-related fetal/neonatal complications and risk of schizophrenia and other nonaffective psychoses: a 19-year longitudinal study. *Am J Psychiatry*. 2000; 157:196–202. [PubMed: 10671387]
6. Tronche F, Kellendonk C, Kretz O, Gass P, Anlag K, Orban PC, Bock R, Klein R, Schutz G. Disruption of the glucocorticoid receptor gene in the nervous system results in reduced anxiety. *Nat Genet*. 1999; 23:99–103. [PubMed: 10471508]
7. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. *Arch Gen Psychiatry*. 1997; 54:625–631. [PubMed: 9236546]
8. Goldstein, JM.; Walder, DJ. Sex differences in schizophrenia: The case for developmental origins and etiological implications. In: Sharma, T.; Harvey, P., editors. *The Early Course of Schizophrenia*. Oxford University Press; United Kingdom: 2002.
9. Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM. Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch Hunger Winter of 1944–45. *Br J Psychiatry*. 1995; 166:601–606. [PubMed: 7620744]

10. Brown AS, van Os J, Driessens C, Hoek HW, Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry*. 2000; 157:190–195. [PubMed: 10671386]
11. Machon RA, Mednick SA, Huttunen MO. Adult major affective disorder after prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry*. 1997; 54:322–328. [PubMed: 9107148]
12. Watson JB, Mednick SA, Huttunen M, Wang X. Prenatal teratogens and the development of adult mental illness. *Dev Psychopathol*. 1999; 11:457–466. [PubMed: 10532619]
13. Jones PB, Tarrant CJ. Specificity of developmental precursors to schizophrenia and affective disorders. *Schizophr Res*. 1999; 39:121–126. [PubMed: 10507522]
14. Brown AS, Susser ES, Lin SP, Gorman JM. Affective disorders in Holland after prenatal exposure to the 1957 A2 influenza epidemic. *Biol Psychiatry*. 1995; 38:270–273. [PubMed: 8547451]
15. Thompson C, Syddall H, Rodin I, Osmond C, Barker DJ. Birth weight and the risk of depressive disorder in late life. *Br J Psychiatry*. 2001; 179:450–455. [PubMed: 11689404]
16. Ley D, Tideman E, Laurin J, Bjerre I, Marsal K. Abnormal fetal aortic velocity waveform and intellectual function at 7 years of age. *Ultrasound Obstetr Gynecol*. 1996; 8:160–165.
17. Wienerroither H, Steiner H, Tomaselli J, Lobendanz M, Thun-Hohenstein L. Intrauterine blood flow and long-term intellectual, neurologic, and social development. *Obstet Gynecol*. 2001; 97:449–453. [PubMed: 11239655]
18. Goldstein JM, Seidman LJ, Buka SL, Horton NJ, Donatelli JAL, Rieder RO, Tsuang MT. Impact of genetic vulnerability and hypoxia on overall intelligence by age 7 in offspring at high risk for schizophrenia compared with affective psychoses. *Schizophr Bull*. 2000; 26:323–334. [PubMed: 10885634]
19. Li J, Lin JC, Wang H, Peterson JW, Furie BC, Furie B, Booth SL, Volpe JJ, Rosenberg PA. Novel role of vitamin k in preventing oxidative injury to developing oligodendrocytes and neurons. *The Journal of Neuroscience*. 2003; 23:5816–5826. [PubMed: 12843286]
20. Kawata M. Roles of steroid hormones and their receptors in structural organization in the nervous system. *Neurosci Res*. 1995; 24:1–46. [PubMed: 8848287]
21. Tobet SA. Genes controlling hypothalamic development and sexual differentiation. *Eur J Neurosci*. 2002; 16:373–376. [PubMed: 12193176]
22. Tobet SA, Hanna IK. Ontogeny of sex differences in the mammalian hypothalamus and preoptic area. *Cell Mol Neurobiol*. 1997; 17:565–601. [PubMed: 9442348]
23. Grimm VE, Frieder B. Differential vulnerability of male and female rats to the timing of various perinatal insults. *Int J Neurosci*. 1985; 27:155–164. [PubMed: 4044127]
24. Amato M, Howald H, Murali GV. Foetal sex distribution of peri-intraventricular haemorrhage in preterm infants. *Eur Neurol*. 1987; 27:20. [PubMed: 3305031]
25. Rantakallio P, Wendt LV. Prognosis for low-birthweight infants up to the age of 14: a population study. *Developmental Medicine and Child Neurology*. 1985; 27:655–663. [PubMed: 4065438]
26. Murray, RM.; Owen, MJ.; Goodman, R.; Lewis, SW. A neurodevelopmental perspective on some epiphenomena of schizophrenia. In: Cazullo, CL.; Invernizzi, G.; Sacchetti, E.; Vita, A., editors. *Plasticity and Morphology of the CNS*. MIT Press; Lancaster: 1989.
27. Niswander, KR.; Gordon, M. *The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke: The Women and Their Pregnancies*. Government Printing Office, U.S. Department of Health, Education, and Welfare; Washington, D.C: 1972.
28. Sebire NJ, Jain V, Talbert DG. Spiral artery associated restricted growth (SPAARG): a computer model of pathophysiology resulting from low intervillous pressure having fetal programming implications. *Pathophysiology*. 2004; 11:87–94. [PubMed: 15364119]
29. Lackman F, Capewell V, Gagnon R, Richardson B. Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. *Am J Obstet Gynecol*. 2001; 185:674–682. [PubMed: 11568797]
30. Salafia CM, Minior VK, Lopez-Zeno JA, Whittington SS, Pezzullo JC, Vintzileos AM. Relationship between placental histologic features and umbilical cord blood gases in preterm gestations. *Am J Obstet Gynecol*. 1995; 173:1058–1064. [PubMed: 7485293]
31. McDermott M, Gillan JE. Chronic reduction in fetal blood flow is associated with placental infarction. *Placenta*. 1995; 16:165–170. [PubMed: 7792280]

32. Becroft DM, Thompson JM, Mitchell EA. Placental infarcts, intervillous fibrin plaques, and intervillous thrombi: incidences, cooccurrences, and epidemiological associations. *Pediatric and Developmental Pathology*. 2004; 7:26–34. [PubMed: 15255032]
33. Beinder E, Mohaupt MG, Schlembach D, Fischer T, Sterzel RB, Lang N, Baylis C. Nitric oxide synthase activity and Doppler parameters in the fetoplacental and uteroplacental circulation in preeclampsia. *Hypertens Pregnancy*. 1999; 18:115–127. [PubMed: 10476613]
34. Kumazaki K, Nakayama M, Sumida Y, Ozono K, Mushiake S, Suehara N, Wada Y, Fujimura M. Placental features in preterm infants with periventricular leukomalacia. *Pediatrics*. 2002; 109:650–655. [PubMed: 11927710]
35. Nelson DM, Crouch EC, Curran EM, Farmer DR. Trophoblast interaction with fibrin matrix. Epithelialization of perivillous fibrin deposits as a mechanism for villous repair in the human placenta. *Am J Pathol*. 1990; 136:855–865. [PubMed: 2327472]
36. Wyatt SM, Kraus FT, Roh CR, Elchalal U, Nelson DM, Sadovsky Y. The correlation between sampling site and gene expression in the term human placenta. *Placenta*. 2005; 26:372–379. [PubMed: 15850641]
37. Wataba K, Saito T, Takeuchi M, Nakayama M, Suehara N, Kudo R. Changed expression of heat shock proteins in various pathological findings in placentas with intrauterine fetal growth restriction. *Medical Electron Microscopy*. 2004; 37:170–176. [PubMed: 15449110]
38. Out HJ, Kooijman CD, Bruinse HW, Derksen RH. Histopathological findings in placentae from patients with intra-uterine fetal death and anti-phospholipid antibodies. *Eur J Obstet Gynecol Reprod Biol*. 1991; 41:179–186. [PubMed: 1936501]
39. Salafia CM, Pezzullo JC, Lopez-Zeno JA, Simmens S, Minior VK, Vintzileos AM. Placental pathologic features of preterm preeclampsia. *Am J Obstet Gynecol*. 1995; 173:1097–1105. [PubMed: 7485300]
40. Mardi K, Sharma J. Histopathological evaluation of placentas in IUGR pregnancies. *Indian J Pathol Microbiol*. 2003; 46:551–554. [PubMed: 15025340]
41. Salafia CM, Minior VK, Pezzullo JC, Popek EJ, Rosenkrantz TS, Vintzileos AM. Intrauterine growth restriction in infants of less than thirty-two weeks' gestation: associated placental pathologic features. *American Journal of Obstetrics and Gynecology*. 1995; 173:1049–1057. [PubMed: 7485292]
42. Salafia CM, Vogel CA, Bantham KF, Vintzileos AM, Pezzullo JC, Silberman L. Preterm delivery: Correlations of fetal growth. *Am J Perinatol*. 1992; 9:190–193. [PubMed: 1575840]
43. Salafia CM, Vintzileos AM, Silberman L, Bantham KF, Vogel CA. Placental pathology of idiopathic intrauterine growth retardation at term. *Am J Perinatol*. 1992; 9:179–184. [PubMed: 1575839]
44. Salafia CM, Lopez-Zeno JA, Sherer DM, Whittington SS, Minior VK, Vintzileos AM. Histologic evidence of old intrauterine bleeding is more frequent in prematurity. *Am J Obstet Gynecol*. 1995; 173:1065–1070. [PubMed: 7485294]
45. Redline RW, Pappin A. Fetal thrombotic vasculopathy: the clinical significance of extensive avascular villi. *Human Pathology*. 1995; 26:80–85. [PubMed: 7821920]
46. Bjoro K Jr. Vascular anomalies of the umbilical cord. II. Perinatal and pediatric implications. *Early Hum Dev*. 1983; 8:279–287. [PubMed: 6685618]
47. Dudiak CM, Salomon CG, Posniak HV, Olson MC, Flisak ME. Sonography of the umbilical cord. *Radiographics*. 1995; 15:1035–1050. [PubMed: 7501849]
48. Liu BN. Pathological analysis of 76 placentae in fetal distress. *Zhonghua Fu Chan Ke Za Zhi*. 1991; 26(3):144–148. 187. [PubMed: 1874056]
49. Gaffney G, Squier MV, Johnson A, Flavell V, Sellers S. Clinical associations of prenatal ischaemic white matter injury. *Arch Dis Child Fetal Neonatal Ed*. 1994; 70:F101–106. [PubMed: 8154901]
50. Brace RA. Physiology of amniotic fluid volume regulation. *Clin Obstet Gynecol*. 1997; 40:280–289. [PubMed: 9199840]
51. Amir H, Weintraub A, Aricha-Tamir B, Apel-Sarid L, Holcberg G, Sheiner E. A piece in the puzzle of intrauterine fetal death: Pathological findings in placentas from term and preterm intrauterine fetal death pregnancies. *Journal of Maternal-Fetal and Neonatal Medicine*. 2009; 22:759–764. [PubMed: 19526426]

52. Kramer MS, Kahn SR, Rozen R, Evans R, Platt RW, Chen MF, Goulet L, Séguin L, Dassa C, Lydon J, McNamara H, Dahhou M, Genest J. Vasculopathic and thrombophilic risk factors for spontaneous preterm birth. *Int J Epidemiol.* 2009; 38:715–723. [PubMed: 19336437]
53. Kramer MS, Chen MF, Roy I, Dassa C, Lamoureux J, Kahn SR, McNamara H, Platt RW. Montreal Prematurity Study Group. Intra- and interobserver agreement and statistical clustering of placental histopathologic features relevant to preterm birth. *Am J Obstet Gynecol.* 2006; 195:1674–1679. [PubMed: 16796983]
54. Salafia CM, Pezzullo JC, Ghidini A, Lopez-Zeno JA, Whittington SS. Clinical correlations of patterns of placental pathology in preterm pre-eclampsia. *Placenta.* 1998; 19:67–72. [PubMed: 9481787]
55. Beebe LA, Cowan LD, Altschuler G. The epidemiology of placental features: Associations with gestational age and neonatal outcome. *Obstet Gynecol.* 1996; 87:771–778. [PubMed: 8677084]
56. Kaplan CG. Fetal and maternal vascular lesions. *Semin Diagn Pathol.* 2007; 24:14–22. [PubMed: 17455858]
57. Langston C, Kaplan CG, Macpherson T, Mancini E, Peevy K, Clark B, Murtagh C, Cox S, Glenn G. Practice guideline for examination of the placenta: Developed by the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists. *Arch Pathol Lab Med.* 1997; 121:449–476. [PubMed: 9167599]
58. Sherer DM. A review of amniotic fluid dynamics and the enigma of isolated oligohydramnios. *Am J Perinatol.* 2002; 19:253–266. [PubMed: 12152144]
59. Robbins, S.; Cotran, R. Robbins and Cotran Pathologic Basis of Disease. 7. Elsevier Saunders; Philadelphia, PA: 2005.
60. Done DJ, Johnstone EC, Frith CD, Golding J, Shepherd PM, Crow TJ. Complications of pregnancy and delivery in relation to psychosis in adult life: Data from the British perinatal mortality survey sample. *Br Med J.* 1991; 302:1576–1580. [PubMed: 1855042]
61. Kubzansky LD, Martin LT, Buka SL. Early manifestations of personality and adult emotional functioning. *Emotion.* 2004; 4:364–377. [PubMed: 15571435]
62. Rothbart, MK.; Bates, JE. Temperament. In: Damon, W.; Eisenberg, N., editors. *Handbook of child psychology.* 5. Vol. 3. New York: Wiley; 1998. p. 105-176.
63. Seidman LJ, Buka SL, Goldstein JM, Horton NJ, Rieder RO, Tsuang MT. The relationship of obstetrical complications to cognitive functioning at age 7 in the New England cohorts of the National Collaborative Perinatal Project. *Schizophr Bull.* 2000; 26:309–321. [PubMed: 10885633]
64. Collaer ML, Hines M. Human behavioral sex differences: a role for gonadal hormones during early development? *Psychological Bulletin.* 1995; 118:55–107. [PubMed: 7644606]
65. Buka S, Seidman L, Goldstein J, Zornberg G, Donatelli J, Denny L, Tsuang M. Impacts of perinatal hypoxia and genetic vulnerability on schizophrenia: The New England Longitudinal Studies of Schizophrenia. *Psychiatric Annals.* 1999; 29:151–156.
66. Corah NL, Anthony EJ, Painter P, Stern JA, Thurston DL. Effects Of Perinatal Anoxia After Seven Years. *Psychological Monographs.* 1965; 79(SUPPL 3):1–34. [PubMed: 14300512]
67. Maneru C, Junque C, Botet F, Tallada M, Guardia J. Neuropsychological long-term sequelae of perinatal asphyxia. *Brain Inj.* 2001; 15:1029–1039. [PubMed: 11712949]
68. Maneru C, Junque C. Cognitive deficit in perinatal asphyxia. *Revista de Neurologia.* 2002; 34:1171–1177. [PubMed: 12134285]
69. Perlman JM. Intervention strategies for neonatal hypoxic-ischemic cerebral injury. *Clin Ther.* 2006; 28:1353–1365. [PubMed: 17062309]
70. Walder DJ, Seidman LJ, Makris N, Tsuang MT, Kennedy DN, Goldstein JM. Neuroanatomic substrates of sex differences in language dysfunction in schizophrenia: a pilot study. *Schizophr Res.* 2007; 90:295–301. [PubMed: 17150336]
71. Goldstein JM, Seidman LJ, Horton NJ, Makris N, Kennedy DN, Caviness VS Jr, Faraone SV, Tsuang MT. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex.* 2001; 11:490–497. [PubMed: 11375910]
72. Schwartz CE, Wright CI, Shin LM, Kagan J, Rauch SL. Inhibited and uninhibited infants “grown up”: adult amygdalar response to novelty. *Science.* 2003a; 300:1952–1953. [PubMed: 12817151]

73. Rosenbaum JF, Biederman J, Bolduc-Murphy EA, Faraone SV, Chaloff J, Hirshfeld DR, Kagan J. Behavioral inhibition in childhood: A risk factor for anxiety disorders. *Harv Rev Psychiatry*. 1993; 1:2–16. [PubMed: 9384823]
74. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS. The epidemiology of major depressive disorder: Results from the National Comorbidity Survey Replication (NCS-R). *The Journal of the American Medical Association*. 2003; 289:3095–3105.
75. Kendler K, Gatz M, Gardner C, Pedersen N. A Swedish national twin study of lifetime major depression. *American Journal of Psychiatry*. 2006; 163:109–114.
76. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *The Journal of the American Academy of Child and Adolescent Psychiatry*. 1999; 38:1008–1015.
77. Mallen CD, Mottram S, Thomas E. Is childhood pain associated with future mental health problems? A population based study of young adults in North Staffordshire. *Soc Psychiatry Psychiatr Epidemiol*. 2009; 44:489–494. [PubMed: 18974908]
78. Goldstein JM, Cherkertzian S, Buka SL, Fitzmaurice G, Susser E, Hornig M, Gillman MW, Factor-Litvak P, Sloan R. Sex-specific impact of maternal-fetal inflammatory risk factors on depression and cardiovascular risk 40 Years Later. *Journal of Developmental Origins of Health and Disease*. 2011 under review.
79. Bale TL, Vale WW. Increased depression-like behaviors in corticotropin-releasing factor receptor-2-deficient mice: sexually dichotomous responses. *Journal of Neuroscience*. 2003; 23:5295–5301. [PubMed: 12832554]
80. McCormick CM, Smythe JW, Sharma S, Meaney MJ. Sex-specific effects of prenatal stress on hypothalamic-pituitary-adrenal responses to stress and brain glucocorticoid receptor density in adult rats. *Brain Res Dev Brain Res*. 1995; 84:55–61.
81. Bale TL, Picetti R, Contarino A, Koob GF, Vale WW, Lee KF. Mice deficient for both corticotropin-releasing factor receptor 1 (CRFR1) and CRFR2 have an impaired stress response and display sexually dichotomous anxiety-like behavior. *J Neurosci*. 2002; 22:193–199. [PubMed: 11756502]
82. Funayama CA, de Moura-Ribeiro MV, Goncalves AL. Hypoxic-ischemic encephalopathy in newborn infants. Acute period and outcome. *Arquivos de Neuro-Psiquiatria*. 1997; 55:771–779. [PubMed: 9629337]
83. Robertson C, Finer N. Term infants with hypoxic-ischemic encephalopathy: outcome at 3.5 years. *Developmental Medicine and Child Neurology*. 1985; 27:473–484. [PubMed: 4029517]
84. Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr*. 1989; 114:753–760. [PubMed: 2469789]
85. Robertson CM, Grace MG. Validation of prediction of kindergarten-age school-readiness scores of nondisabled survivors of moderate neonatal encephalopathy in term infants. *Canadian Journal of Public Health Revue Canadienne de Sante Publique*. 1992; 83(Suppl 2):S51–57. [PubMed: 1468051]

Figure 1.

Differential impact of sex on the effect of chronic fetal hypoxia on age 7 verbal conceptual ability, standardized †

† Tick marks represent adjusted estimates of the inter-quartile range, 25th–75th percentiles

Figure 2.

Differential impact of sex on the effect of chronic fetal hypoxia on age 7 inhibition, standardized †

† Tick marks represent adjusted estimates of the inter-quartile range, 25th–75th percentiles

Table 1

Characteristics of the Sample by Exposure Status

Characteristics	CHP		Acute Perinatal	
	Unexposed (n=9, 915)	Exposed (n=964)	Unexposed (n=9,556)	Exposed (n=1,198)
% male	51%	52%	51%	48% *
Ethnicity, % Caucasian	86%	86%	86%	86%
Family SES, mean (SD)	5.7 (2)	5.5 (2) **	5.7 (2)	5.8 (2) *
% Boston site	75%	61% **	74%	76%
Mother's age at birth	25.2 (6)	25.4 (6.1)	25 (5.9)	26.5 (6.3) **

* p<0.05 for χ^2 tests of differences by exposure status

** p<0.01 for χ^2 tests of differences by exposure status

Table 2**Fetal Hypoxia Diagnostic Criteria; Placental Items**

Fetal Hypoxia
Amnion nodosum
Infarcts>0 are yellowish-white: not marginal AND at least one infarct ≥ 3 cms
One umbilical artery
Infarction in the intervillous space
Macrophage
in amnion/chorion containing hemosiderin
in deciduas containing hemosiderin
In Deciduas
Marked necrosis in basalis
In Terminal Villi
Stromal fibrosis present

Rating points: 1, fetal hypoxia; 0, fetal hypoxia negative

Table 3

Least square means for standardized age 7 cognitive, behavioral, and emotional outcomes by sex and hypoxic exposure¹

CHRONIC HYPOXIA										
	Academic	Verbal ^b	Percep. Mtr. ^a	IQ	Inhibition ^b	Aggression	Conduct	Distress	Attention	Self Regulation
Exposed males	-0.28	-0.12	-0.33	99.1	-0.006	0.15	0.31	0.08	-0.07	0.08
Exposed females	-0.1	-0.38	-0.23	97.4	0.06	0.08	0.18	-0.02	0.05	-0.06
Unexposed males	-0.31	-0.16	-0.26	99.1	0.004	0.15	0.31	0.07	-0.06	0.05
Unexposed females	-0.08	-0.29	-0.16	98.4	-0.01	0.09	0.17	-0.04	0.04	0.003

PERINATAL HYPOXIA										
	Academic	Verbal ^a	Percep. Mtr. ^{aaa}	IQ ^{aa}	Inhibition	Aggression	Conduct	Distress	Attention ^a	Self Regulation
Exposed males	-0.28	-0.2	-0.33	98.3	0.04	0.15	0.33	0.04	-0.09	0.09
Exposed females	-0.11	-0.34	-0.27	97.5	-0.003	0.09	0.17	-0.003	-0.04	0.04
Unexposed males	-0.3	-0.15	-0.24	99.2	-0.001	0.15	0.31	-0.001	-0.06	0.05
Unexposed females	-0.06	-0.27	-0.13	98.7	-0.016	0.08	0.17	-0.016	0.06	0.005

¹Results are from a general linear model. Analyses controlled for main effects of hypoxia, sex, testing site, ethnicity, family SES, and maternal age.

Overall F Test: Wilk's lambda = .99; F(8,10653)= 2.0-p<.05

^aSignificant main effects of chronic and perinatal hypoxia.

For CHP: perceptual motor

For Perinatal: verbal, perceptual motor, general intelligence and attention.

^a p<.05,

^{aa} p<.01,

^{aaa} p>.001

^b Significant 2-way interaction effect of gender and CHP on verbal ability and inhibition;

^b p<.05