Regulatory Sponsor

IND Sponsor

none

Industry Sponsor

None

Project Funding*
Is this project funded by or associated with a grant or contract?
Pending

Sponsor Funding
Is this study funded by an industry sponsor?
No

Status of contract

The following documents are currently attached to this item:

There are no documents attached for this item.

Multi-Site Research

Other Sites

No other sites

Management of Information for Multi-Center Research

The following documents are currently attached to this item:

There are no documents attached for this item.

Protocol

Abstract
The goal of the National Childrens Study (NCS) is to help understand how the environment affects children's health, growth and development. This protocol at Penn includes four ancillary projects ("Formative Research Studies") to the Main NCS Study, which is currently being conducted locally at CHOP. The ancillary projects will be conducted at Penn. The purpose of these ancillary studies is to make recommendations for the NCS regarding study design and methods development. In total, there are 7 Formative Research Studies occurring: 1) QUEX-01 A: Development of an Optimized Measure of Chronic Stress in Pregnancy 2) QUEX-01 B: Evaluating Psychosocial Stressors in Pregnant Women 3) QUEX-01 C: Selection and Validation of self-report and biological measures of maternal stress using ecological momentary assessment (EMA) methodology 4) QUEX-01 D: Biological Moderators of cortisol activity in human pregnancy 5) QUEX-01 E: Validation of cortisol in hair samples for quantification of long-term cortisol exposure 6) ENV-23 B: Placenta studies: Stem Cell Collection and Banking, Morphology Pathology Assessment, Genetic/Genomic Assessment and Environmental Contaminant Assessment 7) PHYS-15: Collection of Circulating Fetal DNA from Maternal Blood and from Cervical Fluid Penn is NOT participating as a site in study numbers 2, 6 and 7 At our institution, prospective data will be collected in a sample of women recruited during pregnancy and followed through delivery and into the first week of their infants' lives. A maximum of four assessments will be conducted, the first during early gestation (T1: 14-20 weeks), the second during late gestation (T2: 28-32 weeks), the third (T3) at birth, and the fourth (T4) within one week of birth. The main study procedures include collection of biological samples (saliva, hair, urine, blood, cervical fluid, umbilical

cord blood and umbilical cord tissue), administration of questionnaires, utility of ambulatory monitoring (actiheart, electronic diary), fetal ultrasound assessments, medical chart abstraction, and measures of neonatal body composition (DXA Scan). Results from the studies described herein will be used to inform the final protocol of the Main Study of the NCS.

Objectives

Overall objectives

1. The overall goal is to conduct a multi-center collaborative formative research project for the empirical evaluation of maternal stress measurement for use in the NCS. 2. To develop a common, core protocol and specific projects to empirically determine the most reliable, acceptable and costefficient approaches for the assessment of maternal stress and stressrelated biomarkers. The proposed sub-studies aim to inform and improve the study design of the Main/Vanguard Study of the NCS.

Primary outcome variable(s)

1.QUEX-01 A: Development of an Optimized Measure of Chronic Stress in Pregnancy This sub-study proposes to utilize Item Response Theory (IRT) modeling to develop an optimized item reduced measure of self-reported maternal stress and then validate this measure against biologic measures of stress. Development of an IRT-optimized maternal stress measure would more efficiently measure chronic stress by allowing for fewer items needed for reliable measurement and, thereby, reduce burden for NCS participants and study centers and reduce study costs. 2. QUEX 01-C EMA The goal of this sub-study is to collect and provide data to empirically inform the selection of measures of maternal stress and stress biology for the NCS. Towards this goal, this study will compare and contrast the reliability and validity of data using the maternal self-report instruments currently proposed in the NCS as well as other additional measures being tested in LOI QUEX 01.1 and 01.2 against self-report and biological data collected using the ecological momentary assessment (EMA) methodology. EMA is currently considered the gold standard for collection of psychosocial and stress-related biological measures. It involves real-time assessments over time and in natural day-to-day settings of respondents psychological state, behavior and physiology, and the use of state-of-the-art statistical approaches using time-series hierarchical regression models (HLM) to compute indices of psychosocial stress and psychobiological stress responsivity (the degree of coupling between psychological and biological states). Procedures involve placing the ActiHeart device on the chest of each participant at baseline and testing the device signal. An electronic diary is introduced to participants and a practice entry is conducted. Diaries are then kept daily until the participant's second visit has concluded. The use of EMA protocols is not feasible in the larger NCS study because of heavy subject burden, however, it represents the gold standard against which self-report questionnaires and interviews should be validated. 3.QUEX 01-D Biological Moderators of Cortisol The goal of this sub-study is to collect and provide data to empirically determine efficiency and quality of detection methods of key biological moderators of cortisol activity in human pregnancy [cortisol binding globulin (CBG), 11HSD activity, glucocorticoid receptor (GR) sensitivity and affinity].4.QUEX-01 E: Validation of cortisol in hair samples for quantification of long-term cortisol exposure A wide range of approaches and protocols are available to assess maternal stress and stress biology in pregnancy, with differing opinions among experts about their feasibility (including scientific merit) and acceptability (respondent burden). The additional measurement of cortisol levels in hair will provide a relatively non-invasive complementary and more cumulative biomarker of stress than what is currently studied through salivary cortisol measures. Comparisons between stress measures obtained from saliva, blood and hair will be informative for the NCS to elucidate which is most appropriate for research exploring the stress/obesity connection as well as other adverse health outcomes such as preterm birth. While this protocol has been demonstrated once within pregnant women, replication of these findings is needed and optimization of hair biomarker usage is essential for NCS biomarker prioritization. The hair provides for not only a quantification (1 cm = average cortisol over a 30-day period) but also a temporal record (cortisol levels in hair at increasing distance up to 6 cm from scalp correspond to cortisol levels at times up to 6 months prior to collection time) of multiple exposures relating to cortisol.

Secondary outcome variable(s)

Not applicable.

Background

QUEX-01 A: Development of an Optimized Measure of Chronic Stress in Pregnancy Premature birth is the major cause of perinatal morbidity in the United States, accounting for 85% of adverse birth

outcomes (Arias et al., 2003). Although multiple studies have shown an association between maternal stress and low birth weight or preterm birth (Dole et al., 2003; Hogue and Bremner, 2005; Hedegaard et al., 1996; Lobel et al., 1992; Nordentoft et al., 1996; Copper et al., 1996; Rini et al., 1999; Borders et al., 2007), there are other studies that do not support this association (Lu and Bhen, 2004; Bryce et al., 1991; Oakley et al., 1990; Orr & Miller, 1995; Hoffman & Hatch, 1996). The inconsistency in study findings may be related to the diversity of tools and constructs used to operationalize stress (Hoffman & Hatch, 1996). In addition, scales that simply tally experienced stressful events may not account for the relevant internal response to external events and may not accurately assess chronic stressors which may be of more physiologic importance for pregnancy outcomes (Lu and Halfon, 2003; Marmot et al., 1998; Kuh et al., 1998). It is likely that the link between chronic stress and preterm birth remains uncertain because an adequate measure of maternal stress has not yet been developed (Hobel and Culhane, 2009; Wadhwa et al., 1993). This sub-study proposes to utilize Item Response Theory (IRT) modeling to develop an optimized item reduced measure of self-reported maternal stress and then validate this measure against biologic measures of stress. Development of an IRT-optimized maternal stress measure would more efficiently measure chronic stress by allowing for fewer items needed for reliable measurement and, thereby, reduce burden for NCS participants and study centers and reduce study costs. QUEX 01-C: EMA Maternal stress assessments over the course of gestation represent an integral part of several major NCS hypotheses and priority outcomes, including pregnancy and birth outcomes, child body composition, metabolic function and obesity, pulmonary function and asthma, and neurodevelopment. The measures included in the current NCS protocol to assess maternal psychosocial stress exclusively consist of self-report, retrospective recall measures. Major weaknesses of these traditional self-reported recall measures relate to (a) biases associated with retrospective recall (these measures rely on autobiographical memory and respondents ability to integrate and summarize states and events across the reporting period), and (b) the failure to assess and account for individual differences in biological stress responsivity. The goal of this sub-study is to collect and provide data to empirically inform the selection of measures of maternal stress and stress biology for the NCS. Towards this goal, this study will compare and contrast the reliability and validity of data using the maternal self-report instruments currently proposed in the NCS as well as other additional measures being tested in LOI QUEX 01.1 and 01.2 against self-report and biological data collected using the ecological momentary assessment (EMA) methodology. EMA is currently considered the gold standard for collection of psychosocial and stress-related biological measures. It involves real-time assessments over time and in natural day-to-day settings of respondents psychological state, behavior and physiology, and the use of state-of-the-art statistical approaches using time-series hierarchical regression models (HLM) to compute indices of psychosocial stress and psychobiological stress responsivity (the degree of coupling between psychological and biological states). The use of EMA protocols is not feasible in the larger NCS study because of heavy subject burden, however, it represents the gold standard against which self-report questionnaires and interviews should be validated. QUEX 01-D: Biological Moderators of Cortisol Many of the priority NCS hypotheses relate to the effects of cortisol exposure over the course of gestation on outcomes including fetal growth and length of gestation, child body composition and obesity risk, child respiratory function/ asthma risk, child neurodevelopment/ brain morphology. The current NCS protocol relies exclusively on measurements of cortisol levels in maternal blood and saliva. This approach may, however, be limited because (a) it is well-recognized that the effect of hormones such as cortisol on its respective target cells depends not only on the amount produced but also on the extra- and intracellular hormone availability, the potency of the hormone, and the ability of the cell to receive and transduce the signal. (b) Moreover, cortisol is known to rise progressively over the course of gestation, with total and free plasma cortisol levels peaking during the third trimester at about two to three times the levels of non-pregnant state (see Mastorakos and Ilias, 2003 for an overview). Peak cortisol levels in the maternal compartment during the third trimester of human pregnancy are comparable to those observed in Cushings disease, severe depression, anorexia nervosa, and in athletes doing strenuous exercise (Abou-Samra et al., 1984; Magiakou et al., 1997; Rosenthal et al., 1969; Taylor and Lebovic, 2004). Thus, pregnancy is a transient, but physiologic, period of relative hypercortisolism even among normal, healthy woman. Accumulating evidence suggests that in addition to peripheral cortisol levels, several other parameters must be taken into consideration when evaluating the potential health risks associated with a hyper- or hyporeactive HPA axis (DeRijk and Sternberg, 1997). The goal of this sub-study is to collect and provide data to empirically determine the additional utility over and above measures of cortisol level of key biological moderators of cortisol activity in human pregnancy [cortisol binding globulin (CBG), 11HSD activity, glucocorticoid receptor (GR) sensitivity and affinity] on some of the priority NCS outcomes [fetal growth in the 3rd trimester and newborn body composition]. These particular outcomes are selected for this sub-study because they represent priority NCS outcomes and they will be available and can be

collected within the stipulated study time frame. QUEX-01 E: Validation of cortisol in hair samples for quantification of long-term cortisol exposure A wide range of approaches and protocols are available to assess maternal stress and stress biology in pregnancy, with differing opinions among experts about their feasibility (including scientific merit) and acceptability (respondent burden). The additional measurement of cortisol levels in hair will provide a relatively non-invasive complementary and more cumulative biomarker of stress than what is currently studied through salivary cortisol measures. Comparisons between stress measures obtained from saliva, blood and hair will be informative for the NCS to elucidate which is most appropriate for research exploring the stress/obesity connection as well as other adverse health outcomes such as preterm birth. While this protocol has been demonstrated once within pregnant women, replication of these findings is needed and optimization of hair biomarker usage is essential for NCS biomarker prioritization. The hair provides for not only a quantification (1 cm = average cortisol over a 30-day period) but also a temporal record (cortisol levels in hair at increasing distance up to 6 cm from scalp correspond to cortisol levels at times up to 6 months prior to collection time) of multiple exposures relating to cortisol.

Study Design

Phase*
Not applicable

Design
Prospective, formative research studies.

Study duration
The study is proposed to enroll subjects for 1.5 years. The subject's participation will involve a maximum of four assessment periods over the course of the pregnancy and into the infants first week of life. The first assessment will take place in early gestation (T1: 14-20 weeks), the second during late gestation (T2: 28-32 weeks), the third (T3) at birth, and the fourth (T4) within one week of birth. The study is proposed to start after all requirements (IRB, contracts, etc) are met. We anticipate starting the study by March 1, 2011.

Resources necessary for human research protection
Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Describe access to a population that would allow recruitment of the targeted number of subjects. If medical or psychological services as a consequence of the research, describe how the subject will be referred to those services. Describe your facilities and justify that the facilities are adequate. Verify that there is sufficient time to conduct and complete the research.

Characteristics of the Study Population

Target population
Adult, pregnant women undergoing antenatal care in the Penn Department of Obstetrics and Gynecology.

Subjects at Penn
50

Subjects at Sites Other than Penn
550

Accrual
Subjects will be recruited from the Department of Obstetrics and Gynecology at Penn. Penn OBGyn has approximately 300 new obstetrical encounters each month, which should be an ample pool from which to recruit 50 women in 18 months. Power and precision of the proposed analysis is greatly enhanced over typical survey data because of the fact that each subject acts as her own control over time. This is because due to the ecological momentary assessment (EMA) component, multiple

conditions or exposures are studied in each subject, and the variability in exposure-response relationships due to between-subject characteristics is controlled for by design due to a reduction in the variability of the response variable without reductions in the magnitude of the exposure-response relationship. Each subject will contribute around 15 repeated observations per day, 60 observations across the four days, and a total of 120 across all three assessments. We based the statistical power analyses on simulation models we developed for this purpose that incorporate conservative estimates of published effect sizes from our previous studies. After verifying that the simulation reproduced the assumed pattern of relationships, we used SAS PROC MIXED to perform the planned analyses for the association between the main predictors (psychological and biological stress) and the main outcomes (length of gestation, birth weight and infant fat mass). The standard errors from these analyses were used to generate power estimates for a sample size of N=600 and = .05 (two-tailed tests). Based on these estimates, the minimum effects detectable with 80%, 90% and 95% power were 0.12, 0.16 and 0.20, respectively (which correspond to effects described as small to medium by Cohen (1969), and which reflect the lower end of our expected effect sizes). Thus, the proposed sample size will provide adequate statistical power to test specific hypotheses concerning within-person main effects, the moderating effects of between-person factors, and the interaction of the two.

Key inclusion criteria
Inclusion criteria: a) adult women (over 18 years age) with a singleton intrauterine pregnancy; b) English speaking; c) less than 20 weeks pregnant.

Key exclusion criteria
Exclusion criteria: a) presence of any prior or present obstetric risk conditions such as systemic maternal disease, placental or cord abnormalities, uterine anomalies, infection, congenital malformations, chromosomal abnormalities, previous preterm labor/delivery/low birth weight, and b) presence of any conditions that may dysregulate neuroendocrine or cardiovascular function and metabolism such as endocrine, hepatic, renal or autoimmune disorder, hypertension, or use of corticosteroid medications in the last month.

Vulnerable Populations

	Children (refer to SOP 501 for definition of children) Form
x	**Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form**
x	**Fetuses and/or Neonates Form**
	Prisoners Form
	Other
	None of the above populations are included in the research study

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion
Prisoners or mentally disabled persons will not be enrolled in this study. Economically disadvantaged persons may be included, however there is no compensation that could be perceived as coercive. Employees or students of Penn may be included if they present to the clinic for prenatal services and meet eligibility criteria. However, this group of people will not be specifically targeted for recruitment. Pregnant women and children will be included. Plans to protect this population are included on the attached supplemental forms.

Subject recruitment
Eligible women undergoing antenatal care in the Penn Department of Obstetrics and Gynecology will be approached by a member of the study staff at the time of a clinical appointment to assess their interest in enrollment into the study.

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There are no documents attached for this item.