Initial Proposal for Core Hypothesis\Question

I. Proposed Core Hypothesis\Question:
**Excessive maternal psychosocial stress during pregnancy, in conjunction with maternal and fetal genetic susceptibilities, is reflected in specific measures of biologic function and results in an altered trajectory of fetal growth and development. These consequences predispose to adverse outcomes, such as preterm birth, fetal/infant demise, cognitive/neurobehavioral dysfunction, and adult onset of cardiovascular disease.**

II. Workgroup: Pregnancy and the Infant

III. Contact Person for Proposed Core Hypothesis\Question:


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IV. Public Health Significance

We think of the fetus in a relatively nonstressful world with a warm fluid environment, and little or no effort expended in acquiriing nutrients or oxygen. The operative word here, however, is “relatively”, since there are now emerging data that maternal psychosocial stress during pregnancy is associated with adverse fetal outcome (Barker,1998). Adverse outcomes include miscarriage, prematurity, low birth weight, infant mortality, impaired emotional and cognitive development in children, and heart disease, diabetes, and stroke in adult life. Moreover, numerous animal studies link maternal stress with biological effects upon the hypothalamic-pituitary-adrenal (HPA) axis, corticosteriod release, and the development of the central and autonomic nervous systems at the structural, neurochemical, cellular, and molecular levels. In addition, various illicit and psychotropic drugs, as well as alcohol and nicotine in cigarette smoke, interact with neurotransmitter systems in the developing brain. Given that neurotransmitters in early development act as growth factors, as well as signaling molecules, brain development is altered.

The magnitude of the exposure to psychosocial stress is not completely known, but there are many situations of maternal stress that affect a wide number of mothers. Mothers in stress include working mothers, single mothers, teenage mothers, depressed mothers, schizophrenic mothers, anxious mothers. The magnitude is underscored by the recognition that up to 70% of pregnant women have depressive symptoms, with 10-16% of pregnant women fulfilling diagnostic criteria for major depressive disorder (Newport DJ et al. 2001), and up to 6% of pregnant women are physically abused each year.

The outcomes associated with exposure to stress represent a large public health burden. Preterm delivery accounts for 70 percent of perinatal mortality and nearly half of the long-term neurologic morbidity of newborns. Despite years of intense effort to reduce preterm delivery rates, eleven percent of all births in the United States are still preterm and the incidence of very early preterm births has been rising in recent years. Preterm births are twice as high among African American women as among any other group of women in the United States, with an even greater discrepancy in the rate of very early preterm birth. The prevalence of children between 6 and 11years with learning disabilities, attention deficit-hyperactivity disorder or both is 11% and increases to 18% among those born low birthweight.

Heart disease is the leading cause of death in the U.S., with a rate of 17.6 deaths /1000. The prevalence of heart disease among individuals 45-64 years of age is 117.4/1000 and much greater among those with a family income under $20,000: 205/1000. Similarly the prevalence of hypertension among individuals 45-64 years of age is 200.4/1000, increasing to 376/1000 among blacks and 291/1000 among those with a family income under $20,000.

If the contributions of psychosocial stress can be assessed, and the sources identified, it should be possible to develop interventions to reduce their contribution. It is unknown how the contribution of prenatal stress, genetic susceptibility, and postnatal factors interact to result in these conditions. In addition, while there are many potential psychosocial stressors in the prenatal environment, it is likely that these vary widely in type and scope within subpopulations. .

**The ultimate significance of the study:** The ultimate outcome of the proposed study of maternal psychosocial stress during pregnancy may be nothing short of a revolution in the way we care for pregnant women in this country. If the medical and scientific data that are generated from this study indicate that maternal stress adversely impacts the fetus in multiple ways, including beyond infancy, and well into adulthood, as studies in animal models suggest, then multiple issues related to the pregnant woman and prenatal care will need to be rethought, and potentially addressed in completely different and new ways. It may, for example, become a societal decision to provide economic support so that women do not work at certain jobs (all jobs?) during pregnancy. American girls, then, would grow up learning and knowing pregnancy is a special time in their lives that must be accounted for separately, and that the ideas related to prenatal care are not based upon gender prejudice, but rather, upon biological data related to the health of the fetus. It may become a societal decision to ban maternal cigarette smoking during pregnancy, as it is in some communities to ban cocaine and alcohol use during pregnancy. Society may legislate the implementation of the ideas and programs (examples listed below) in regards to working pregnant women, and to the need for prenatal mental health resources.

Potential examples for change:

- Paid leave from work during pregnancy and guarantee of job position when back from pregnancy leave
- Promotions at work based on built-in factor for women's time away from the job for pregnancy, labor and delivery, and postpartum infant care
- Societal acceptance that women on different "tracks" (that factor in pregnancy) from men
- Widely available and subsidized mental health facilities for the mother during prenatal care
- Widely available and subsidized prenatal programs that counsel in the cessation of drinking, smoking, and abusing drugs during pregnancy

## V. Justification for a large, prospective, longitudinal study

Psychosocial stress is a complex entity, including both subjective and physiologic aspects. In order to study the effect of maternal stress during pregnancy on fetal development and subsequent childhood and adult disease, it is necessary to have a prospective study, to collect data on stress as well as fetal function

and growth during the actual pregnancy, and then continue with assessment of infant and child outcomes on into adulthood. Just as there are critical periods in fetal development, there may well be periods in pregnancy when the fetus is especially sensitive to the effects of stress. Thus, repeated measures of stress at different gestational ages are needed.

As is being found with more and more conditions, it is very possible that gene-environment interactions play a role in the relationship between stress during pregnancy and adverse outcomes for the fetus, newborn and adult. In order to have the statistical power to evaluate such interactions, a large cohort would be necessary. For example, to measure a 1.5 increased relative risk for preterm delivery (birth prevalence 7%) associated with stress (exposure 10%) with a power of .8 and an alpha of .05, approximately 6,000 infants in a given strata (e.g race/ethnicity) would need to be studied. However, if there is an effect of genotype on this relationship, to obtain this level of statistical power stratifying by genotype might require ten times this number for less common alleles. Looking at the effects of other potentially confounding exposures would add to the need for large numbers. For outcomes less common than preterm delivery, a cohort size of 100,000 may not be large enough. For example, given the conditions cited above, about 75,000 pregnant women need to be enrolled to detect a 1.5 increased risk of fetal death associated with stress. If the relative risk is increased to 2.0, then the following number of pregnant women would need to be enrolled for the following outcomes: fetal death, 25,000; SIDS, 200,000; infant deaths/short gestation and low birthweight, 180,000. Given that black and American Indian/Alaskan Native infants are at increased risk but make up 15% and 1% of the general population respectively, it will be necessary to oversample these populations.

Few studies cohort studies have examined multiple psychosocial stressors and the maternal response. In addition there are few studies that examine protective mechanisms that may operate to reduce the influence of external stressors in certain cultures, reducing the burden of disease. The National Children's study provides the opportunity to conduct these investigations.

## VI. Scientific Merit

A compelling body of human epidemiologic and animal experimental data has been compiled over the last ten years to show that a sub-optimal intra-uterine environment is associated with an increased incidence of altered pituitary-adrenal function, heart disease, diabetes, and stroke in adult life. This work has been summarized in two recent reviews of the supporting experimental data (Schneider et al. 20002; Walker et al. 1998). Maternal stress has been shown to be one of the major environmental factors in animal studies that adversely impact life- time health. Several physiologic and cellular mechanisms by which excessive maternal stress may affect fetal development in ways that have long-term consequences have been extensively investigated in animal studies.

Adult plasma cortisol levels are elevated in men who were of low birth weight. Recent human epidemiologic studies have clearly demonstrated that low birth weight is a risk factor for disordered endocrine function, hypertension, stroke, cardiac disease, diabetes and obesity in later life (Schneider et al. 20002; Walker et al. 1998). Disordered metabolic states present in diabetes, obesity and insulin resistance are all associated with altered endocrine function. Extensive human epidemiologic studies have been conducted on populations for which various measures of the adequacy of fetal development are available - birth weight, placental weight, biparietal diameter, ponderal index, abdominal circumference - and have been related to adult disease . One major strength of these epidemiologic correlations of the existing conditions during life in the womb with disease in later life resides in the fact that the information comes from many ethnic and geographical sources in addition to the United States: the United Kingdom, Scandinavia, the Indian subcontinent, China, and Chile.

A large body of evidence showing that pre-natal stress alters function of the brain - glucocorticoid axis in post-natal life has been produced using a variety of paradigms in several species. However, most of these

studies have by far entailed work with pregnant rats. Rhesus monkey mothers repeatedly removed from their cages and subjected to unpredictable noise from 90 to 145 days of gestation had higher basal ACTH and GC levels in comparison to controls when blood sampled under anesthesia and also when unanesthetized in their home cages. However, when subjected to 4 levels of stress they showed higher concentrations of ACTH, but not GC (Lou et al. 1994). In another study of pre-natal stress, these same workers concluded that early gestation i.e., the time of neuronal migration is a period of enhanced vulnerability for stress effects (Schneider et al. 1998).

Two of the primary systems that may mediate the possible influence of maternal mood dysregulation on the fetus are the autonomic nervous system and the endocrine system, in particular, the HPA–axis (Glover, Teixeira, Gitau & Fisk, 1999). Elevated and/or chronic sympathetic activation is associated with the release of catecholamines and vasoconstriction. Increased catecholamine levels may affect the fetus directly by contributing to vasoconstriction and increased blood pressure (BP) (McCubbin et al., 1996) (Shnider, Wright & Levinson, 1979). Vasoconstriction is believed to alter uteroplacental blood flow, causing subsequent oxygen and calorie reduction to the fetus and thereby affecting fetal growth (Copper et al., 1996) (McCubbin et al., 1996) and possibly influencing fetal CNS development (Teixeira, Fisk & Glover, 1999).

Recent data suggest that pregnant women's cortisol crosses the placenta (Gitau, Cameron, Fisk & Glover, 1998) (Glover et al., 1999) and that CRH and ACTH also are synthesized by the placenta (Sandman, Wadhwa, Chicz-DeMet, Porto & Garite, 1999). Moreover, emerging data suggest that fetal exposure to high levels of CRH may influence fetal brain development by affecting CRH receptors in the hippocampal and limbic areas. In addition, fetal exposure to heightened levels of CRH may affect fetal glucocorticoid secretion as well as overall HPA–axis regulation and autonomic and endocrine functioning (Sandman et al., 1999).

The effects of women's HPA axis and cardiovascular activity on fetal behavior is supported by recent studies showing correlations between: pregnant women's anxiety and uterine artery resistance (Teixeira et al., 1999) and women's social support and their levels of adrenocorticotropin releasing factor (ACTH) (Wadhwa et al., 1996); women's acute cardiovascular activity and fetal heart rate changes (Monk, Fifer, Myers, Sloan & Ellman, (in press)) (DiPietro, Costigan, Pressman & Doussard-Roosevelt, 2000); as well as pregnant women's and newborns' levels of stress hormones and dopamine I(Lundy et al., 1999). Recent studies indicate that such risk can be assessed along multiple lines, such as neurobehavioral, immune and physiological regulation and attention capacities.

Extensive data from animal and human studies suggests that the development of attention is negatively influenced by heightened stress during pregnancy (Schneider et al., 1999) (Brouwers, van Baar & Pop, 2001). For example, in a study of non–human primates, Schneider found that offspring exposed to prenatal stress had poorer orientation scores on a modified Infant Behavioral Assessment Scale (Schneider et al., 1999). In a recent study of over 3,000 pregnant women and their offspring, women's increased anxiety during pregnancy was found to be associated with elevated risk for Attention Deficit Hyperactivity Disorder in four-year-old boys I(O'Connor, Heron, Golding & Glover, (in press)). Even when not identified as a mental disorder, general attention deficits also have been implicated in long–term school success as well as behavior problems, and frank psychopathology.

Extensive data indicate that assays of salivary cortisol either in response to a stressor and/or sampled over a 24–hour time period can be used to identify differences in newborn and infant HPA–axis regulation (Gunnar, Porter, Wolf, Rigatuso & Larson, 1995). For example, infants classified by Kagan's system as 'high reactive' also have higher tonic levels of cortisol (Kagan, Reznick & Snideman, 1987), which can suggest reduced efficiency of HPA–axis glucocorticoid negative feedback (Meaney et al., 1996) (Clarke,

Wittwer, Abbott & Schneider, 1994) and the possibility of a ceiling effect during stress (Clarke et al., 1994).

However, cortisol reactivity data are inconsistent. In newborns, one study showed that greater changes in cortisol in response to the NBAS were associated with poorer behavioral organization I(Spangler & Scheubeck, 1993) while another found that higher cortisol levels in response to the same probe were related to greater motor maturity and state regulation (Gunnar, Isensee & Fust, 1987) and, at 6 months, lower scores on the temperament rating "distress to limitations" (Gunnar et al., 1995). Given these findings, current examinations of HPA–axis functioning focus on characterizing differences in "reactivity" and "regulation". Specifically, two aspects of reactivity and two aspects of regulation can be examined: They are, respectively, (1) threshold level, i.e., intensity of stimulus needed for a response; (2) response magnitude, (1) timing of return to baseline; (4) reactivation, i.e., how quickly system is re–aroused (Lewis, 1989). Beyond a simple measurement of response magnitude, such evaluations of cortisol activity can better capture individual differences in neurobiological regulation that might be relevant for future adaptation to life stress and risk for mental illness.

## VII. Potential for innovative research

As discussed above there is a large body of carefully controlled evidence from a wide variety of paradigms that different forms of maternal stress adversely impact the fetal neuroendocrine, metabolic and cardiovascular development. Since the stressors studied in animals have been very different from experiment to experiment, a longitudinal cohort study in human pregnancy will provide data on the effects of our complex environment on fetal development and long term consequences of maternal stress.

Innovative approaches will include the ability provided by a large cohort to evaluate the myriad different environmental factors that impact women's level of stress during pregnancy. These maternal stressors will differ randomly across the cohort and hence can be associated with the different outcomes. The common psychosocial stressors include, amongst others, marital and family emotional health, economic, mental health status. There is very little information on the prevalence of depression or anxiety during pregnancy and their influence on outcome. While there is a large literature on the effect of adverse health behaviors such as excessive cigarette smoking or binge drinking on pregnancy outcomes, the biologic consequences of these behaviors have not been examined in the context of psychosocial stress.

The National Children's Study will provide a unique opportunity to obtain tissue samples and plasma and potentially other body fluids such as saliva, connected to detailed longitudinal individual health histories. Powerful techniques such as gene array technologies can be employed against a background of a major database. This study will make available resources and information that will provide a multitude of opportunities for epidemiologic and laboratory research investigations. A large cohort provides the opportunity to evaluate gender and sex differences. There will also be the opportunity to develop tests such as noninvasive challenges that evaluate hypothalamo-pituitary-adrenal function.

Since part of the study design will include evaluation of fetal growth, new methods to analyze intrauterine growth patterns can be devised using the data obtained in pregnancies with normal outcomes. Through multivariate analysis, a formula for normal fetal growth can be derived and later applied to determine individualized growth potential in future studies and clinical evaluation. Unlike the Gardosi method currently available, the method from this large group of longitudinally followed pregnancies will be more specific to the U.S. population and its different ethnic subgroups.

The availability of tissue and data banks will allow testing of multiple variables simultaneously for the prediction of adverse pregnancy outcomes. Multivariate analysis and neural networks will provide a model for prediction of adverse pregnancy outcomes. The associations uncovered during extensive analysis of such a large cohort will undoubtedly be novel and will improve our understanding of the mechanisms leading to these adverse outcomes such as preterm labor, fetal growth restriction, hypertension, etc. More effective interventions that are targeted to patients at risk for these adverse outcomes and are more specific to the pathogenic mechanisms will certainly be a by-product of this study. Simultaneous analysis of multiple variables is not possible without a large cohort. Without such a study, investigations will have to be limited to single or few pathogenic pathways, a process that is at odds with the multifactorial nature of most obstetrical conditions.

Animal studies have shown an association between the parental origin of genetic defects and vascular function in later life, a mechanism akin to genetic imprinting. Therefore, the fetal origin of disease may not be independent of the parental genetic contributions. Maternal polymorphisms transmitted to the fetus may be responsible for the abnormal uterine environment as well as the risk for adult diseases in the offspring. Such polymorphisms may be operating in pregnancies complicated by preeclampsia, fetal growth restriction, and diabetes to name just a few. Examples include the polymorphsims in thrombophilias, nitric oxide synthase gene, or angiotensinogen gene, all of which are reported to be associated with adverse pregnancy outcomes. In addition there may be polymorphisms, such as those described for the serotonin transporter that influence maternal mental health and the ability to cope with stress during pregnancy. The availability of genetic material from parents and offspring at such a large scale will allow high-throughput profiling of gene polymorphism and expression using DNA microarrays, as well as protein interactions using protein arrays and proteomics. These techniques are rapidly evolving and should allow fingerprinting of biological and pathological processes associated with normal and adverse pregnancy outcomes.

## VIII. Feasibility

**Critical Period for Exposure & Outcomes.** From animal studies, and the emerging human data, it is hypothesized that stress and psychiatric symtomatology, alters the *in utero* environment and in turn influences neurobiological development (Wadhwa, Dunkel–Schetter, Chicz–DeMet, Porto & Sandman, 1996). There is evidence that exposure to stress during different time periods in pregnancy is associated with varied outcomes. For example, in a study with non–human primates, early gestational stress versus mid to late–gestational stress was associated with lower birth weight and more pronounced motor impairments (Schneider, Roughton, Koehler & Lubach, 1999). Work with humans also indicates variation in risk for future pathology depending on the timing of fetal exposure (Brown, Susser, Lin, Neugebauer & Gorman, 1995; Brown, van Os, Driessens, Hoek & Susser, 2000). Specifically, prenatal insults such as severe maternal nutritional deprivation or influenza during the second trimester, but not others, are associated with future risk for psychopathology (Susser, Brown & Matte, 1999). In addition, data suggest that for human subjects, reports of mood disturbance (which include not only stress, but anxiety and depression) tend to be higher in the first and third trimesters (Altshuler, Hendrick & Cohen, 1998; Evans, 2001) (Da Costa, Larouche, Drista & Brender, 1999). Taken together, these findings indicate that multiple assessments throughout the course of pregnancy are required to determine the relationship between exposure during critical periods of pregnancy and child development.

**Sampling Needs.**

**Contact:** During pregnancy women's mood and life events will be evaluated at three time points: between 10–20 weeks gestation, between 21 and 30 weeks gestation, and after 31 weeks gestation. Outcome measures will be obtained during late gestation, at birth and the first days of life as the times for

standard well baby visits. The prenatal and postnatal time points were selected to allow for a thorough characterization of fetal exposure to maternal stress and for the assessment of adverse outcomes ranging from miscarriage, premature birth and congenital anomalies, to sudden infant death and early markers for psychopathology.

It is recognized that the ideal first contact would be pre-conception to assess the maternal environment and baseline maternal stress exposure and response.

**Measurement Tools**

**Women's Stress Assessments:** To accurately measure/characterize stress during pregnancy, a multi dimensional approach in both definition and tools is needed. The approach must include assessments that objectively count significant events in a subject's life and the number and nature of stressors. In addition, because people can experience the same event very differently, it is important to evaluate the overall disposition and psychiatric symptoms, which moderate pregnant women's stress responses (Lobel, 1994; Lobel, DeVincent, Kaminer & Mayer, 2000). In particular, depression, which is known to affect approximately 10% of all pregnant women (with fully 70% of them reporting some symptomatology) (Llewellyn, Stowe & Nemeroff, 1997), significantly magnifies the perceived burden of a stressful event. The following assessment tools are appropriate for this study. Importantly, all of the scales listed below have been validated in pregnant women, can be administered over the telephone, are inexpensive and of minimal risk, require minimal expertise to administer and take approximately 3-8 min each to complete. Thus, their burden to research staff and risk to participants is minimal.

Assessment of life events: The Prenatal Life Events Questionnaire (Lobel et al, 1992).
Assessment of coping capacity and attitude: Life Orientation Test (Scheier & Carver, 1985).
Assessment of anxiety: Spielberger's State -Trait Anxiety Questionnaire (Spielberger)
Assessment of depression: Beck Depression Inventory (Beck ) and Center for Epidemiologic Studies-Depression Scale (CES-D)
Assessment of stress: Perceived Stress Scale (Cohen & Williamson, 1988), and
Prenatal Distress Questionnaire (Yali & Lobel, 1999).
Maternal cardiovascular response to a standard laboratory stressor (Monk et al)

**Routine Fetal and Child Assessments.**

**Prenatal**

Fetal growth evaluation by sonogram:
10-13 weeks, 16-20 weeks, 22-25 weeks
Fetal movement and uterine activity logs:
24 weeks – term
Fetal Doppler
At regular intervals in third trimester
Fetal heart rate and movement patterns:
At regular intervals in third trimester
*Intrapartum*
Standard fetal monitoring and detailed intrapartum history

**Placenta**

Standardized protocol

**Neonatal**

Birth history, Apgar, umbilical cord blood gases, length, head circumference, birth weight, skin fold thickness

**Samples for genetic analysis from biological mother, father, child (live or dead), placenta.**

**Postnatal Neurobiological Evaluations**: Two systems integral to biobehavioral regulation and adaptation to environmental challenge, the autonomic nervous system and the HPA–axis—have been repeatedly shown to be altered in offspring exposed to prenatal stress (e.g., (Weinstock, Poltyrev, Schorer-Apelbaum, Men & McCarty, 1998)). Other recent studies indicates that such changes in the offspring's neurobiological regulation may make the individual vulnerable to the influence of future life stress and thus to the development of stress–induced depression or other psychopathologies (Heim & Nemeroff, 1999). Extensive data indicate that assays of salivary cortisol either in response to a stressor and/or sampled over a 24–hour time period can be used to identify differences in newborn and infant HPA–axis regulation (Gunnar, Porter, Wolf, Rigatuso & Larson, 1995). Assessment of patterns of cardiorespiratory activity during sleep offers a non-invasive measure of autonomic function in the newborn. Infant cardiorespiratory monitoring in the home has been developed and validated as part of the Collaborative Home Infant Monitor Evaluation (CHIME: Neuman et al, 2001 ). This non-invasive monitoring approach measures infant breathing by respiratory inductance plethysmography and transthoracic impedance, infant electrocardiogram, heart rate and R-R interval, hemoglobin O2 saturation of arterial blood at the periphery, and sleep position. The following battery of non-invasive, low cost, minimal risk, validated assessments are recommended.

Newborn

Standard newborn neurobehavioral assessment: NAPI (Korner, 1991)

Cardiorespiratory assessment during 30 minute sleep recording (Schectman et al,1993; Sahni et al ,2000)

Infant

Salivary cortisol reactivity to standard inoculations at 2, 4 and 12 months (Gunnar, 1995)

Cardiorespiratory overnight recording prior to inoculations at 2 and 4 months

**References:**


Altshuler, L., Hendrick, V., & Cohen, L. (1998). Course of mood and anxiety disorders during pregnancy and the postpartum period. Journal of Clinical Psychiatry, 59, 29–33.

Barker DJP 1998 Mothers, Babies and Health in Later Life - Second Edition. Churchill Livingstone, London, 2 edn

Brouwers, A., van Baar, A., & Pop, V. (2001). Maternal anxiety during pregnancy and subsequent infant development. Infant Behavior and Development, 24(1), 95-106.

Brown, A., Susser, E., Lin, S., Neugebauer, R., & Gorman, J. (1995). Increased risk of affective disorders in males after second trimester prenatal exposure to the dutch hunger winter 1944–45. British Journal of Psychiatry, 166(5), 601–606.

Brown, A., van Os, J., Driessens, C., Hoek, H., & Susser, E. (2000). Further evidence of relation between prenatal famine and major affective disorder. American Journal of Psychiatry, 157(2), 190-5.

Clarke, A., Wittwer, D., Abbott, D., & Schneider, M. (1994). Long-term effects of prenatal stress on HPA axis activity in juvenile rhesus monkeys. Develpmental Psychobiology, 27(5), 257-269.

Copper, R., Goldenberg, R., Das, A., Elder, N., Swain, M., Norman, G., Ramsey, R., Cotroneo, P., Collins, B., Johnson, F., Jones, P., & Meier, A. (1996). The preterm prediction study: Maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. American Journal of Obstetrics & Gynecology, 175, 1286-1292.

Da Costa, D., Larouche, J., Drista, M., & Brender, W. (1999). Variations in stress levels over the course of pregnancy: Factors associated with elevated hassles, state anxiety and pregnancy–specific stress. ???, 47(6), 609–21.

DiPietro, J., Costigan, K., Pressman, E., & Doussard-Roosevelt, J. (2000). Antenatal origins of individual differences in heart rate. Developmental Psychobiology, 37(4), 221–228.

Evans, J. e. a. (2001). Cohort study of depressed mood during pregnancy and after childbirth. BMJ, 323(4 August 2001), 257-260.

Gitau, R., Cameron, A., Fisk, N., & Glover, V. (1998). Fetal exposure to maternal cortisol. The Lancet, 352, 707–708.

Glover, V., Teixeira, J., Gitau, R., & Fisk, N. M. (1999). Mechanisms by which maternal mood in pregnancy may affect the fetus. Contemporary Reviews in Obstetrics & Gynecology, 155-160.

Gunnar, M., Porter, F., Wolf, C., Rigatuso, J., & Larson, M. (1995). Neonatal stress reactivity: Predictions to later emotional temperament. Child Development, 66, 1–13.

Gunnar, M. R., Isensee, J., & Fust, L. S. (1987). Adrenocortical activity and the Brazelton Neonatal Assessment Scale: Moderating effects of newborn's biomedical status. Child Development, 58, 1448-1458.

Heim, C., & Nemeroff, C. (1999). The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. Biological Psychiatry, 46, 1509-1522.

Kagan, J., Reznick, J., & Snideman, N. (1987). The physiology and psychology of behavioral inhibition in children. Child Development, 58, 1459–1473.

Lewis, M. (1989). Culture and biology: the role of temperament. In P. R. Zelazo & R. G. Barr (Eds.), Challenges to Developmental Paradigms: Implications for Theory, Assessment and Treatment, . Hilldale, NJ: Lawrence Erlbaum Associates.

Llewellyn, A., Stowe, Z., & Nemeroff, C. (1997). Depression during pregnancy and the puerperium. Journal of Clinical Psychiatry, 58(Supplement 15), 26–32.

Lobel, M. (1994). Conceptualizations, measurement, and effects of prenatal maternal stress on birth outcomes. Journal of Behavioural Medicine, 17(3), 225–272.

Lobel, M., DeVincent, C., Kaminer, A., & Mayer, B. (2000). The impact of prenatal maternal stress and optimistic disposition on birth outcomes in medically high–risk women. Health Psychology, 19(6), 544-53.

Lou HC, Hansen D, Nordentoft N, Pryds O, Jensen F, Nim J, Hemmingsen R, Prenatal stressors of human life affect fetal brain development, Dev. Med. Child Neurol. (1994) 36: 826-832.

Lundy, B., Jones, N., Field, T., Nearing, G., Davalos, M., Pietro, P., Schanberg, S., & Kuhn, C. (1999). Prenatal depression affects neonates. Infant Behavior & Development, 22, 119–129.

McCubbin, J., Lawson, E., Cox, S., Sherman, J., Norton, J., & Read, J. (1996). Prenatal maternal blood pressure responsee to stress predicts birth weight and gestational age: A preliminary study. American Journal of Obstetrics and Gynecology, 175, 706–712.

Meaney, M., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., Sharma, S., Seckl, J., & Plotsky, P. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. Developmntal Neuroscience, 18, 49–72.

Monk, C., Fifer, W. P., Myers, M. M., Sloan, R. P., & Ellman, L. M. ((in submission)). The effects of women's stress–elicited physiological activity and chronic anxiety on fetal heart rate.

Nathanielsz PW 1999 Life in the Womb: The Origin of Health and Disease. Promethean Press, Ithaca.

Newport DJ, Wilcox MM, Stowe ZN. Antidepressants during pregnancy and lactation: defining exposure and treatment issues. Semin Perinatol 2001; 25: 177-190.

O'Connor, T. G., Heron, J., Golding, J., & Glover, V. ((in submission)). Maternal antenatal anxiety is linked with hyperactivity in four year old boys. .

Sandman, C., Wadhwa, P., Chicz-DeMet, A., Porto, M., & Garite, T. (1999). Maternal corticotropin-releasing hormone and habituation in the human fetus. Developmental Psychobiology, 34, 163-173.

Schneider, M., Roughton, E., Koehler, A., & Lubach, G. (1999). Growth and development following prenatal stress exposure in primates: An examination of ontogenetic vulnerability. Child Development, 70, 263-274.

Schneider ML, Clarke AS, Kraemer GW, Roughton EC, Lubach GR, Rimm-Kaufman S, Schmidt D, Ebert M. Prenatal stress alters brain biogenic amine levels in primates, Dev. Psychopathol. (1998) 10: 427-440.

Schneider ML, Moore CF, Kraemer GW, Roberts AD, DeJesus OT. The impact of prenatal stress, fetal alcohol exposure, or both on development: perspectives from a primate model. Psychoneuroendocrinology, (2002) 27: 285-298.

Shnider, S., Wright, R., & Levinson, G. (1979). Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology, 50, 524–527.

Spangler, G., & Scheubeck, R. (1993). Behavioral organization in newborns and its relation to adrenocoritcal and cardiac activity. Child Development, 64, 622–633.

Susser, E., Brown, A., & Matte, T. (1999). Prenatal factors and adult mental and physical health. Canadian Journal of Psychiatry, 44, 326–334.

Takahashi, L., & Kalin, N. (1991). Early developmental and temporal characteristics of stress-induced secretion of pituitary-adrenal hormones in prenatally stressed rat pups. Brain Research, 558, 75-78.

Teixeira, J., Fisk, N., & Glover, V. (1999). Association between maternal anxiety in pregnancy and increased uterine artery resistance index: Cohort based study. British Medical Journal, 318, 153-157.

Vallee, M., Mayo, W., Dellu, F., Le Moal, M., Simon, H., & Maccari, S. (1997). Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. The Journal of Neuroscience, 17(7), 2626-2636.

Wadhwa, P., Dunkel–Schetter, C., Chicz–DeMet, A., Porto, M., & Sandman, C. (1996). Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. Psychosomatic Medicine, 58, 432–446.

Walker BR, Phillips DIW, Noon JP, Panarelli M, Andrew R, Edwards HV, Holton DW, Seckl JR, Webb DJ, Watt GCM. Increased glucocorticoid activity in men with cardiovascular risk factors. Hypertension (1998) 31:891-895

Weinstock, M., Poltyrev, T., Schorer-Apelbaum, D., Men, D., & McCarty, R. (1998). Effect of prenatal stress on plasma corticosterone and catecholamines in response to footshock in rats. Physiology and Behavior, 64(4), 439-444.